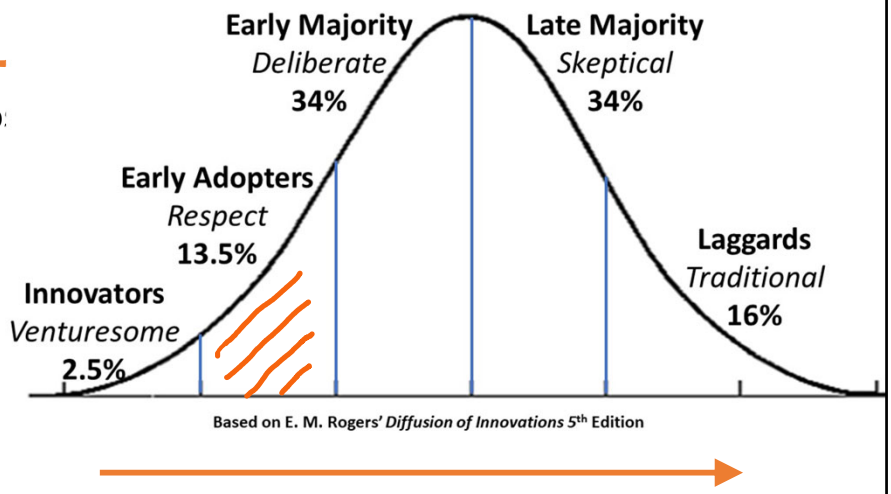
Orthobiologics in 2023

Guy Nicolette, MD, CAQSM

1

My Biases

- No monetary disclo
- Early adopter
- Technophile
- Optimistic



2

Questions

- How do you define PRP? Stem cell treatment?
- Why not call it 'regenerative medicine'?
- Why not just steroids and 'caines'?
- Does it matter how it is prepared?
- Are there responders vs nonresponders?
- How do you translate current science and expert opinions to practical application?

3

Definitions

PRP = >4-6x baseline concentration of platelets

LP = < 1.0x baseline leukocytes

LR = > 1.0x baseline leukocytes

HMW HA = >1800 kDa

4

Semantics?

- PRP has not been proven to consistently regenerate tissue
  - Affects matrix and synovium, cytokine release and expression
  - Provides a better environment for the body to heal & to reduce pain
- Orthobiologics is my preferred term
  - PRP
  - Stem cells
  - BMAC
  - Stromal vascular fraction
  - Many others

5

So if this isn't regenerative, why not use –caines & steroids?

PM R 11 (2019) 379-400 www.pmrjournal.org

Analytical-Systematic Review—CME

Chondrotoxic Effects of Local Anesthetics on Human Knee Articular Cartilage: A Systematic Review

Prathap Jayaram, MD, David J. Kennedy, MD, Peter Yeh, MD, Jason Dragoo, MD

Lidocaine 1% & 2% reduced chondrocyte viability

Bupivicaine all concentrations reduced viability

Ropivicaine >.75% reduced viability

Using steroid along with these increases chondrotoxicity

All dose-dependent

6

The preparation of biologics matters!

7

Table 2 Application of DEPA score to 20 PRP preparations in which biological characteristics are available on publications indexed in PubMed

