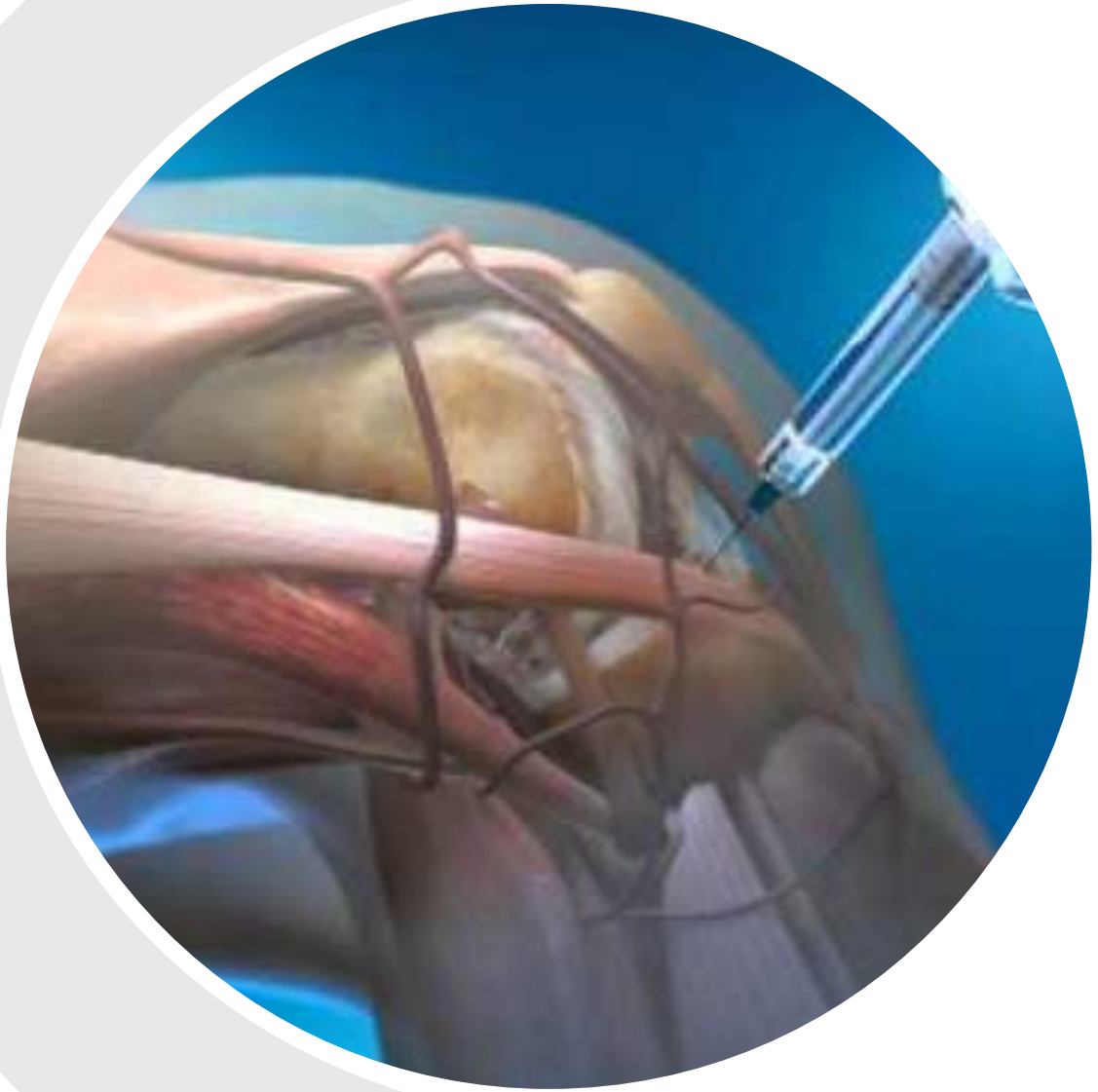


UCLA Health

PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials

CHRISTOPHER SILVA, M.D.

BACKGROUND

PLATELET RICH PLASMA (PRP) DEFINITION AND FORMULATION

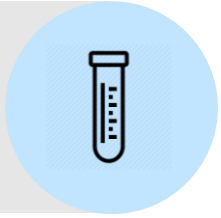
PLATELET RICH PLASMA

PRP is an autologous sampling of a patient's blood, which is centrifuged down to separate the plasma, which is rich in platelets, WBC, RBCs, growth factors, which are important in healing injuries

