Supplementary table S1

Table S1. Database search formulas

Data base	Search terms for query
Pubmed	
#1	(osteoarthrit*) OR (degenerat*)
#2	(knee*) OR (patellofemoral) OR (tibiofemoral)
#3	(prolotherapy) OR (dextrose prolotherapy) OR (dextrose injection) OR (regenerative injection)
#4	#1 AND #2 AND #3
Excerpta Medica dataBASE (EMBASE)	
#1	Osteoarthritis OR 'degenerative disease'
#2	Knee OR patellofemoral OR tibiofemoral
#3	prolotherapy OR 'dextrose prolotherapy' OR 'dextrose injection' OR 'regenerative injection'
#4	#1 AND #2 AND #3
Cochrane Library Database	
#1	(osteoarthrit*) OR (degenerat*)
#2	(knee*) OR (patellofemoral) OR (tibiofemoral)
#3	(prolotherapy) OR (dextrose prolotherapy) OR (dextrose injection) OR (regenerative injection)
#4	#1 AND #2 AND #3
Scopus	
#1	(TITLE-ABS-KEY(osteoarthrit*) OR (degenerat*) AND ((knee*) AND (prolotherapy) OR (dextrose AND injection)

Supplementary table S2. Risk of bias summary: review authors' judgments about each risk of bias item for each included trial.

	Dumais 2012	EROĞLU 2017	Hashemi 2012	Hashemi 2015	Pishgahi 2020	Rabago 2013a	Rabago 2013b	Rahimzadeh 2014	Rahimzadeh 2018	Reeves 2000	Rezasoltani 2020	Sert 2020	Sit 2020	Waluyo 2020
Random sequence generation (selection bias)	+	?	+	?	?	+	−	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	?	?	?	−	+	−	?	?	?	−	?	+	+
Blinding of participants and personnel (performance bias)	?	?	+	?	−	+	?	?	?	?	−	+	+	+
Blinding of clinician (performance bias)	?	?	?	?	−	+	?	?	?	+	−	−	+	−
Blinding of outcome assessment (detection bias)	?	?	+	?	−	+	?	?	?	+	−	?	+	+
Incomplete outcome data (attrition bias)	?	+	+	+	+	−	−	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	?	+	?	+	+	?	+	+	+	+	+	+	+
Other bias	?	?	?	?	?	?	?	?	+	?	?	?	+	?

Supplementary Table S3

Table S3. Summary of subgroup analyses results for treatment effects on main outcomes

Subgroups	Pain				Function				Quality of life			
	n[a]	SMD (95%CI)	*P* value	I^2 (%)	n[a]	SMD (95%CI)	*P* value	I^2 (%)	n[a]	SMD (95%CI)	*P* value	I^2 (%)
Control group type												
Placebo	6	0.53 (0.30, 0.75)[†]	<0.00001	0	4	0.68 (0.26, 1.11)[‡]	0.002	54	2	0.48 (0.11, 0.84)[†]	0.01	0
Other injection	8	−0.05 (−0.36, 0.27)[‡]	n.s.	68	7	−0.06 (−0.63, 0.50)[‡]	n.s.	89	2	0.82 (0.36, 1.28)[†]	0.0005	0
Exercise	5	0.59 (0.34, 0.84)[†]	<0.00001	52	5	1.72 (0.94, 2.49)[‡]	<0.0001	85	2	0.58 (0.18, 0.99)[†]	0.005	0
Subgroup difference			0.02	75.6			0.003	82.5			n.s.	0
Injection technique												
IA	9	0.06 (−0.21, 0.33)[‡]	n.s.	62	7	0.29 (−0.31, 0.89)[‡]	n.s.	90	4	0.56 (0.25, 0.87)[†]	0.0005	0
IA + EA	10	0.62 (0.41, 0.84)[†]	<0.00001	0	9	1.04 (0.45, 1.62)[‡]	0.0005	83	2	0.64 (0.10, 1.18)[†]	0.02	0
Subgroup difference			0.001	90.4			n.s.	67.5			n.s.	0

[†]Fixed-model effect
[‡]Random-model effect
[a]Number of comparisons.
EA, extra-articular; IA, intra-articular; SMD, standard mean difference; I^2, heterogeneity; n.s., non-significant (P>0.05); NA, not applicable.

Supplementary Table S4

Table S4. Results of univariate meta−regression for pain and function outcomes

Variable	Pain (SMD)				Function (SMD)			
	Comparison (n)	R^2 (%)	β	*p* value	Comparison (n)	R^2 (%)	β	*p* value
Participant characteristics								
Age (years)	22	0.28	−0.04	n.s.	19	0	−0.02	n.s.
BMI (kg/m^2)	18	0	0.03	n.s.	18	22.02	0.26	0.037
Sex ratio (male/female)	20	2.41	−0.66	n.s.	18	0.80	−0.98	n.s.
Disease severity (K-L grade)	21	7.15	0.39	n.s.	18	3.06	0.27	n.s.
Disease duration (year)	12	0	0.005	n.s.	12	22.15	0.09	n.s.
Intervention design								
Number of injections	22	60.54	0.60	< 0.0001	19	0	0.26	n.s.
Injection technique[a]	22	28.39	0.79	0.008	19	1.29	0.59	n.s.
Study design								
Control type[b]	22	20.87	0.43	0.023	19	20.20	0.66	0.039
Follow up time (week)	22	0.71	0.01	n.s.	19	32.58	0.14	0.008

n.s. = non-significant ($P > 0.05$).
[a]Injection technique is coded as, intra-articular = 1; intra-articular combined with extra-articular = 2.
[b]Control type is coded as other injection = 1, placebo control = 2, and active exercise control = 3.
SMD, standard mean difference; K-L grade, Kellgren-Lawrence Classification of Osteoarthritis.

Supplementary Table S5

Table S5. Summary of withdraw and adverse events in the included trials

Study author (year)	Invasive type	Dosage per each injection	EG (events or patients/group sample)		CG (events or patients/group sample)					
					Non-invasive active control		Invasive active control		Placebo	
Withdraw (drop out)[a]			Related to disease	Unrelated to disease	Related to disease	Unrelated to disease	Related to disease	Unrelated to disease	Related to disease	Unrelated to disease
Dumais, 2012	IA + EA	IA (20%, 5 mL); EA (15%, 8 mL)								
period 1			N	N	N	X (5/24)				
period 2			X (1/19)	N	X (1/21)	X (2/21)				
Rabago, 2013a	IA + EA	IA (25%, 6 mL); EA (15%, 22.5 mL)	N	X (3/33)	N	X (3/34)			N	X (2/31)
Rabago, 2013b	IA + EA	IA (25%); EA (15%)	X (1/27)	X (2/27)	X (1/9)	X (2/9)			X (1/9)	X (1/9)
Sert, 2020	IA + EA	IA (25%, 5 mL); EA (15%, 10 mL)	N	X (1/22)	N	N			N	X (3/22)
Waluyo, 2020	IA + EA	IA (25%, 5 mL); EA (15%, 30–40 mL)	X (1/44)	X (13/44)			X (2/32)	X (9/32)		
Eroğlu, 2016	IA + EA	IA (6 mL); EA (22.5 mL)	N	N			N	X (2/20)	N	N
Reeves, 2000	IA	10%, 9 mL	X (1/38)	X (2/38)					X (3/39)	X (3/39)
Hashemi, 2015	IA	12.5%, 7 mL	NR	NR			NR	NR		
Rezasoltani, 2020	IA	20%, 8 mL	X (1/30)	X (1/30)	X (1/30)	X (1/30)	X (3/60)	X (1/60)		
Hashemi, 2012	IA	25%, 2 mL	NR	NR			NR	NR		
Rahimzadeh, 2014	IA	25%, 2 mL	N	N	N	N	N	N		
Rahimzadeh, 2018	IA	25%, 7 mL	N	N			N	N		
Sit, 2020	IA	25%, 5 mL	X (1/38)	N					X (1/38)	X (2/38)
Pishgahi, 2020	IA	50%, 2 mL	N	N			N	N		
Summary, Number of trials (Number of patient/total study arm sample)			6 (6/196)	6 (22/194)	3 (3/60)	5 (13/118)	2 (5/92)	3 (12/112)	3 (5/86)	5 (11/139)
Adverse events[a]			Related to DP	Unrelated to DP	Related to comparison treatment	Unrelated to comparison treatment	Related to comparison treatment	Unrelated to comparison treatment	Related to comparison treatment	Unrelated to comparison treatment
Dumais, 2012	IA + EA	IA (20%, 5 mL); EA (15%, 8 mL)								
period 1			N	N	N	N				
period 2			X (1/19)	N	N	N				
Rabago, 2013a	IA + EA	IA (25%, 6 mL); EA (15%, 22.5 mL)	NR	NR	NR	NR			NR	NR
Rabago, 2013b	IA + EA	IA (25%); EA (15%)	N	N	N	N			N	N
Sert, 2020	IA + EA	IA (25%, 5 mL); EA (15%, 10 mL)	N	N	N	N			N	N
Waluyo, 2020	IA + EA	IA (25%, 5 mL); EA (15%, 30–40 mL)	X (1/44)	N	N	N				
Eroğlu, 2016	IA + EA	IA (6 mL); EA (22.5 mL)	N	N			N	N	N	N
Reeves, 2000	IA	10%, 9 mL	N	N					X (1/33)	N
Hashemi, 2015	IA	12.5%, 7 mL	NR	NR			NR	NR		
Rezasoltani, 2020	IA	20%, 8 mL	N	N	N	N	N	N		
Hashemi, 2012	IA	25%, 2 mL	NR	NR			NR	NR		
Rahimzadeh, 2014	IA	25%, 2 mL	N	N	N	N	N	N		
Rahimzadeh, 2018	IA	25%, 7 mL	N	N			N	N		
Sit, 2020	IA	25%, 5 mL	N	X (2/38)					N	X (6/38)
Pishgahi, 2020	IA	50%, 2 mL	N	N			N	N		
Summary, Number of trials (Number of patient/total study arm sample)			2 (2/63)	1 (2/38)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)	1 (1/33)	1 (6/38)