		DEPA classification									
		Dose of injected platelets (billions)			Efficiency of the process (platelet recovery rate %)			Purity of the PRP (relative composition in platelets %)			
		A	>5	Very high dose	A	>90	High	A	>90	Very pure PRP	
		B	3–5	High dose	B	70–90	Medium	B	70–90	Pure PRP	
		C	1–3	Medium dose	C	30–70	Low	C	30–70	Heterogeneous PRP	Final DEPA
		D	<1	Low dose	D	<30	Poor	D	<30	Whole blood PRP	score
Kaux *et al*[15]	Homemade	D	0.74	Low dose	C	46.2	Low	A	90.3	Very pure PRP	DCA
	Curasan	D	0.55	Low dose	C	32.4	Low	A	97.7	Very pure PRP	DCA
	Plateltex	D	0.23	Low dose	D	19.4	Poor	B	87.5	Pure PRP	DDB
	GPS II	C	2.28	Medium dose	D	22.8	Poor	D	6.0	Whole blood PRP	CDD
	RegenLab	D	0.95	Low dose	B	79.3	Medium	A	97.5	Very pure PRP	DBA
Castillo *et al*[14]	Cascade	C	2.43	Medium dose	C	67.5	Low	B	81.5	Pure PRP	CCB
	GPS III	C	2.48	Medium dose	D	22.6	Poor	D	27.0	Whole blood PRP	CDD
	Magellan	B	3.41	High dose	C	65.8	Low	C	60.4	Heterogeneous PRP	BCC
Magalon *et al*[12]	Selphyl	D	0.95	Low dose	C	59.5	Low	B	73.9	Pure PRP	DCB
	RegenPRP	D	0.99	Low dose	C	61.7	Low	C	46.0	Heterogeneous PRP	DCC
	Mini GPS III	C	2.56	Medium dose	C	34.6	Low	C	51.8	Heterogeneous PRP	CCC
	Arthrex	C	1.06	Medium dose	C	48.0	Low	B	81.0	Pure PRP	CCB
	Homemade	C	1.81	Medium dose	C	30.2	Low	B	80.7	Pure PRP	CCB
Kushida *et al*[14]	JP200	C	1.04	Medium dose	D	26.0	Poor	D	19.6	Whole blood PRP	CDD
	GLO	D	0.64	Low dose	C	37.4	Low	C	38.2	Heterogeneous PRP	DCC
	Magellan	A	5.43	Very high dose	C	45.3	Low	C	32.9	Heterogeneous PRP	ACC
	Kyocera	B	3.12	High dose	B	78.1	Medium	D	29.4	Whole blood PRP	BBD
	Selphyl	D	0.21	Low dose	D	13.1	Poor	A	99.7	Very pure PRP	DDA
	MyCells	D	0.98	Low dose	C	48.8	Low	B	87.3	Pure PRP	DCB
	Dr. Shin	D	0.78	Low dose	C	45.9	Low	D	18.8	Whole blood PRP	DCD

DEPA, Dose of injected platelets, Efficiency of production, Purity of the PRP, Activation of the PRP; PRP, platelet-rich plasma.

Magalon J, et al. BMJ Open Sport Exerc Med 2016; 2:e000060. doi:10.1136/bmjsem-2015-000060

8

TABLE 2.1 Commercial Systems for Preparation

System name	Blood Volume mls	Anti-coagulant	Centri-fugation speed, force (g) First spin/ Second spin	Centri-fugation time (Mins)	PRP volume (mls)	Cell capture: PL/BC	Platelet count X103 micro L	White Cell Count x103 Micro L	Red cell count
ACP	11[50]	ACD	1500	5	6	PL[23]	372-413[23, 38]	0.3-1.3[23, 38]	<1[23]
Cascade	9	Sodium Citrate	1100/1450	6/15	2	PL[27]	443-2900[3, 12]	<1.1[3, 12]	0.1[12]
Endoret	9	Sodium Citrate	580[50] 270[2]	8 7	2	PL	414-650[50, 52]	<1[52]	<1[52]
Plateltex	9/6	ACD[2]	180/1000	10/10	0.34	PL	<1000[39]	<1	
Selphyl	9	Sodium citrate[2]	1100	6	4	PL	330[38]	1.3[38]	
Angel	40-180	ACD				BC	1056-1688[8, 47]	18-40[8, 47]	18[8]
GLO	9		1200/600	5/2	0.6	BC[27]			
GPS III	30-60	ACD	3200[2]	15	6	BC[27]	566-2500[3, 12, 20, 23, 49]	15-52[23, 49]	1.03-1.5[12, 23]
KYOCERA	20		600/2000	7/5	2	BC	543[39]		
Magellan	60	ACD	610/1240	4/6	3	BC[27]	600-1500[3, 12, 23]	1-31[3, 12, 23]	0.5-1.03[12, 23]
Prosys	30		1660/2008	3/3	3	BC	600[49]	15[49]	100[49]
Regen PRP	8	Sodium Citrate	1500	5-9[2, 50]	4	BC	453[38]	11[38]	
SmartPrep	60	ACD[2]	1250/1050[50] 2500/2300[2]	14/10 4/10	10	BC[27]	800-2600[3, 23]	8-35[3, 23]	1.4[23]

Biologics Assoc 2023 Symposium– J Kirkpatrick

9

Responders vs nonresponders

- Increased IL-17, TNF-a PBPP expression
- Decreased TNF-a CCL5 expression

www.nature.com/scientificreports

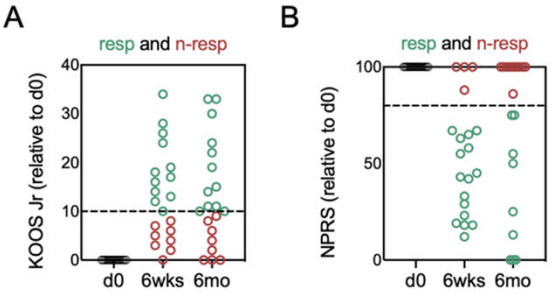
scientific reports

Check for updates

OPEN

In vitro responses to platelet-rich-plasma are associated with variable clinical outcomes in patients with knee osteoarthritis