ALPHA GRANULES

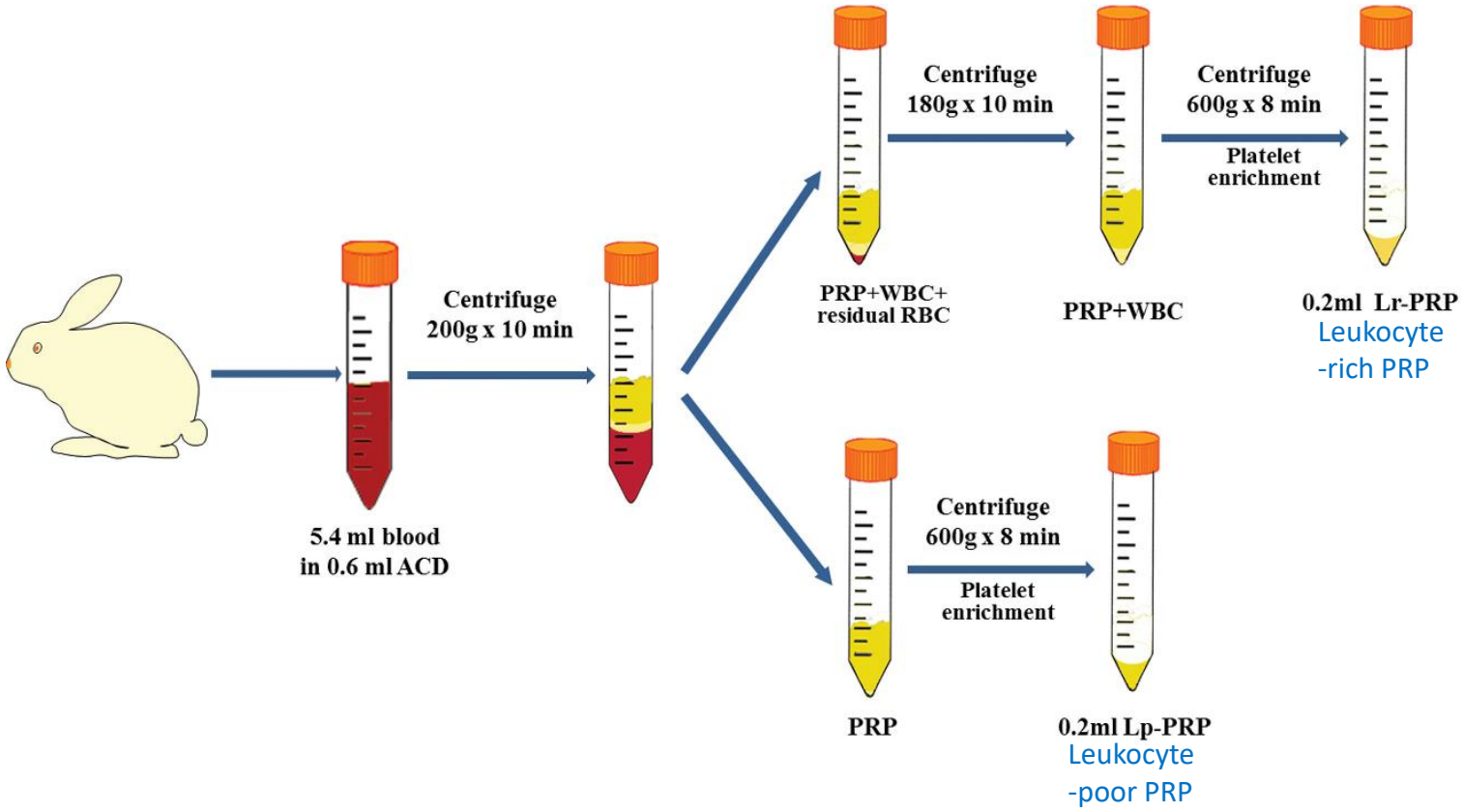
Alpha granules contain critical GFs, cytokines, chemokines, ADP, ATP, histamine, serotonin, dopamine and additionally release antibacterial and fungicidal proteins that protect against infection

FORMULATION METHODS



There are different methods of formulating PRP with variance in technique and composition

PRP FORMULATION METHODOLOGY IS NOT STANDARDIZED



ARTICLE INTRODUCTION

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PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials

Giuseppe Filardo[1,2], Davide Previtali[2], Francesca Napoli[2], Christian Candrian[2], Stefano Zaffagnini[1], and Alberto Grassi[1]

Abstract

Objective. To evaluate effectiveness, in terms of patient-reported outcome measures, of platelet-rich plasma (PRP) injections for knee osteoarthritis compared to placebo and other intraarticular treatments. *Design*. PubMed, Cochrane Library, Scopus, Embase, Web of Science, as well as the gray literature were searched on January 17, 2020. Randomized controlled

THE NUTS AND BOLTS

Hypothesis: *PRP injection could provide better results compared with other injective treatments for knee OA*

Study design: meta analysis

Methods: PubMed, Cochrane Library, Scopus, Embase, Web of Science, and Grey literature

Inclusion criteria: RCTs (level 1 or 2) comparing PRP injections with other IA treatments, in any language, on humans. Risk of bias was assessed following Cochrane guidelines and the quality of evidence was graded using the GRADE guidelines

CHARACTERISTICS OF INCLUDED STUDIES

POPULATION

34 randomized controlled trials

- 1403 knees in PRP groups
- 1426 in control groups
- M/F 0.64 PRP vs M/F 0.60 control
- Age 49.8-65.5yr PRP vs 46.6 to 68yr control
- BMI 24-31.4 PRP vs 24.1-31.1 control

INTERVENTION

PRP vs controls

- Hyaluronic acid (21 studies)
- Saline (8 studies)
- Steroid injections (6 studies)
- Ozone (2 studies)
- Prolotherapy (1 study)

PATIENT CHARACTERISTICS OF THE INCLUDED STUDIES

Table 1. Patients Characteristics of the Included Studies.