[a]The occurrence of adverse events is denoted as "X" with the number of events per study arm sample. N = the trial reported no complication event; NR = data of the complications or adverse events were not reported.

[b]Data is estimated.

[c]The events did not occur during exercise periods.

EA, extra-articular injection; IA, intra-articular injection; DP, dextrose prolotherapy.

Supplementary Table S6

Table S6. Summary of subgroup analyses results for patient compliance and safety

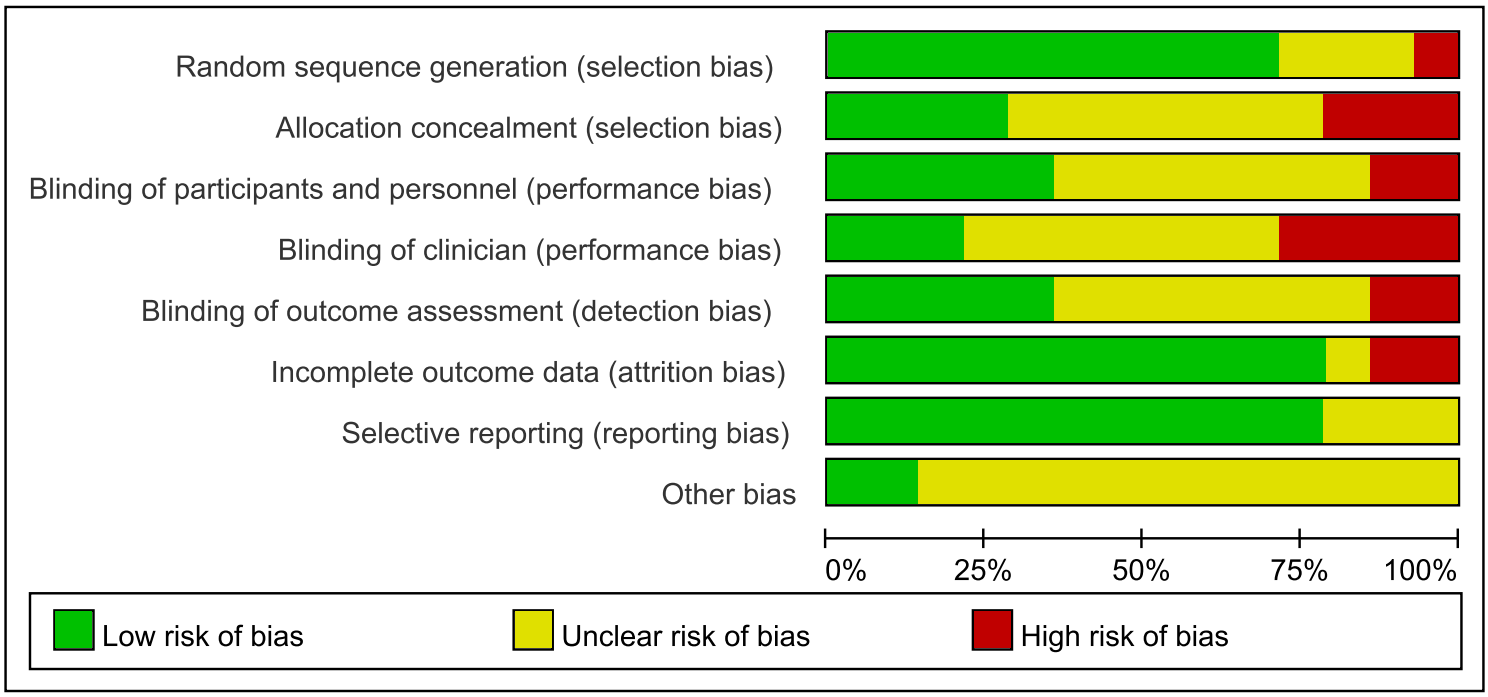
Subgroups	Compliance (patient dropout rate)				Adverse event			
	n[a]	OR (95%CI)[†]	*P* value	I^2 (%)	n[a]	OR (95%CI)[†]	*P* value	I^2 (%)
Control group type								
Placebo	4	0.40 (0.15, 1.03)	n.s.	0	2	0.30 (0.07, 1.31)	n.s.	0
Other injection	3	0.78 (0.35, 1.75)	n.s.	0	1	2.24 (0.09, 56.81)	n.s.	NA
Exercise	5	0.47 (0.21, 1.07)	n.s.	0	1	3.49 (0.13, 90.86)	n.s.	NA
Subgroup difference			n.s.	0			n.s.	23.3
Injection technique								
IA	3	0.56 (0.21, 1.52)	n.s.	0	2	0.30 (0.07, 1.31)	n.s.	0
IA + EA	6	0.56 (0.30, 1.03)	n.s.	0	2	2.79 (0.28, 27.72)	n.s.	0
Subgroup difference			n.s.	0			n.s.	61.1

[†]Fixed-model effect

[a]Number of comparisons.

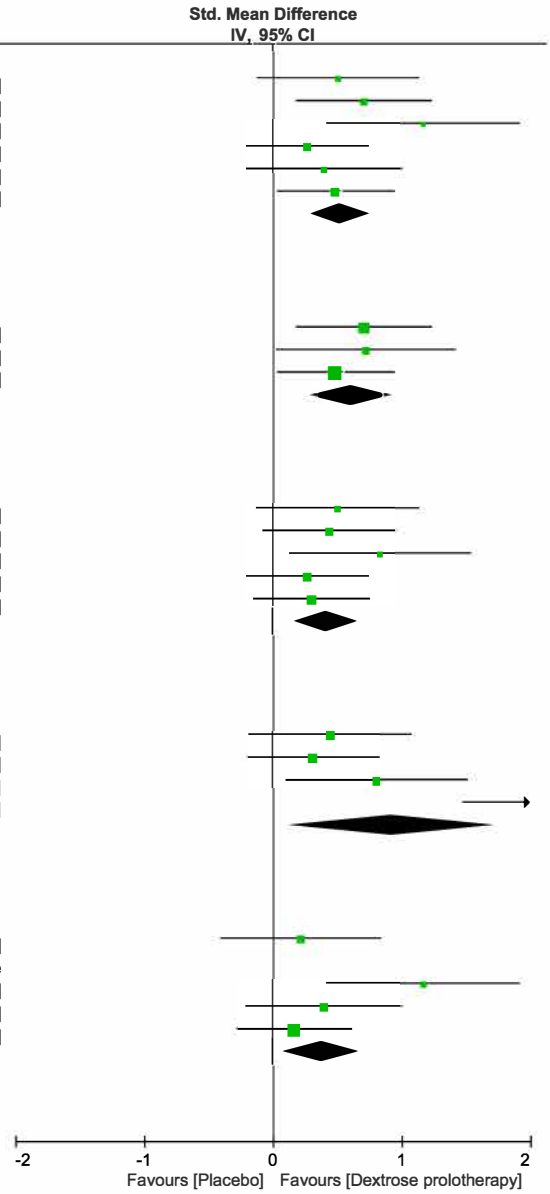
EA, extra-articular; IA, intra-articular; OR, odds ratio; I^2, heterogeneity; n.s., non-significant (P>0.05); NA, not applicable.