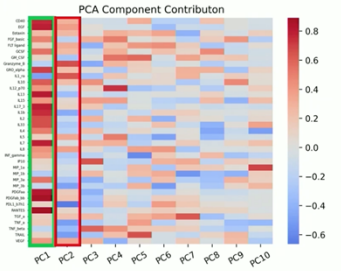
Habib Zahir[1,2,8], Bijan Dehghani[1,8], Xiaoning Yuan[1,3], Yurii Chinenov[1,4], Christine Kim[1,5], Alissa Burge[1], Reyna Bandhari[1], Daniel Nemirov[1], Patrick Fava[1], Peter Moley[1,6], Hollis Potter[1], Joseph Nguyen[1], Brian Halpern[1,6], Laura Donlin[1,7], Lionel Ivashkiv[1,4], Scott Rodeo[1,6,8] & Miguel Otero[1,6,7,8]



10

Submitted By The Biologic Association, Jason L Dragoo MD

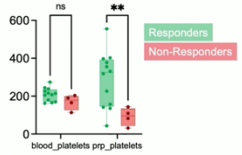
Unbiased Multivariate Cluster Analysis



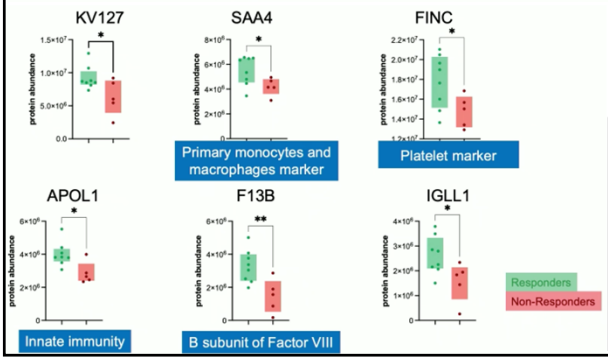
Top 10 factors correlated with Responders

RANTES
PDGF BB
PDGF AA
IL-13
IL-7
EGF
IL-17
CD40

Platelet counts: PRP and Whole Blood



Significantly more platelets in the PRP of responders vs non-responders



Primary monocytes and macrophages marker

Platelet marker

Innate immunity

B subunit of Factor VIII

- 2nd study suggesting IL-17 as a factor correlated with PRP response in knee OA
- Higher platelet counts and lymphocytes
- 10 points on KOOS = responder

11

Submitted By The Biologic Association, Jason L Dragoo MD

Unbiased Multivariate Cluster Analysis

PCA Component Contributon

Top 10 factors correlated with Responders

RANTES
PDGF BB
PDGF AA
IL-13
IL-7
EGF
IL-17
CD40

Innate immunity

B subunit of Factor VIII

- Higher platelet counts and lymphocytes
- 10 points on KOOS = responder

12

TABLE 3: Comparison of inflammatory cytokines and chondrodegenerative markers (mean ± standard deviation) evaluated on the day of ACL reconstruction between patients with KOOS QOL scores above and below the PASS threshold of 62.5 points.

Biomarker	< PASS	≥ PASS	p[a]	d[e]
N	6	16	-	-
Female/Male (n)	3/3	6/10	0.66	-
Steroid/Placebo (n)	4/2	12/4	> 0.99	-
Age (years)	18.0 ± 2.6	20.0 ± 4.5	0.42	-
BMI (kg/m^2)	22.4 ± 2.9	24.8 ± 3.6	0.15	-
Graft (BTB/Hamstring)	5/1	13/3	> 0.99	-
Medial meniscus injury	5	9	0.35	-
Lateral meniscus injury	2	12	0.12	-
Bone bruise volume (mm^3)	7.99 ± 8.93	11.07 ± 9.33	0.50	0.30
COMP (μg/ml)	32.3 ± 12.5	39.3 ± 14.0	0.42	0.51
CTX-II (ng/ml)	1.57 ± 0.93	1.52 ± 1.97	0.38	0.03
uCTX-II[d] (μg/mmol)	5.72 ± 4.86	2.42 ± 2.09	0.08	0.99
sGAG (μg/ml)	190.9 ± 69.9	264.7 ± 168.3	0.83	0.49
IL-1α (pg/ml)	***9.47 ± 7.65***	***2.21 ± 2.20***	***0.004***	***1.36***
IL-1β[c] (pg/ml)	0.11 ± 0.13	0.45 ± 1.48	0.76	0.26
IL-1ra (pg/ml)	***2,593.2 ± 3,576.4***	***2,086.3 ± 5,507.0***	***0.03***	***0.10***
MMP-1 (ng/ml)	640.07 ± 81.58	394.06 ± 667.06	0.27	0.35
MMP-3 (ng/ml)	4,017.2 ± 4,576.41	2,532.80 ± 3,066.43	0.56	0.43
MMP-9 (ng/ml)	***30.99 ± 35.96***	***6.94 ± 10.30***	***0.01***	***1.07***
NTX-I (nM BCE)	30.3 ± 7.9	22.7 ± 7.1	0.055	0.97
TSG-6 (U)	286.4 ± 165.7	260.1 ± 157.3	0.83	0.11