Study	Type of Control	Patients (Knees) Included		Patients (Knees) Follow-up		Sex		Age		BMI	
		PRP	Control	PRP	Control	PRP	Control	PRP	Control	PRP	Control
Ahmad, 2018[59]	HA	45 (45)	45 (45)	45 (45)	44 (44)	M14, F31	M15, F30	56.2 ± 6.8	56.8 ± 7.4	26.7 ± 3.6	26.5 ± 3.5
Buendía-López, 2019[60]	HA	35 (35)	36 (36)	33 (33)	32 (32)	M16, F17	M15, F17	56.2 ± 3	56.6 ± 2.9	24.9 ± 0.3	24.9 ± 0.4
Cerza, 2012[61]	HA	60 (60)	60 (60)	60 (60)	60 (60)	M25, F35	M28, F32	66.5 ± 11.3	66.2 ± 10.6	NR	NR
Cole, 2016[53]	HA	52 (52)	59 (59)	49 (49)	50 (50)	M28, F21	M20, F30	55.9 ± 10.4	56.8 ± 10.5	27.4 ± 3.9	29 ± 6.4
Di Martino, 2019[13]	HA	96 (96)	93 (93)	85 (85)	82 (82)	M53, F32	M47, F35	52.7 ± 13.2	57.5 ± 11.7	27.2 ± 7.6	26.8 ± 4.3
Duymus, 2017[62]	HA or ozone	41 (41)	HA 40 (40) Ozone 39 (39)	33 (33)	HA 34 (34) Ozone 35 (35)	M1, F32	HA M1, F33 Ozone M4, F31	60.4 ± 5.1	HA 60.3 ± 9.1 Ozone 59.4 ± 5.7	27.6 ± 4.6	HA 28.4 ± 3.6 Ozone 27.6 ± 4.4
Elik, 2019[62]	Saline	30 (30)	30 (30)	30 (30)	27 (27)	M1, F29	M3, F24	61.3 ± 7.91	60.19 ± 6.8	30.37 ± 4.5	30.7 ± 4.0
Filardo, 2015[23]	HA	96 (96)	96 (96)	94 (94)	89 (89)	M60, F34	M52, F37	53.32 ± 13.2	57.55 ± 11.8	26.6 ± 4	26.9 ± 4.4
Forogh, 2016[63]	CS	24 (24)	24 (24)	23 (23)	16 (16)	M7, F17	M9, F15	59.13 ± 7.03	61.13 ± 6.7	28.9 ± 2.9	29.2 ± 3.4
de Menezes Freire, 2018[64]	CS	25 (25)	25 (25)	25 (25)	25 (25)	NR	NR	64.15 ± 8.02	60.2 ± 5.9	76% overweight	88% overweight
Gaballa, 2019[38]	Ozone	20 (20)	20 (20)	20 (20)	20 (20)	M5, F15	M4, F16	53.6 ± 4.6	56.3 ± 4.4	NR	NR
Ghai, 2019[65]	Saline	20 (20)	20 (20)	20 (20)	20 (20)	M5, F15	M5, F15	49.8 ± 9.4	49.8 ± 9.4	NR	NR
Görmeli, 2017[66]	HA or saline	46 (46)	Saline 45 (45) 3× HA 46 (46)	39 (39)	Saline 40 (40) 3× HA 39 (39)	M16, F23	S M20, F20 HA M17, F22	53.7 ± 13.1	S 52.8 ± 12.8 HA 53.5 ± 14	28.7 ± 4.8	S 29.5 ± 3.2 HA 29.7 ± 3.7
Montañez-Heredia, 2016[67]	HA	28 (28)	27 (27)	27 (27)	26 (26)	M12, F15	M9, F17	66.3 ± 8.3	61.5 ± 8.6	29 ± 5.5	30.4 ± 4.9
Huang, 2019[28]	HA or CS	40 (40)	HA 40 (40) CS 40 (40)	40 (40)	HA 40 (40) CS 40 (40)	M25, F15	HA M19, F21 CS M21, F19	54.5 ± 1.2	HA 54.8 ± 1.1 CS 54.3 ± 1.4	25.2 ± 4.2	HA 25.4 ± 3.1 CS 24.6 ± 3.6