Supplementary figure S1. Summary of the risk of bias across all studies.



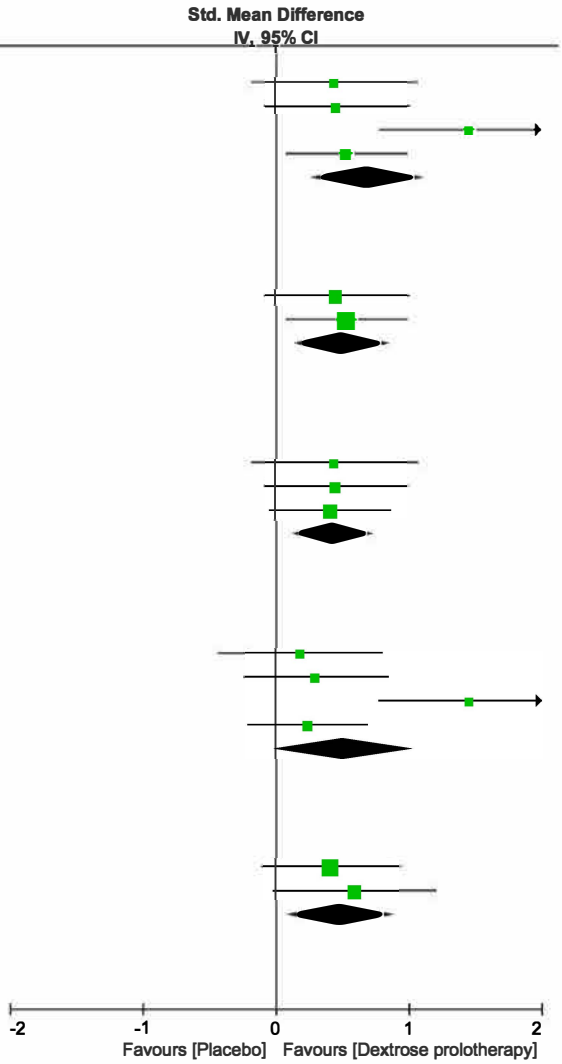
Supplementary figure S2. Effects of dextrose prolotherapy on pain versus placebo injection at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, 95% CI
1.1.1 Pain, overall follow-up duration; fixed effect								
EROĞLU 2016, PG vs PLA	1.65	3.97	20	0.2	0.6	20	12.7%	0.50 [-0.13, 1.13]
Rabago 2013a, PG vs PLA	0.92	1.15	30	0.11	1.13	29	18.2%	0.70 [0.17, 1.23]
Rabago 2013b, PG vs Con (pooled)	17.1	13.23	24	1.1	13.86	12	9.0%	1.16 [0.42, 1.91]
Reeves 2000, PG vs PLA	0.14	0.2	35	0.09	0.17	33	22.1%	0.27 [-0.21, 0.74]
Sert 2020, PG vs PLA	3.1	1.31	21	2.5	1.64	22	13.8%	0.40 [-0.21, 1.00]
Sit 2020, PG vs PLA	2.71	2.25	38	1.61	2.25	38	24.2%	0.48 [0.03, 0.94]
Subtotal (95% CI)			**168**			**154**	**100.0%**	**0.53 [0.30, 0.75]**
Heterogeneity: Chi² = 4.57, df = 5 (P = 0.47); I² = 0%								
Test for overall effect: Z = 4.59 (P < 0.00001)								
1.1.2 Pain, follow up ≥12 mo; fixed effect								
Rabago 2013a, PG vs PLA	0.92	1.15	30	0.11	1.13	29	34.4%	0.70 [0.17, 1.23]
Rabago 2013b, PG vs Con (pooled)	18.1	18.62	24	4.6	18.03	13	19.7%	0.72 [0.02, 1.41]
Sit 2020, PG vs PLA	2.71	2.25	38	1.61	2.25	38	45.9%	0.48 [0.03, 0.94]
Subtotal (95% CI)			**92**			**80**	**100.0%**	**0.60 [0.30, 0.91]**
Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
1.1.3 Pain, follow up ≥6 mo, <12 mo; fixed effect								
EROĞLU 2016, PG vs PLA	1.65	3.97	20	0.2	0.6	20	14.3%	0.50 [-0.13, 1.13]
Rabago 2013a, PG vs PLA	0.92	1.37	30	0.33	1.29	29	21.3%	0.44 [-0.08, 0.95]
Rabago 2013b, PG vs Con (pooled)	16.5	16.66	24	2.7	15.5	13	11.5%	0.83 [0.13, 1.53]
Reeves 2000, PG vs PLA	0.14	0.2	35	0.09	0.17	33	25.0%	0.27 [-0.21, 0.74]
Sit 2020, PG vs PLA	2.91	2.25	38	2.23	2.25	38	27.9%	0.30 [-0.15, 0.75]
Subtotal (95% CI)			**147**			**133**	**100.0%**	**0.41 [0.17, 0.65]**
Heterogeneity: Chi² = 2.04, df = 4 (P = 0.73); I² = 0%								
Test for overall effect: Z = 3.37 (P = 0.0008)								
1.1.4 Pain, follow up ≥3 mo, <6 mo; random effect								
EROĞLU 2016, PG vs PLA	1.2	2.64	20	0.3	0.94	20	25.4%	0.45 [-0.18, 1.07]
Rabago 2013a, PG vs PLA	0.51	1.47	30	0.06	1.4	29	26.8%	0.31 [-0.20, 0.82]
Rabago 2013b, PG vs Con (pooled)	15.4	14.69	24	3.5	14.06	13	24.4%	0.80 [0.10, 1.51]
Sert 2020, PG vs PLA	6.1	1.4	21	2.8	1.48	22	23.4%	2.25 [1.47, 3.03]
Subtotal (95% CI)			**95**			**84**	**100.0%**	**0.92 [0.13, 1.71]**
Heterogeneity: Tau² = 0.54; Chi² = 17.96, df = 3 (P = 0.0004); I² = 83%								
Test for overall effect: Z = 2.28 (P = 0.02)								
1.1.5 Pain, follow up <3 mo; fixed effect								
Rabago 2013a, PG vs PLA	0.48	1.36	15	0.19	1.34	29	21.3%	0.21 [-0.41, 0.84]
Rabago 2013a, PG vs PLA	0.25	1.42	30	0.07	1.4	29		Not estimable
Rabago 2013b, PG vs Con (pooled)	17.1	13.23	24	1.1	13.86	12	14.8%	1.16 [0.42, 1.91]
Sert 2020, PG vs PLA	3.1	1.31	21	2.5	1.64	22	22.8%	0.40 [-0.21, 1.00]
Sit 2020, PG vs PLA	2.11	2.25	38	1.74	2.25	38	41.0%	0.16 [-0.29, 0.61]
Subtotal (95% CI)			**98**			**101**	**100.0%**	**0.37 [0.09, 0.66]**
Heterogeneity: Chi² = 5.38, df = 3 (P = 0.15); I² = 44%								
Test for overall effect: Z = 2.55 (P = 0.01)								



