Comparative Effectiveness of Different Nonsurgical Treatments for Patellar Tendinopathy: A Systematic Review and Network Meta-analysis

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Purpose: To investigate the functional improvement and pain reduction of different nonsurgical treatments for patellar tendinopathy (PT), a systematic review with network meta-analysis was performed. **Methods:** Studies were comprehensively searched for without language restrictions in the CENTRAL, MEDLINE, EMBASE, Web of Science, Physiotherapy Evidence Database, and SPORTDiscus databases from inception to May 2018. Randomized controlled trials about nonsurgical treatments for PT were included. The outcome measurements were the Victorian Institute of Sports Assessment (VISA) scale and pain scores (such as the visual analog scale or Numerical Rating Scale). Study quality was evaluated using the Physiotherapy Evidence Database score. Direct comparisons were performed using pairwise meta-analysis, whereas network meta-analysis was performed using a frequentist method in a multivariate random-effects model. **Results:** Eleven studies with 430 affected patellar tendons were included in the systematic review. The summary mean difference of improvement in the VISA scale versus the control group for corticosteroid injection was −23.00 (95% confidence interval [CI] −36.73 to -9.27), for leukocyte-rich platelet-rich plasma (LR-PRP) was 13.22 (95% CI 2.37-24.07), for focused extracorporeal shockwave therapy (ESWT) was −1.28 (95% CI −6.25 to 3.68), for radial ESWT was −6.68 (95% CI −20.20 to 6.84), for ultrasound was −0.70 (95% CI −11.23 to 9.83), for autologous blood injection was −0.60 (95% CI −9.30 to 8.10), for dry needling was 17.51 (95% CI −2.57 to 37.60), for topical glyceryl trinitrate was −0.90 (95% CI −13.07 to 11.27), and for skin-derived tendon-like cells was 10.40 (95% CI −1.59 to 22.39). LR-PRP (Surface Under the Cumulative Ranking curve [SUCRA] = 87.5%) or dry needling (SUCRA = 90.5%) was most likely to be ranked the best in terms of improvement on the VISA scale. Compared with the control group, the summary mean difference of the change in pain score for corticosteroid injection was 0.80 (95% CI −3.48 to 5.08), for LR-PRP was −1.87 (95% CI −3.28 to −0.46), for focused ESWT was 0.13 (95% CI −0.68 to 0.93), for radial ESWT was 0.03 (95% CI −1.92 to 1.98), for ultrasound was −0.20 (95% CI −1.49 to 1.09), for autologous blood injection was 0.60 (95% CI −0.73 to 1.93), for dry needling was −0.37 (95% CI −2.71 to 1.97), and for topical glyceryl trinitrate was −0.50 (95% CI −2.55 to 1.55). The treatment most likely to be ranked the best in terms of change in pain score was LR-PRP (SUCRA = 94.9%). **Conclusions:** The network meta-analysis demonstrated that LR-PRP has the greatest functional improvement and pain reduction for PT compared with other treatment options. However, the treatment effect estimates can be biased by the possible intransitivity and should not be overestimated. **Level of Evidence:** Level I, meta-analysis of Level I studies.

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Patellar tendinopathy (PT) is commonly seen among elite and recreational athletes owing to repetitive activities.[1,2] The overall prevalence of PT was reported to be 8.5%, with greater rates in volleyball and soccer players, according to one cross-sectional study.[3] The chronic and refractory nature of PT can affect athletes' training frequencies and competitive performance. There is no consensus with regards to the gold-standard treatment for PT, and conservative treatment is usually the first-line therapy, including adequate rest, nonsteroidal anti-inflammatory drugs, local cryotherapy, stretching and eccentric exercise training, patellar tendon straps, or therapeutic ultrasound.[4,5] In the literature, eccentric exercise training has been identified as a stimulation treatment with the capability to increase remodeling of collagen fibers in the tendon in response to stress. Functional improvement and pain-reducing effect of this training in the early stages of PT have been demonstrated in several studies.[6,7] Patellar tendon straps are effective in reducing pain and increasing proprioception of knee joints in patients with PT, but the study designs are case−control, cohort, or single-arm with pretest−post-test research designs.[8-10] Therapeutic ultrasound was used to treat chronic PT in 1 randomized controlled trial[11] but did not provide additional benefit over placebo treatment.