Joshi Jubert, 2017[68]	CS + anesthetic	35 (35)	30 (30)	34 (34)	30 (30)	M12, F23	M6, F24	65.56 ± 8.6	68 ± 7.2	31.2 ± 4.4	31.0 ± 4.2
Kon, 2017[13]	Saline	31 (31)	15 (15)	29 (29)	14 (14)	M18, F13	M9, F6	57 (41-68)	54 (44-67)	NR	NR
Lana, 2016[69]	HA	36 (36)	36 (36)	36 (36)	36 (36)	M7, F29	M3, F33	60.9 ± 7	60 ± 6.6	27.4 ± 6.9	28.2 ± 8.8
Lin, 2019[24]	HA or saline	31 (31)	HA 29 (29) Saline 27 (27)	30 (30)	HA 27 (27) Saline 26 (26)	M9, F22	HA M10, F19 S M10, F17	61.2 ± 13.1	HA 62.5 ± 3.0 S 62.2 ± 3.1	24.0 ± 2.6	HA 26.3 ± 3.0 S 25.0 ± 3.1
Lisi, 2018[70]	HA	31 (31)	31 (31)	31 (31)	31 (31)	M20, F10	M16, F12	53.5 ± 15.1	57.1 ± 10.0	NR	NR
Louis, 2017[52]	HA	28 (NR)	28 (NR)	17 (NR)	17 (NR)	M14, F10	M11, F13	53.2 ± 11.7	48.5 ± 11.5	25.6 ± 2.9	27.0 ± 2.9
Nabi, 2018[71]	CS	36 (36)	36 (36)	33 (33)	34 (34)	M5, F28	M7, F27	50.09 ± 7.79	58.6 ± 8.8	28.4 ± 2.8	27.8 ± 3.3
Papalia, 2016[72]	HA	24 (NR)	24 (NR)	23 (NR)	24 (NR)	NR	NR	NR	NR	NR	NR
Patel, 2013[73]	Saline	27 (54)	26 (52)	26 (52)	23 (46)	M11, F16	M6, F17	53.1 ± 11.6	53.7 ± 8.2	26.3 ± 3.2	26.2 ± 2.9
Paterson, 2016[74]	HA	12 (12)	11 (11)	10 (10)	9 (9)	M8, F3	M7, F3	49.9 ± 13.7	52.7 ± 10.3	27.9 ± 11.9	30.9 ± 5.6
Raeissadat, 2015[25]	HA	87 (87)	73 (73)	77 (77)	62 (62)	M8, F69	M15, F47	56.9 ± 9.1	61.1 ± 7.5	28.2 ± 4.6	27.0 ± 4.2
Raeissadat, 2017[75]	HA	41 (41)	36 (36)	36 (36)	33 (33)	M7, F29	M6, F27	57.0 ± 7.2	59.5 ± 7.5	28.6 ± 2.8	27.5 ± 2.9
Rahimzadeh, 2018[29]	Dextrose	21 (21)	21 (21)	21 (21)	21 (21)	M10, F11	M11, F10	65.5 ± 6.6	64.3 ± 5.3	28.6 ± 1.8	28.3 ± 1.9
Sánchez, 2012[76]	HA	89 (89)	87 (87)	79 (79)	74 (74)	M43, F46	M29, F45	60.5 ± 7.9	58.9 ± 8.2	27.9 ± 2.9	28.2 ± 2.7
Smith, 2016[77]	Saline	15 (15)	15 (15)	15 (15)	15 (15)	M5, F10	M6, F9	53.5 ± 8.2	46.6 ± 9.4	29.5 ± 6.9	27.5 ± 4.8
Su, 2018[78]	HA	26 (26)	32 (32)	25 (25)	30 (30)	M11, F14	M12, F18	54.2 ± 6.6	53.13 ± 6.4	28.17 ± 1.4	28.7 ± 1.1
Güvendi, 2018[27]	CS	19 (19)	19 (19)	19 (19)	17 (17)	M1, F18	M2, F15	62.3 ± 1.6	62.8 ± 1.7	31.4 ± 0.7	31.1 ± 1.0
Vaquerizo, 2013[79]	HA	48 (48)	48 (48)	48 (48)	42 (42)	M16, F32	M22, F26	62.4 ± 6.6	64.8 ± 7.7	30.7 ± 3.6	31.0 ± 4.6
Wu, 2018[80]	Saline	20 (20)	20 (20)	20 (20)	20 (20)	M5, F15	M1, F15	63.3 ± 6.8	63.3 ± 6.8	24.1 ± 2.9	24.1 ± 2.9