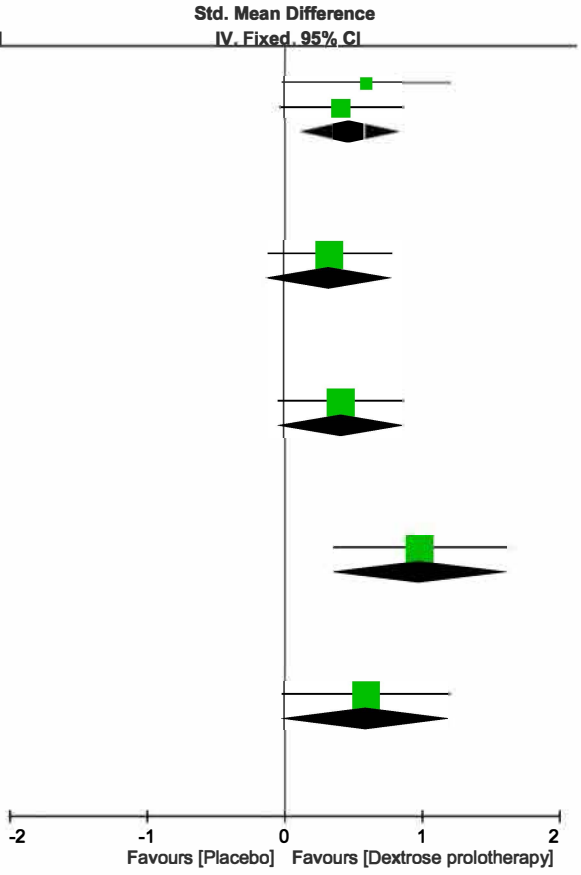
Supplementary figure S3. Effects of dextrose prolotherapy on global function versus placebo injection at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, 95% CI
2.1.1 Global function, overall duration; random effect								
EROĞLU 2016, PG vs PLA	2.8	6.98	20	0.55	1.34	20	23.0%	0.44 [-0.19, 1.07]
Rabago 2013a, PG vs PLA	15.32	16.93	26	7.59	16.8	25	25.8%	0.45 [-0.11, 1.01]
Sert 2020, PG vs PLA	36	7.28	21	22.5	10.58	22	21.2%	1.45 [0.77, 2.13]
Sit 2020, PG vs PLA	20.6	18.06	38	10.95	18.06	38	30.1%	0.53 [0.07, 0.99]
Subtotal (95% CI)			**105**			**105**	**100.0%**	**0.68 [0.26, 1.11]**
Heterogeneity: Tau² = 0.10; Chi² = 6.56, df = 3 (P = 0.09); I² = 54%								
Test for overall effect: Z = 3.16 (P = 0.002)								
2.1.2 Global function, follow up ≥12 mo; fixed effect								
Rabago 2013a, PG vs PLA	15.32	16.93	26	7.59	16.8	25	40.4%	0.45 [-0.11, 1.01]
Sit 2020, PG vs PLA	20.6	18.06	38	10.95	18.06	38	59.6%	0.53 [0.07, 0.99]
Subtotal (95% CI)			**64**			**63**	**100.0%**	**0.50 [0.14, 0.85]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 2.76 (P = 0.006)								
2.1.3 Global function, follow up ≥6 mo, <12 mo; fixed effect								
EROĞLU 2016, PG vs PLA	2.8	6.98	20	0.55	1.34	20	23.6%	0.44 [-0.19, 1.07]
Rabago 2013a, PG vs PLA	15.85	17.25	28	8.12	16.65	25	31.2%	0.45 [-0.10, 1.00]
Sit 2020, PG vs PLA	20.1	17.66	38	12.76	17.66	38	45.1%	0.41 [-0.04, 0.87]
Subtotal (95% CI)			**86**			**83**	**100.0%**	**0.43 [0.12, 0.73]**
Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%								
Test for overall effect: Z = 2.76 (P = 0.006)								
2.1.4 Global function, follow up ≥3 mo, <6 mo; random effect								
EROĞLU 2016, PG vs PLA	3.15	8.09	20	0.35	19.3	20	23.8%	0.19 [-0.44, 0.81]
Rabago 2013a, PG vs PLA	13.31	17.25	27	8.19	16.51	24	25.6%	0.30 [-0.25, 0.85]
Sert 2020, PG vs PLA	36	7.28	21	22.5	10.58	22	22.3%	1.45 [0.77, 2.13]
Sit 2020, PG vs PLA	18.6	17.66	38	14.27	17.66	38	28.3%	0.24 [-0.21, 0.69]
Subtotal (95% CI)			**106**			**104**	**100.0%**	**0.51 [-0.01, 1.04]**
Heterogeneity: Tau² = 0.20; Chi² = 10.17, df = 3 (P = 0.02); I² = 71%								
Test for overall effect: Z = 1.92 (P = 0.05)								
2.1.5 Global function, follow up <3 mo; fixed effect								
Rabago 2013a, PG vs PLA	13.91	17.69	30	6.75	16.67	26	57.1%	0.41 [-0.12, 0.94]
Sert 2020, PG vs PLA	24.3	7.24	21	18.7	10.88	22	42.9%	0.59 [-0.02, 1.20]
Subtotal (95% CI)			**51**			**48**	**100.0%**	**0.49 [0.09, 0.89]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 2.38 (P = 0.02)								



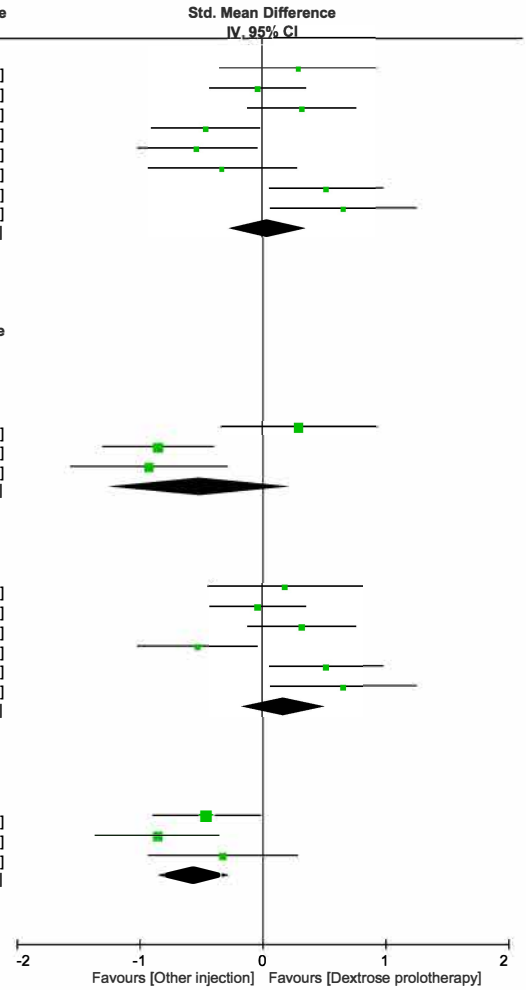
Supplementary figure S4. Effects of dextrose prolotherapy on quality of life versus placebo injection at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.1.1 Quality of life, overall duration								
Sert 2020, PG vs PLA	14.4	10.45	21	8	10.64	22	35.5%	0.60 [-0.02, 1.21]
Sit 2020, PG vs PLA	0.16	0.23	38	0.06	0.25	38	64.5%	0.41 [-0.04, 0.87]
Subtotal (95% CI)			**59**			**60**	**100.0%**	**0.48 [0.11, 0.84]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 2.56 (P = 0.01)								
3.1.2 Quality of life, follow up ≥12 mo								
Sit 2020, PG vs PLA	0.15	0.23	38	0.07	0.25	38	100.0%	0.33 [-0.12, 0.78]
Subtotal (95% CI)			**38**			**38**	**100.0%**	**0.33 [-0.12, 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
3.1.3 Quality of life, follow up ≥6 mo, <12 mo								
Sit 2020, PG vs PLA	0.16	0.23	38	0.06	0.25	38	100.0%	0.41 [-0.04, 0.87]
Subtotal (95% CI)			**38**			**38**	**100.0%**	**0.41 [-0.04, 0.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.78 (P = 0.08)								
3.1.4 Quality of life, follow up ≥3 mo, <6 mo								
Sert 2020, PG vs PLA	22.5	10.05	21	11.6	11.52	22	100.0%	0.99 [0.35, 1.62]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**0.99 [0.35, 1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.04 (P = 0.002)								
3.1.5 Quality of life, follow up <3 mo								
Sert 2020, PG vs PLA	14.4	10.45	21	8	10.64	22	100.0%	0.60 [-0.02, 1.21]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**0.60 [-0.02, 1.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								