For patients with refractory symptoms, further nonsurgical interventions, including dry needling, corticosteroid injection, extracorporeal shockwave therapy (ESWT), and platelet-rich plasma (PRP) have been administered for reactivation of the repair process; however, the reported results are inconsistent.[12-15] Regarding ESWT, mechanical load is considered a major factor in the reactivation of tissue regeneration. ESWT is considered a good alternative to surgery in patients who decline surgery or are poor surgical candidates.[16] It also has shown good analgesic effect for chronic tendinitis around the shoulder and elbow,[17,18] but the outcome of ESWT in PT remains inconsistent.[12,19] In the category of PRP, in which whole blood drawn from the patient is spun in a centrifuge and cells are separated out of the blood, the condensed platelets in PRP can initiate the healing process in the tendon when they reach the site of injury.[20] In a meta-analysis, PRP showed promising results in cases of refractory PT.[21] However, despite PRP exhibiting positive results for the treatment of PT, Liddle and Rodriguez-Merchan[22] reported no significant superiority of PRP over other alternative treatments. In addition, the standard protocol of PRP therapy has not yet been established with regards to the number and interval of injections for PT.

After thorough searching of the existed literature, we found that the effectiveness of different nonsurgical treatment options for functional improvement and pain reduction in patients with PT has not been compared at the same time in a meta-analysis. The aim of this network meta-analysis was to investigate the functional improvement and pain reduction of different nonsurgical treatments for PT. The hypothesis of this study was that PRP would be the most effective treatment in functional improvement and pain reduction for patients with PT.

Methods

Search Methods for Identification of Studies

This systematic review was conducted following the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[23] and was registered prospectively in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD 42018086696). We comprehensively searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science, Physiotherapy Evidence Database (PEDro), and SPORTDiscus from inception to May 31, 2018. We also searched using the World Health Organization International Clinical Trials Registry Platform search portal, which includes various trial registers such as ISRCTN and ClinicalTrials.gov, to identify further studies. The search strategies are presented in Appendix 1. Search filters developed by the Hedges Project (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_home.aspx) were employed to achieve the best balance of sensitivity and specificity. References included in identified studies also were searched to avoid non-inclusion of related clinical trials. All of the literature search was performed in June 2018.

Inclusion Criteria

Types of Study

The study was level of evidence 1 for all included studies and included randomized controlled trials. Studies comparing different types of exercise program were excluded. Studies were excluded if the follow-up period was shorter than 3 months. Studies also were excluded if outcome measures could not be extracted.

Types of Participant

Participants with clinically- or image-confirmed PT were included. Participants who had received surgery, corticosteroid injection, ESWT, or other interventions for affected knees previously were excluded. To avoid interference from other chronic diseases, patients with rheumatoid arthritis, septic arthritis, or other inflammatory arthritis were excluded.

Types of Intervention

There were no restrictions in terms of dose or duration of nonsurgical treatments. As eccentric exercise

training usually is prescribed along with other conservative management techniques, it could be considered a control group in these comparisons. There was no restriction regarding the type, frequency, intensity, or duration of eccentric exercise training.

Outcome Measures

The outcome measures assessed in our systematic review were improvement in functional and pain scores for each treatment strategy for PT. The severity of PT can be evaluated by a simple and practical questionnaire-based index, the Victorian Institute of Sport Assessment (VISA) questionnaire.[24] This brief questionnaire assesses symptoms, function, and ability to play sport. The VISA score ranges from 0 (greatest severity) to 100 points (an asymptomatic, fully-performing individual). We also focused on patellar pain symptoms during activities of daily living and used the visual analog scale (VAS) or Numeric Rating Scale (NRS) for evaluation. The pain severity on the VAS or NRS is rated from 0 (no pain) to 10 points (worst pain).

Data Collection and Analysis

Selection of Studies

Two authors (one physiatrist, P-C. C., and one orthopedic surgeon, K-T. W.) independently screened the titles and abstracts of studies and identified those that could be included. After initial screening, the full text of studies with the potential to be included was reviewed by at least one of the authors for further selection. Any ongoing trials identified primarily through the World Health Organization International Clinical Trials Registry Platform also were followed-up until data analysis began in June 2018. Discrepancies in the selection of studies were resolved through discussion.

Data Extraction and Management

Two authors independently extracted the following data:

1. Author and publication year.
2. Journal of publication.
3. Inclusion and exclusion criteria.
4. Participant characteristics, such as age, sex (male/female), and duration of symptoms of PT.