OUTCOMES

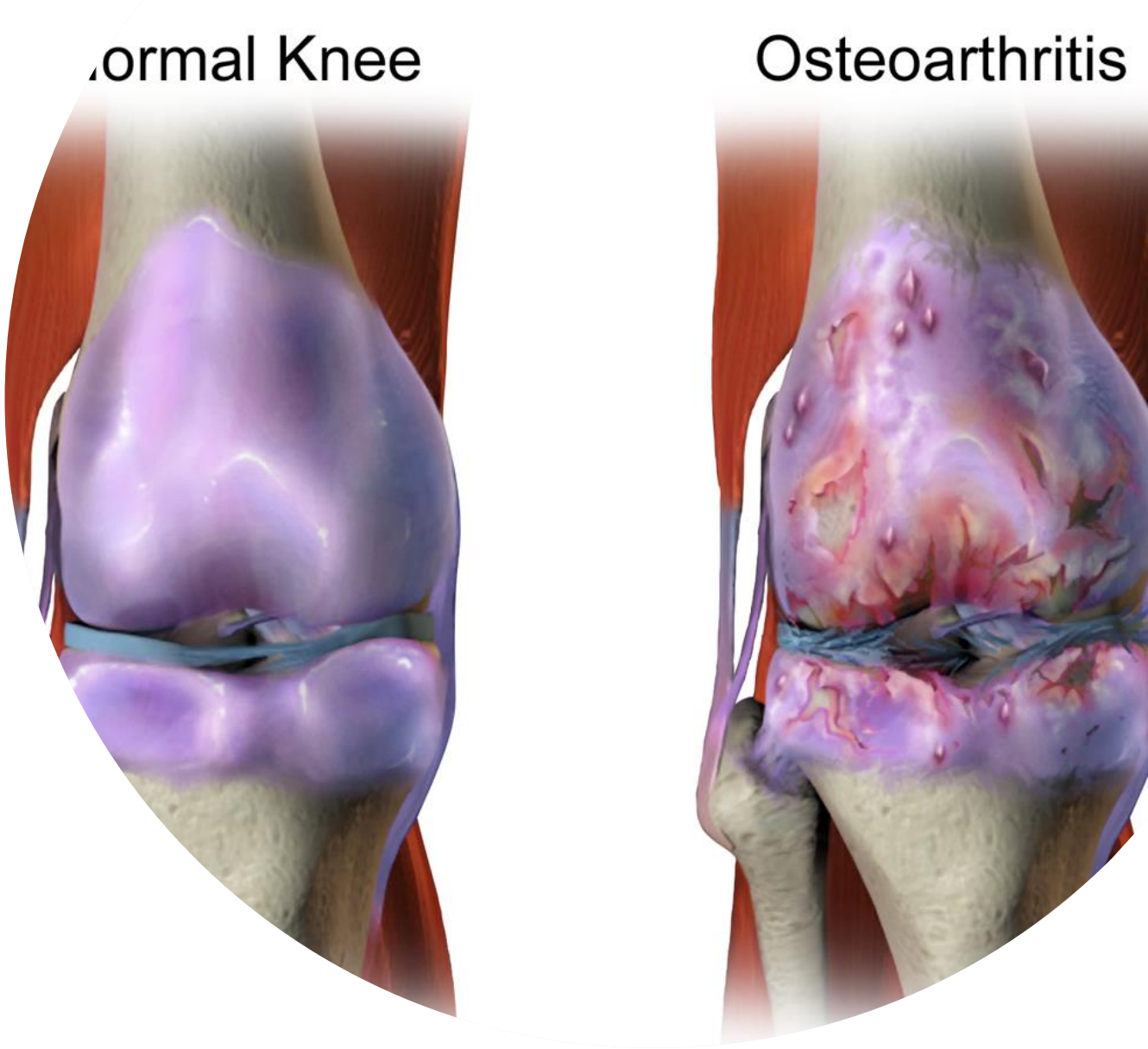
PRIMARY OUTCOME

Primary outcomes measured were patient reported outcomes based on overall WOMAC scores at 6 months and 12 months

SECONDARY OUTCOME

Secondary outcomes were based on the overall WOMAC scores at 1 and 3 months as well as WOMAC sub scores of pain, stiffness, function and other scoring scales (VAS, KOOS, IKDC)