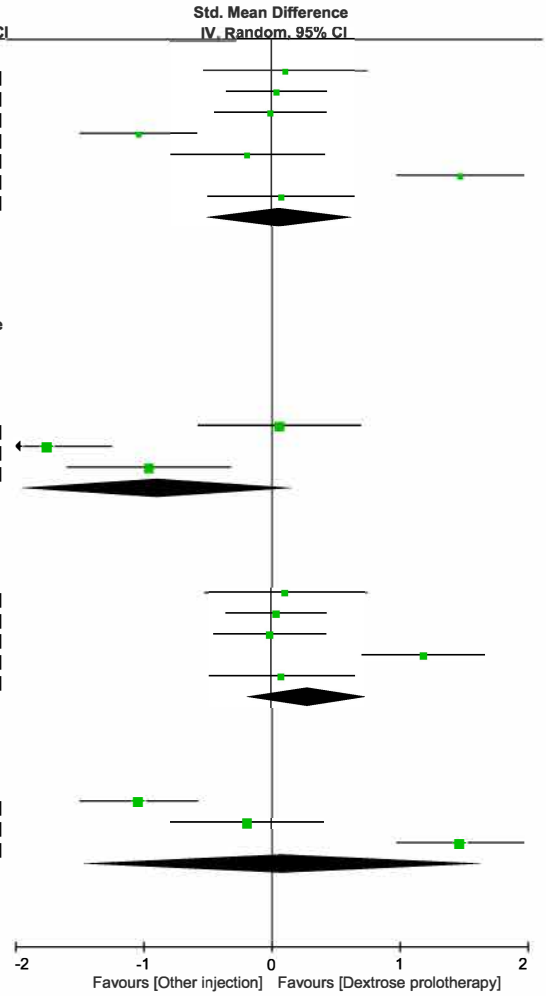
Supplementary figure S5. Effects of dextrose prolotherapy on pain versus other invasive therapies at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Invasive active control Mean	SD	Total	Weight	Std. Mean Difference IV, 95% CI
1.2.1 Pain, invasive active control, overall duration; random effect								
EROĞLU 2016, PG vs PRP	1.65	3.97	20	0.34	4.78	18	10.4%	0.29 [-0.35, 0.93]
Hashemi 2012, PG vs HA	24.2	12	50	24.7	14.61	50	14.4%	-0.04 [-0.43, 0.35]
Hashemi 2015, PG vs Ozone	5.1	0.9	40	4.8	0.95	40	13.6%	0.32 [-0.12, 0.76]
Pishgahi 2020, PG vs Other invasive	3.67	10.54	30	9.72	14.16	62	13.6%	-0.46 [-0.90, -0.02]
Rahimzadeh 2014, PG vs Other invasive (pooled)	1.58	1.15	26	2.29	1.41	44	12.7%	-0.53 [-1.03, -0.04]
Rahimzadeh 2018, PG vs PRP	5.1	1.5	21	5.6	1.5	21	10.9%	-0.33 [-0.94, 0.28]
Rezasoltani 2020, PG vs Other invasive	11.6	6.8	28	7.0196	9.5984	56	13.3%	0.52 [0.06, 0.98]
Waluyo 2020, PG vs HA	3.01	1.37	26	2.08	1.42	21	11.2%	0.66 [0.07, 1.25]
Subtotal (95% CI)			**241**			**312**	**100.0%**	**0.05 [-0.27, 0.36]**
Heterogeneity: Tau² = 0.14; Chi² = 22.04, df = 7 (P = 0.002); I² = 68%								
Test for overall effect: Z = 0.28 (P = 0.78)								
1.2.2 Pain, , follow up ≥12 mo; random effect								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.2.3 Pain, , follow up ≥6 mo, <12 mo; random effect								
EROĞLU 2016, PG vs PRP	1.65	3.97	20	0.34	4.78	18	31.8%	0.29 [-0.35, 0.93]
Pishgahi 2020, PG vs Other invasive	3.7	11.69	30	16.5	16.14	62	36.3%	-0.85 [-1.31, -0.40]
Rahimzadeh 2018, PG vs PRP	6.6	1.51	21	8.6	2.58	21	31.9%	-0.93 [-1.57, -0.29]
Subtotal (95% CI)			**71**			**101**	**100.0%**	**-0.51 [-1.24, 0.22]**
Heterogeneity: Tau² = 0.33; Chi² = 9.69, df = 2 (P = 0.008); I² = 79%								
Test for overall effect: Z = 1.38 (P = 0.17)								
1.2.4 Pain, follow up ≥3 mo, <6 mo; random effect								
EROĞLU 2016, PG vs PRP	1.2	2.64	20	0.77	1.86	18	13.5%	0.18 [-0.46, 0.82]
Hashemi 2012, PG vs HA	24.2	12	50	24.7	14.61	50	19.4%	-0.04 [-0.43, 0.35]
Hashemi 2015, PG vs Ozone	5.1	0.9	40	4.8	0.95	40	18.1%	0.32 [-0.12, 0.76]
Rahimzadeh 2014, PG vs Other invasive (pooled)	1.58	1.15	26	2.29	1.41	44	16.8%	-0.53 [-1.03, -0.04]
Rezasoltani 2020, PG vs Other invasive	11.6	6.8	28	7.0196	9.5984	56	17.6%	0.52 [0.06, 0.98]
Waluyo 2020, PG vs HA	3.01	1.37	26	2.08	1.42	21	14.5%	0.66 [0.07, 1.25]
Subtotal (95% CI)			**190**			**229**	**100.0%**	**0.17 [-0.16, 0.51]**
Heterogeneity: Tau² = 0.11; Chi² = 14.06, df = 5 (P = 0.02); I² = 64%								
Test for overall effect: Z = 1.01 (P = 0.31)								
1.2.5 Pain, follow up <3 mo; fixed effect								
Pishgahi 2020, PG vs Other invasive	3.67	10.54	30	9.72	14.16	62	43.8%	-0.46 [-0.90, -0.02]
Rahimzadeh 2014, PG vs Other invasive (pooled)	2.46	0.99	26	3.34	1.03	44	33.2%	-0.86 [-1.36, -0.35]
Rahimzadeh 2018, PG vs PRP	5.1	1.5	21	5.6	1.5	21	23.0%	-0.33 [-0.94, 0.28]
Subtotal (95% CI)			**77**			**127**	**100.0%**	**-0.56 [-0.85, -0.27]**
Heterogeneity: Chi² = 2.09, df = 2 (P = 0.35); I² = 4%								
Test for overall effect: Z = 3.76 (P = 0.0002)								