[a] Statistically significant differences denoted with ***bold and italics font.***
[b] Number of patients in the corticosteroid or placebo group from the original randomized trial.
[c] There was also no difference in the number of samples below LLOD between groups.
< Pass=3/6 versus ≥ PASS=8/16, p > 0.99.
[d] u = urinary, the remaining biomarkers were measured in synovial fluid. Urinary CTX-II normalized to creatinine level (μg/mmol).
[e] Cohen's d effect sizes calculations were also performed in order to identify potentially clinically-meaningful findings within these pilot data, with d > 0.80 considered a large effect size.

13

Too many trials to list here

One can find as many studies suggesting PRP "works" as those that don't

The Knee 32 (2021) 173–182

Contents lists available at ScienceDirect

The Knee

journal homepage:

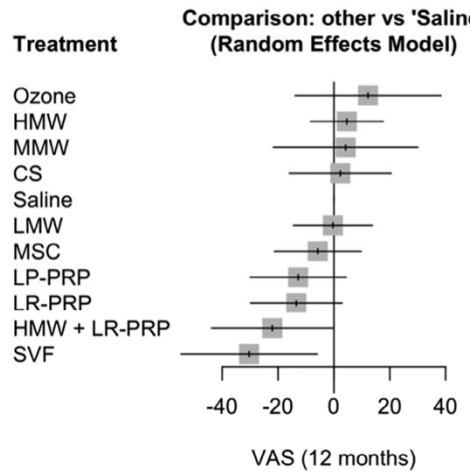
Review

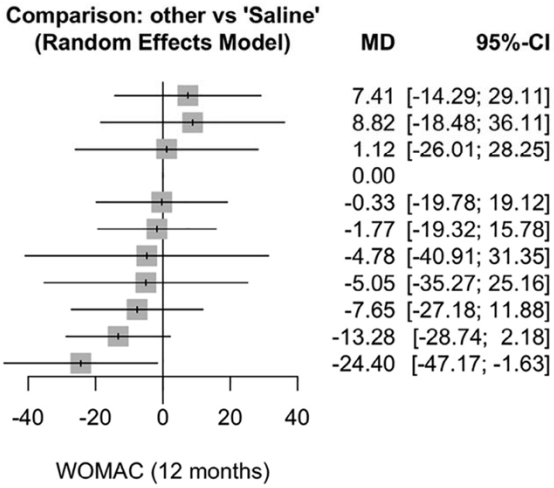
The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials

Utkarsh Anil, Danielle H. Markus *, Eoghan T. Hurley, Amit K. Manjunath, Michael J. Alaia, Kirk A. Campbell, Laith M. Jazrawi, Eric J. Strauss

NYU Langone Orthopedic Hospital, Division of Sports Medicine, 333 E 38th Street, New York, NY 10016, United States

14





Only intervention worse than placebo was ozone
HA + PRP was significantly better than placebo

15

Summary A: high variability in outcomes; why?

1) Difficulty designing a good RCT
2) Non standardized (often not well described) methodology or system for obtaining platelet & plasma (i.e. no objective 'dose')
3) Appear to be responders and non-responders

16

Summary B: a clinical application

PRP = 4-6x baseline concentration of platelets

LP = < 1.0x baseline white cells

LR = > 1.0x baseline white cells

HMW = >1800 kDa

Patient naïve to orthobiologics with knee OA, or isolated chondral injury:

LP-PRP + HMW hi-conc (>1mg/ml) HA
q1-2 weeks x 3

Maintenance:

LP-PRP + HMW hi-conc 1-dose HA
q 3-12 months