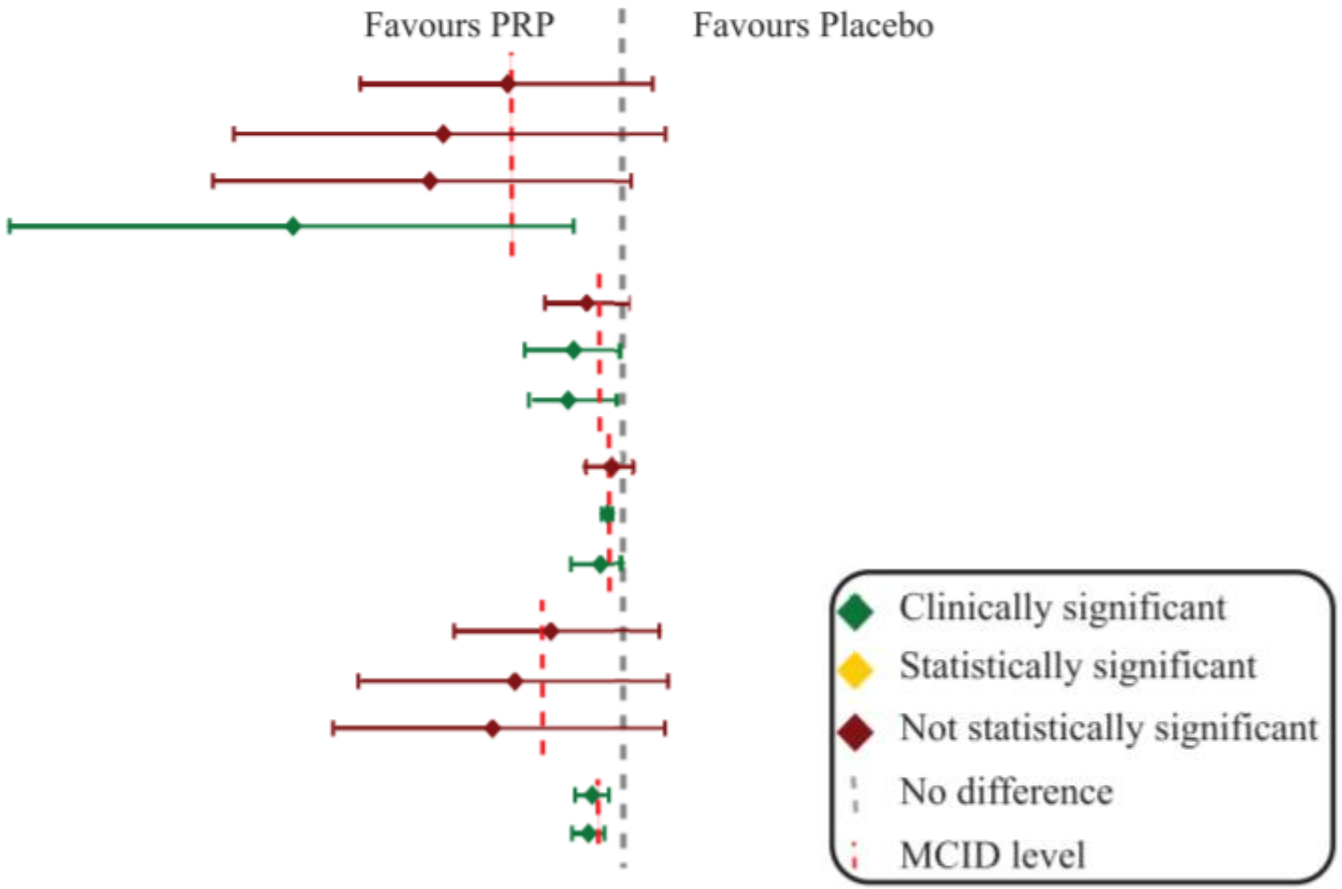
RESULTS



PRP VS. PLACEBO (FIGURE 2)

Compared treatment	Outcome	Follow-up	No. of trials	No. of pts	Mean difference [95% C.I.]
Placebo					
	WOMAC overall	1 month	6	266	-6.47 [-14.39, 1.45]
		3 months	4	153	-10.71 [-23.71, 2.29]
		6 months	6	266	-12.50 [-25.69, 0.69]
		12 months	3	129	-19.38 [-36.04, -2.72]
	WOMAC pain	1 month	5	210	-1.66 [-3.87, 0.55]
		3 months	4	153	-3.03 [-5.74,-0.32]
		6 months	5	210	-3.08 [-5.51, -0.65]
	WOMAC stiffness	1 month	5	210	-0.55[-1.77, 0.66]
		3 months	4	153	-0.89 [-1.26, -0.52]
		6 months	5	210	-1.32 [-2.59,-0.05]
	WOMAC function	1 month	5	210	-4.43 [-11.45, 2.58]
		3 months	4	153	-6.78 [-16.89, 3.33]
		6 months	5	210	-8.03 [-18.57, 2.51]
	VAS	1 month	3	140	-1.47 [-2.12, -0.82]
		6 months	4	238	-1.91 [-2.71, -1.10]