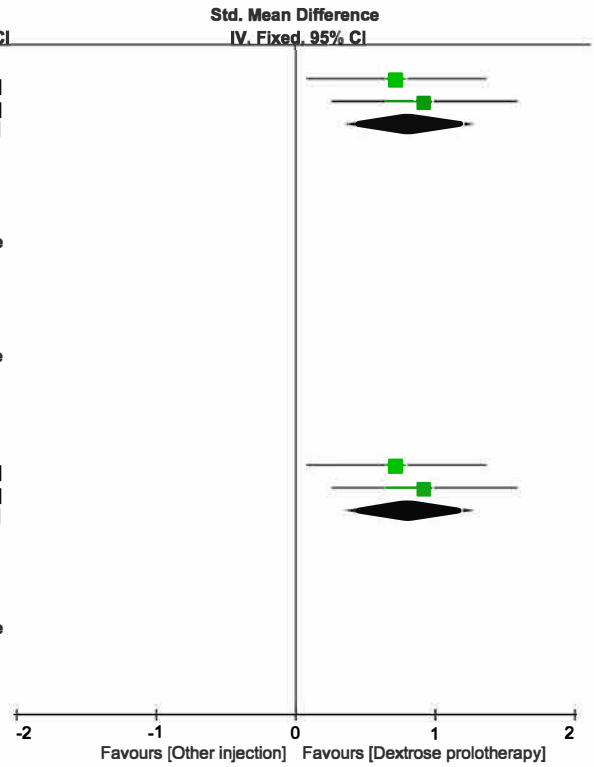
Supplementary figure S6. Effects of dextrose prolotherapy on global function versus other invasive therapies at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Invasive active control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Global function, Invasive active control, overall duration								
EROĞLU 2016, PG vs PRP	3.15	8.09	20	2.37	5.72	18	13.5%	0.11 [-0.53, 0.75]
Hashemi 2012, PG vs HA	28.3	11.65	50	27.8	12.87	50	15.1%	0.04 [-0.35, 0.43]
Hashemi 2015, PG vs Ozone	25.2	14.4	40	25.3	12.74	40	14.8%	-0.01 [-0.45, 0.43]
Pishgahi 2020, PG vs Other invasive	-5.74	11.74	30	10.09	16.44	62	14.7%	-1.04 [-1.50, -0.58]
Rahimzadeh 2018, PG vs PRP	23.3	8.05	21	25	9.58	21	13.7%	-0.19 [-0.79, 0.42]
Rezasoltani 2020, PG vs Other invasive	53.9	14	30	27.05	19.92	56	14.4%	1.47 [0.97, 1.97]
Waluyo 2020, PG vs HA	13.73	10.71	26	12.89	10.54	21	13.9%	0.08 [-0.50, 0.65]
Subtotal (95% CI)			**217**			**268**	**100.0%**	**0.06 [-0.50, 0.63]**
Heterogeneity: Tau² = 0.51; Chi² = 53.43, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 0.22 (P = 0.82)								
2.2.2 Global function, follow up ≥12 mo								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.2.3 Global function, follow up ≥6 mo, <12 mo								
EROĞLU 2016, PG vs PRP	2.8	6.98	20	2.17	13.77	18	32.9%	0.06 [-0.58, 0.69]
Pishgahi 2020, PG vs Other invasive	-6.4	10.08	30	18.13	15.35	62	34.4%	-1.75 [-2.26, -1.25]
Rahimzadeh 2018, PG vs PRP	28.4	7.34	21	36.5	9.1	21	32.8%	-0.96 [-1.60, -0.32]
Subtotal (95% CI)			**71**			**101**	**100.0%**	**-0.90 [-1.96, 0.16]**
Heterogeneity: Tau² = 0.78; Chi² = 19.06, df = 2 (P < 0.0001); I² = 90%								
Test for overall effect: Z = 1.67 (P = 0.10)								
2.2.4 Global function, follow up ≥3 mo, <6 mo								
EROĞLU 2016, PG vs PRP	3.15	8.09	20	2.37	5.72	18	17.5%	0.11 [-0.53, 0.75]
Hashemi 2012, PG vs HA	28.3	11.65	50	27.8	12.87	50	22.1%	0.04 [-0.35, 0.43]
Hashemi 2015, PG vs Ozone	25.2	11.23	40	25.3	9.97	40	21.2%	-0.01 [-0.45, 0.43]
Rezasoltani 2020, PG vs Other invasive	52.4	10.2	30	30.47	21.43	56	20.5%	1.18 [0.71, 1.66]
Waluyo 2020, PG vs HA	13.73	10.71	26	12.89	10.54	21	18.7%	0.08 [-0.50, 0.65]
Subtotal (95% CI)			**166**			**185**	**100.0%**	**0.28 [-0.18, 0.74]**
Heterogeneity: Tau² = 0.21; Chi² = 17.56, df = 4 (P = 0.002); I² = 77%								
Test for overall effect: Z = 1.20 (P = 0.23)								
2.2.5 Global function, follow up <3 mo								
Pishgahi 2020, PG vs Other invasive	-5.74	11.74	30	10.09	16.44	62	33.6%	-1.04 [-1.50, -0.58]
Rahimzadeh 2018, PG vs PRP	23.3	8.05	21	25	9.58	21	32.9%	-0.19 [-0.79, 0.42]
Rezasoltani 2020, PG vs Other invasive	53.9	14	30	27.05	19.92	56	33.5%	1.47 [0.97, 1.97]
Subtotal (95% CI)			**81**			**139**	**100.0%**	**0.08 [-1.46, 1.63]**
Heterogeneity: Tau² = 1.79; Chi² = 53.33, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.10 (P = 0.92)								



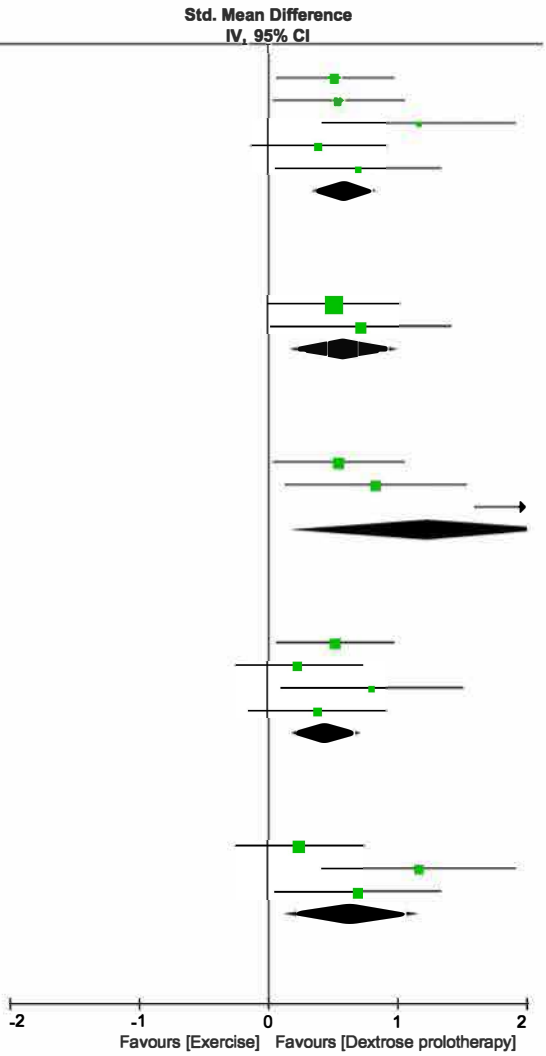
Supplementary figure S7. Effects of dextrose prolotherapy on quality of life versus other invasive therapies at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Other injection Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.2.1 Quality of life, overall duration								
Rezasoltani 2020, PG vs BNT	5.5	3	15	3.1	3.4	29	51.6%	0.72 [0.08, 1.36]
Rezasoltani 2020, PG vs HA	5.5	3	15	1.7	4.5	27	48.4%	0.92 [0.26, 1.59]
Subtotal (95% CI)			**30**			**56**	**100.0%**	**0.82 [0.36, 1.28]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 3.47 (P = 0.0005)								
3.2.2 Quality of life, follow up ≥12 mo								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.2.3 Quality of life, follow up ≥6 mo, <12 mo								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.2.4 Quality of life, follow up ≥3 mo, <6 mo								
Rezasoltani 2020, PG vs BNT	5.5	3	15	3.1	3.4	29	51.6%	0.72 [0.08, 1.36]
Rezasoltani 2020, PG vs HA	5.5	3	15	1.7	4.5	27	48.4%	0.92 [0.26, 1.59]
Subtotal (95% CI)			**30**			**56**	**100.0%**	**0.82 [0.36, 1.28]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 3.47 (P = 0.0005)								
3.2.5 Quality of life, follow up <3 mo								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



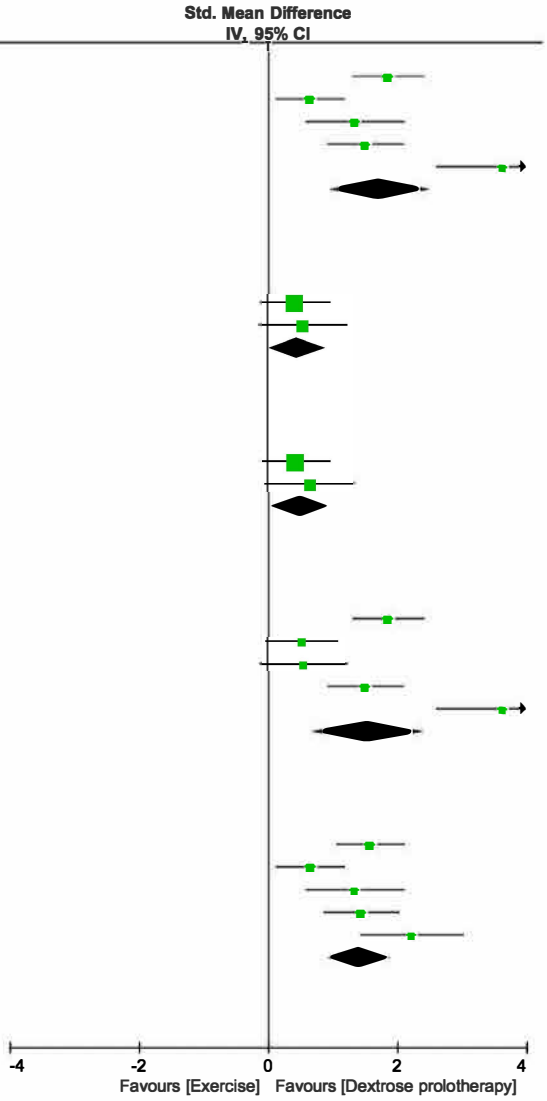
Supplementary figure S8. Effects of dextrose prolotherapy on pain versus noninvasive control therapy at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Exercise Mean	SD	Total	Weight	Std. Mean Difference IV, 95% CI
1.3.1 Pain, non-invasive active control, overall follow-up duration; fixed effect								
Dumais 2012, PG vs Ex	2.46	2.38	39	1.34	1.88	37	29.3%	0.52 [0.06, 0.97]
Rabago 2013a, PG vs Ex	0.92	1.37	30	0.16	1.39	31	23.4%	0.54 [0.03, 1.06]
Rabago 2013b, PG vs Con (pooled)	17.1	13.23	24	1.1	13.86	12	10.9%	1.16 [0.42, 1.91]
Rezasoltani 2020, PG vs Ex	11.6	6.8	28	9.2	5.3	27	21.5%	0.39 [-0.15, 0.92]
Sert 2020, PG vs Ex	3.1	1.31	21	2.1	1.51	19	14.9%	0.70 [0.05, 1.34]
Subtotal (95% CI)			**142**			**126**	**100.0%**	**0.59 [0.34, 0.84]**
Heterogeneity: Chi² = 3.05, df = 4 (P = 0.55); I² = 0%								
Test for overall effect: Z = 4.69 (P < 0.00001)								
1.3.2 Pain, follow up ≥12 mo; fixed effect								
Rabago 2013a, PG vs Ex	0.92	1.15	30	0.32	1.17	31	65.1%	0.51 [-0.00, 1.02]
Rabago 2013b, PG vs Con (pooled)	18.1	18.62	24	4.6	18.03	13	34.9%	0.72 [0.02, 1.41]
Subtotal (95% CI)			**54**			**44**	**100.0%**	**0.58 [0.17, 0.99]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 2.77 (P = 0.006)								
1.3.3 Pain, follow up ≥6 mo, <12 mo; random effect								
Rabago 2013a, PG vs Ex	0.92	1.37	30	0.16	1.39	31	35.6%	0.54 [0.03, 1.06]
Rabago 2013b, PG vs Con (pooled)	16.5	16.66	24	2.7	15.5	13	33.1%	0.83 [0.13, 1.53]
Sert 2020, PG vs Ex	6.1	1.4	21	2.5	1.51	19	31.2%	2.43 [1.59, 3.26]
Subtotal (95% CI)			**75**			**63**	**100.0%**	**1.23 [0.18, 2.28]**
Heterogeneity: Tau² = 0.74; Chi² = 14.49, df = 2 (P = 0.0007); I² = 86%								
Test for overall effect: Z = 2.29 (P = 0.02)								
1.3.4 Pain, follow up ≥3 mo, <6 mo; fixed effect								
Dumais 2012, PG vs Ex	2.46	2.38	39	1.34	1.88	37	33.5%	0.52 [0.06, 0.97]
Rabago 2013a, PG vs Ex	0.51	1.47	30	0.16	1.5	31	27.6%	0.23 [-0.27, 0.74]
Rabago 2013b, PG vs Con (pooled)	15.4	14.69	24	3.5	14.06	13	14.2%	0.80 [0.10, 1.51]
Rezasoltani 2020, PG vs Ex	11.6	6.8	28	9.2	5.3	27	24.6%	0.39 [-0.15, 0.92]
Subtotal (95% CI)			**121**			**108**	**100.0%**	**0.45 [0.18, 0.71]**
Heterogeneity: Chi² = 1.82, df = 3 (P = 0.61); I² = 0%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
1.3.5 Pain, follow up <3 mo; random effect								
Rabago 2013a, PG vs Ex	0.48	1.36	30	0.15	1.33	31	40.0%	0.24 [-0.26, 0.75]
Rabago 2013b, PG vs Con (pooled)	17.1	13.23	24	1.1	13.86	12	27.5%	1.16 [0.42, 1.91]
Sert 2020, PG vs Ex	3.1	1.31	21	2.1	1.51	19	32.5%	0.70 [0.05, 1.34]
Subtotal (95% CI)			**75**			**62**	**100.0%**	**0.64 [0.12, 1.16]**
Heterogeneity: Tau² = 0.11; Chi² = 4.19, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 2.42 (P = 0.02)								



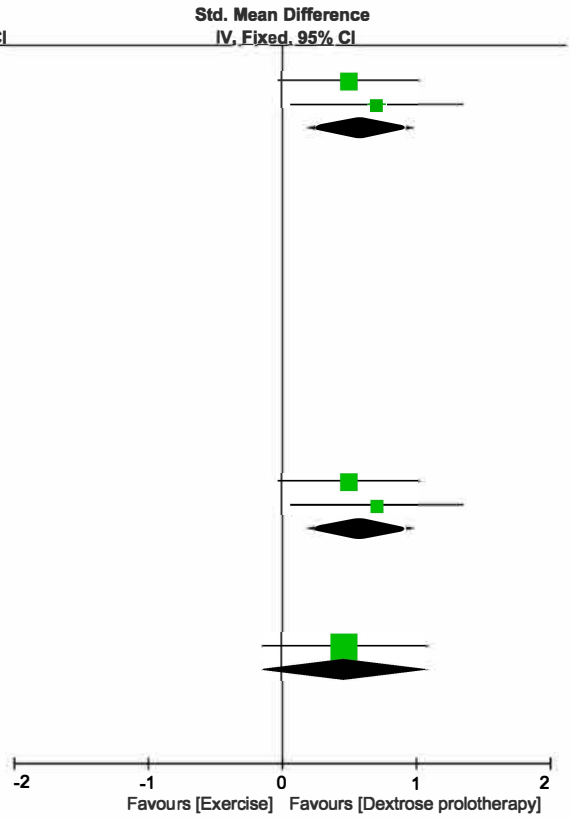
Supplementary figure S9. Effects of dextrose prolotherapy on global function versus noninvasive control therapy at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Exercise Mean	SD	Total	Weight	Std. Mean Difference IV, 95% CI
2.3.1 Global function, overall duration; random effect								
Dumais 2012, PG vs Ex	16.25	6.01	36	2.9	8.08	36	21.3%	1.85 [1.30, 2.41]
Rabago 2013a, PG vs Ex	13.91	17.69	30	2.51	16.94	27	21.5%	0.65 [0.11, 1.18]
Rabago2013b, PG vs Con (pooled)	17.4	10.78	24	2.5	11.09	12	19.4%	1.34 [0.57, 2.11]
Rezasoltani 2020, PG vs Ex	52.4	10.2	30	35.5	12	27	21.0%	1.50 [0.91, 2.10]
Sert 2020, PG vs Ex	36	7.28	21	9.1	7.24	19	16.7%	3.63 [2.59, 4.67]
Subtotal (95% CI)			**141**			**121**	**100.0%**	**1.72 [0.94, 2.49]**
Heterogeneity: Tau² = 0.65; Chi² = 27.52, df = 4 (P < 0.0001); I² = 85%								
Test for overall effect: Z = 4.34 (P < 0.0001)								
2.3.2 Global function, follow up ≥12 mo; fixed effect								
Rabago 2013a, PG vs Ex	15.32	16.93	26	8.24	16.98	26	61.0%	0.41 [-0.14, 0.96]
Rabago 2013b, PG vs Con (pooled)	17.6	15.68	24	8.6	18.03	13	39.0%	0.53 [-0.15, 1.22]
Subtotal (95% CI)			**50**			**39**	**100.0%**	**0.46 [0.03, 0.89]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 2.09 (P = 0.04)								
2.3.3 Global function, follow up ≥6 mo, <12 mo; fixed effect								
Rabago 2013a, PG vs Ex	15.85	17.25	28	8.48	17.04	27	62.6%	0.42 [-0.11, 0.96]
Rabago 2013b, PG vs Con (pooled)	16.2	15.19	24	6.6	12.98	13	37.4%	0.65 [-0.04, 1.34]
Subtotal (95% CI)			**52**			**40**	**100.0%**	**0.51 [0.08, 0.93]**
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 2.35 (P = 0.02)								
2.3.4 Global function, follow up ≥3 mo, <6 mo; random effect								
Dumais 2012, PG vs Ex	16.25	6.01	36	2.9	8.08	36	21.0%	1.85 [1.30, 2.41]
Rabago 2013a, PG vs Ex	13.31	17.25	27	4.26	16.8	25	21.0%	0.52 [-0.03, 1.08]
Rabago 2013b, PG vs Con (pooled)	14.2	13.23	24	7	12.26	13	20.1%	0.55 [-0.14, 1.23]
Rezasoltani 2020, PG vs Ex	52.4	10.2	30	35.5	12	27	20.7%	1.50 [0.91, 2.10]
Sert 2020, PG vs Ex	36	7.28	21	9.1	7.24	19	17.3%	3.63 [2.59, 4.67]
Subtotal (95% CI)			**138**			**120**	**100.0%**	**1.55 [0.68, 2.42]**
Heterogeneity: Tau² = 0.86; Chi² = 35.58, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.48 (P = 0.0005)								
2.3.5 Global function, follow up <3 mo; random effect								
Dumais 2012, PG vs Ex	12	4.63	36	1.65	7.93	36	22.4%	1.58 [1.04, 2.11]
Rabago 2013a, PG vs Ex	13.91	17.69	30	2.51	16.94	27	22.4%	0.65 [0.11, 1.18]
Rabago2013b, PG vs Con (pooled)	17.4	10.78	24	2.5	11.09	12	17.4%	1.34 [0.57, 2.11]
Rezasoltani 2020, PG vs Ex (1)	53.9	14	30	32	16.1	27	21.2%	1.44 [0.85, 2.02]
Sert 2020, PG vs Ex	24.3	7.24	21	7.9	7.25	19	16.7%	2.22 [1.41, 3.02]
Subtotal (95% CI)			**141**			**121**	**100.0%**	**1.41 [0.92, 1.89]**
Heterogeneity: Tau² = 0.20; Chi² = 11.88, df = 4 (P = 0.02); I² = 66%								
Test for overall effect: Z = 5.67 (P < 0.00001)								