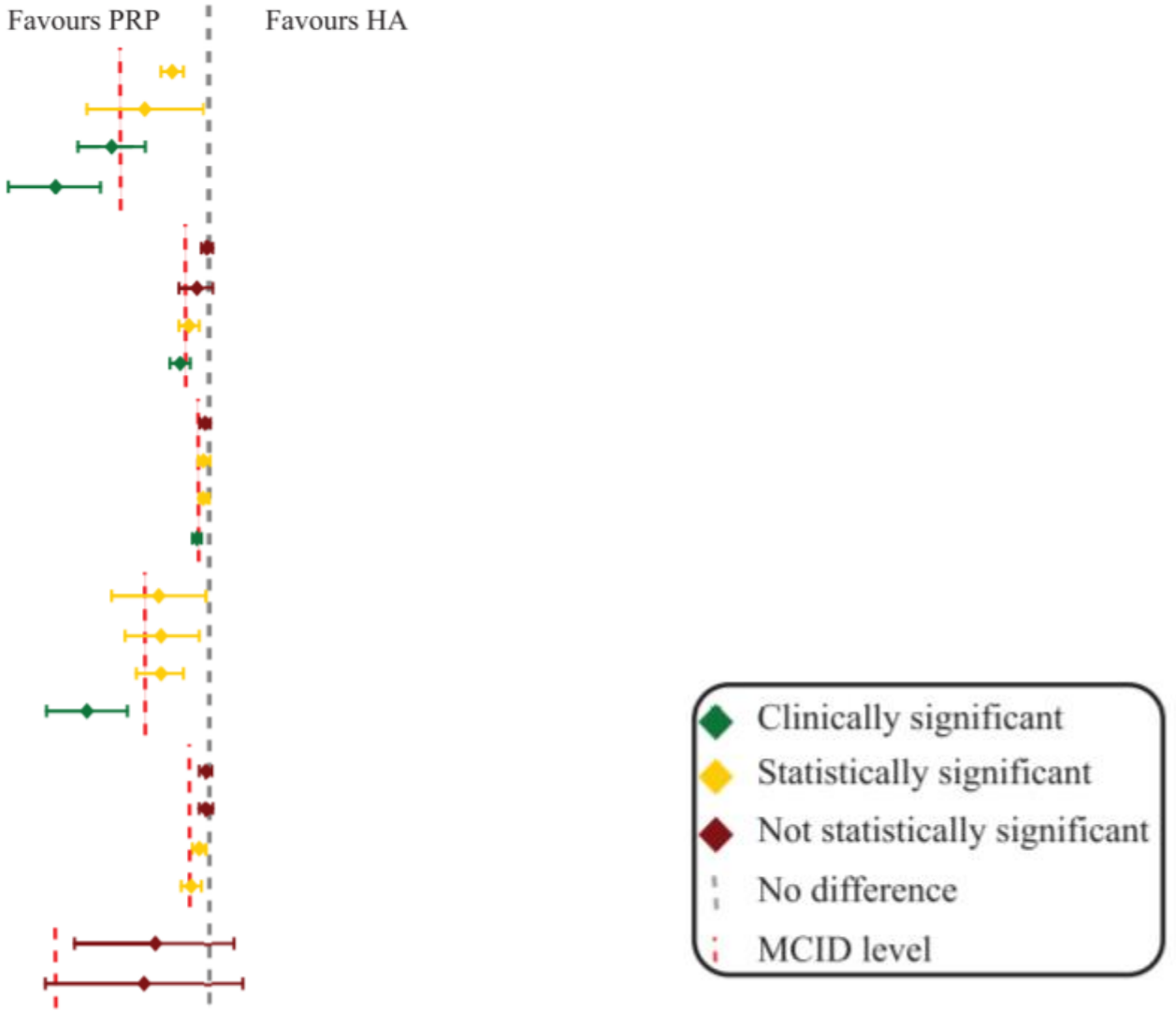
Results of the meta-analysis



PRP VS. HYALURONIC ACID (FIGURE 2)

HA

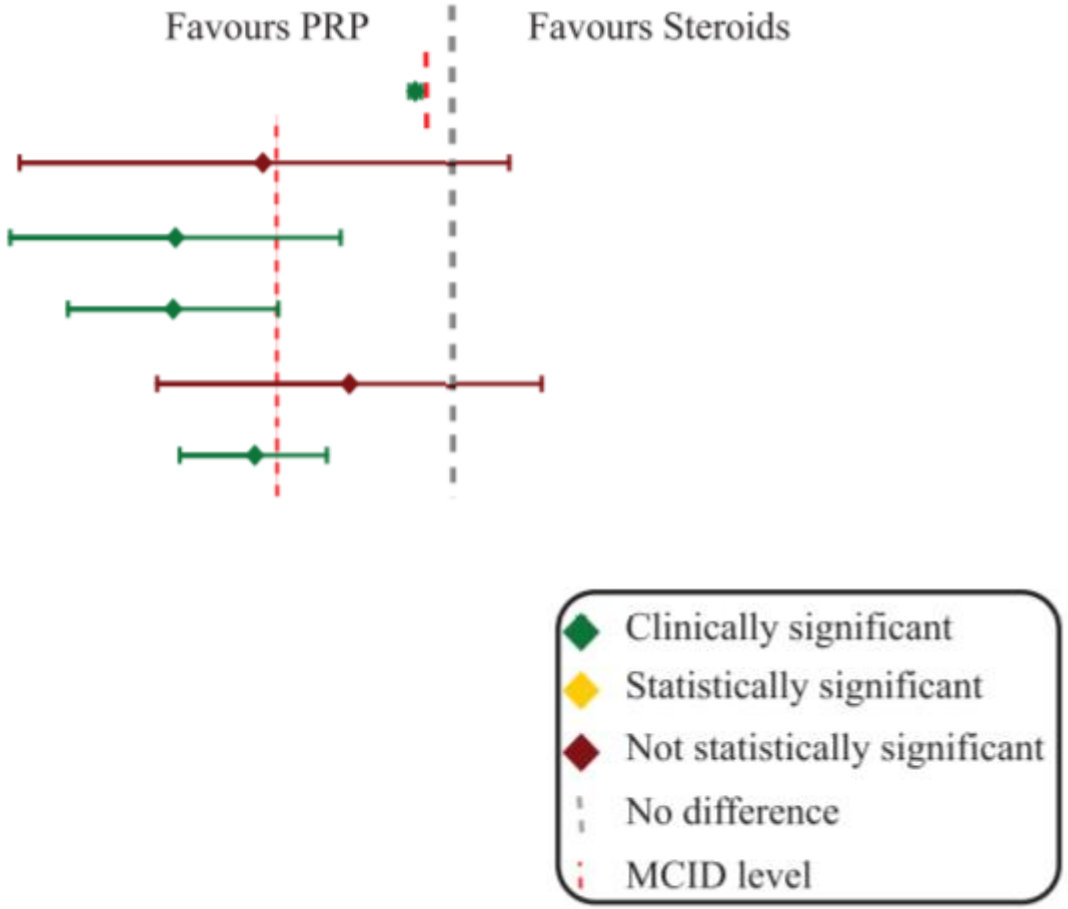
WOMAC overall	1 month	5	338	-2.62 [-3.47, -1.77]
	3 months	5	356	-4.59 [-8.91, -0.26]
	6 months	10	790	-7.13 [-9.57, -4.68]
	12 months	7	553	-11.34 [-14.78, -7.91]
WOMAC pain	1 month	5	325	-0.08 [-0.44, 0.29]
	3 months	5	324	-0.86 [-2.09, 0.38]
	6 months	9	702	-1.33 [-2.09, -0.56]
	12 months	6	440	-2.05 [-2,85. -1.25]
WOMAC stiffness	1 month	4	201	-0.08 [-0.33, 0.17]
	3 months	4	200	-0.39 [-0.64, -0.15]
	6 months	8	565	-0,28 [-0.52, -0.03]
	12 months	6	445	-0.76 [-1.10, -0.41]
WOMAC function	1 month	4	228	-3.60 [-7.12, -0.08]
	3 months	4	228	-3.41 [-6.17, -0.64]
	6 months	8	605	-3.49 [-5.21, -1.77]
	12 months	6	486	-8.89 [-11,87, -5.91]
VAS	1 month	6	345	-0.21 [-0.67, 0.26]
	3 months	8	481	-0.17 [-0.70, 0.35]
	6 months	9	596	-0.59 [-1.07, -0.12]
	12 months	6	398	-1.21 [-1.91, -0.50]
IKDC	6 months	5	475	4.09 [-1.82, 10.00]
	12 months	4	324	4.61 [-2.68, 11.90]



PRP VS. STEROIDS (FIGURE 2)

Steroids

VAS	6 months	4	206	-2.03 [-2.38, -1.67]
KOOS sympt	6 months	3	170	10.18 [-3.37, 23.73]
KOOS pain	6 months	3	170	15.23 [6.10, 24.36]
KOOS ADL	6 months	3	170	15.51 [9.71, 21.31]
KOOS sports	6 months	3	170	5.86 [-4.77, 16.49]
KOOS QoL	6 months	3	170	10.91 [6.88, 14.94]



DISCUSSION AND INTREPRETATION

ISSUES WITH THIS STUDY

HETEROGENEITY OF STUDIES

- Different indices used in compiled studies
- Differences in methodology for formulating PRP injections
- Differences in timing and frequency of PRP injections

RISK OF BIAS

- 27 studies had questionable levels of risk of bias due to unclear methods to guarantee allocation concealment
- Inherent risk of self-reporting bias

KEY TAKEAWAYS

PRP offers benefits that can increase over time, notably at the 12 month mark, but can start as early as 6 months

Data suggests that PRP injections can be effective over placebo, HA and steroid injections

Different studies use different scales (WOMAC vs VAS) and unclear methods of preparation, frequency and timing of giving PRP makes it tough to say where the benefit is coming from

CLINICAL TAKEAWAYS

Delayed onset of patient perceived benefits can impact physician counseling to patients in terms of when to expect relief

Procedure is cost-prohibitive and not covered by most insurance companies so it can only be offered to select socioeconomic populations

QUESTIONS?