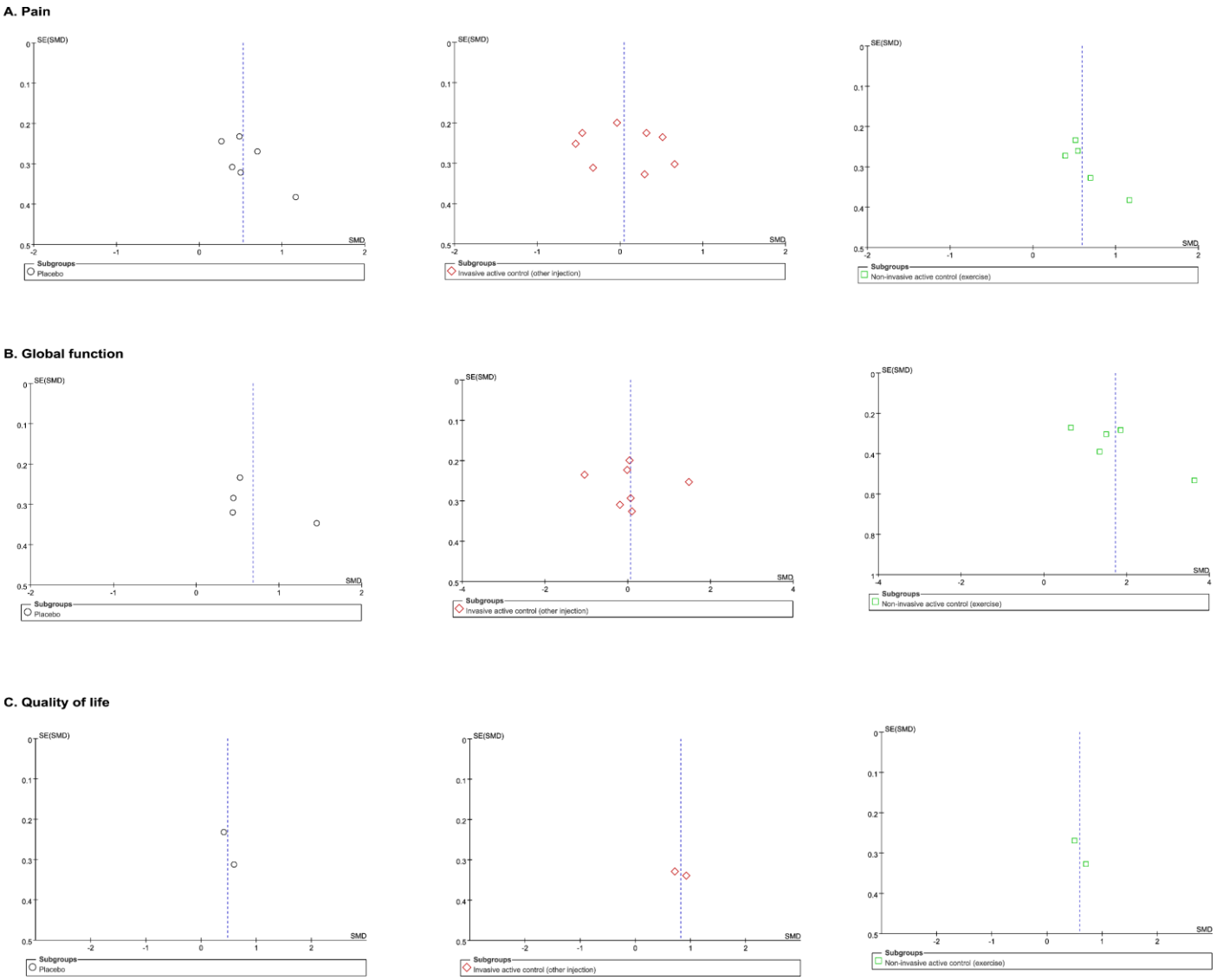


Supplementary figure S10. Effects of dextrose prolotherapy on quality of life versus noninvasive control therapy at an overall duration and each follow-up time point.

Study or Subgroup	Dextrose prolotherapy Mean	SD	Total	Exercise Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.3.1 Quality of life, overall duration								
Rezasoltani 2020, PG vs Ex	5.5	3	30	3.8	3.7	27	59.6%	0.50 [-0.03, 1.03]
Sert 2020, PG vs Ex	22.5	10.05	21	15	10.73	19	40.4%	0.71 [0.07, 1.35]
Subtotal (95% CI)			**51**			**46**	**100.0%**	**0.58 [0.18, 0.99]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 2.81 (P = 0.005)								
3.3.2 Quality of life, follow up ≥12 mo								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable			**0**					
Test for overall effect: Not applicable								
						0		
3.3.3 Quality of life, follow up ≥6 mo, <12 mo								
Subtotal (95% CI)								**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.3.4 Quality of life, follow up ≥3 mo, <6 mo								
Rezasoltani 2020, PG vs Ex	5.5	3	30	3.8	3.7	27	59.6%	0.50 [-0.03, 1.03]
Sert 2020, PG vs Ex	22.5	10.05	21	15	10.73	19	40.4%	0.71 [0.07, 1.35]
Subtotal (95% CI)			**51**			**46**	**100.0%**	**0.58 [0.18, 0.99]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 2.81 (P = 0.005)								
3.3.5 Quality of life, follow up <3 mo								
Sert 2020, PG vs Ex	14.4	10.45	21	9.1	11.85	19	100.0%	0.47 [-0.16, 1.10]
Subtotal (95% CI)			**21**			**19**	**100.0%**	**0.47 [-0.16, 1.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.45 (P = 0.15)								



Supplementary figure S11



Supplementary figure S11. Funnel plots of the intervention effects for (A) pain, (B) global function, and (C) quality of life. Each circle represents an independent comparison, with the x-axis representing standard mean difference (SMD) over control comparisons and the y-axis showing the standard error (SE) of SMD. The vertical dotted line indicates the mean value of the SMDs.