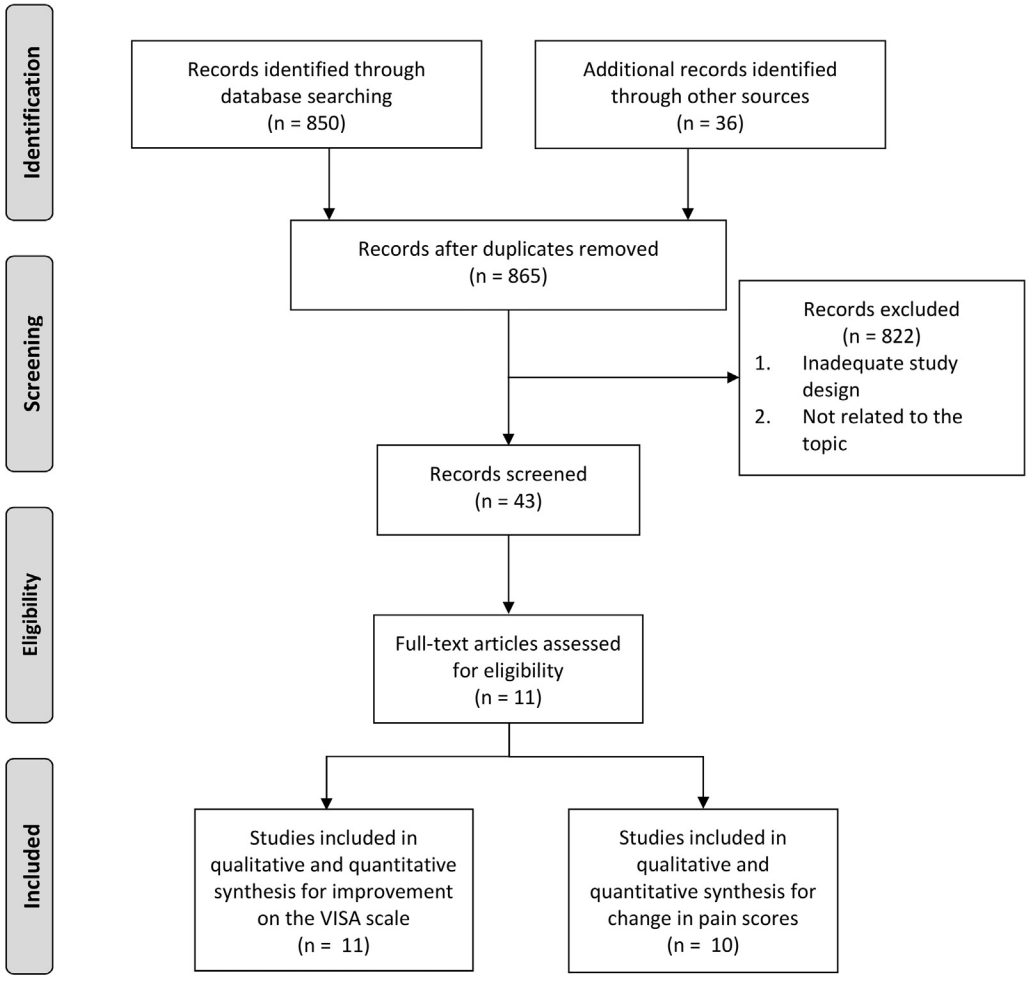

Fig 1. Flow diagram of the literature search and identification of articles for review. (VISA, Victorian Institute of Sport Assessment.)

Table 1. Characteristics of the Included Studies

Study	Diagnosis Confirmed by Imaging	N	Age, y	Sex (Male/ Female)	Duration of Symptoms	Treatment	Follow-up	Outcome Measures	Level of Evidence
Warden et al., 2008[11]	Yes	17	27 ± 7	12/5	3.4 ± 3.1 y	Therapeutic ultrasound	12 wk	(1) VAS-U (usual pain) and VAS-W (worst pain) (2) VISA	I
		20	27 ± 7	18/2	4.1 ± 3.8 y	Control			
Kongsgaard et al., 2009[15]	Yes	12	34.3 ± 10.0	12/0	18.3 ± 14.1 mo	Corticosteroid injection	12, 24 wk	(1) VISA (2) VAS (3) Ultrasonographic findings (4) Biomechanical outcomes	I
		12	31.3 ± 8.3	12/0	18.8 ± 13.0 mo	Control			
Clarke et al., 2011[39]	Yes	33	Unknown	Unknown	Unknown	SDTLC + ABI	6 wk, 3 mo, 6 mo	(1) VISA (2) Ultrasonographic findings	I
		27	Unknown	Unknown	Unknown	ABI			
Zwerver et al., 2011[19]	No	31	24.2 ± 5.2	20/11	7.3 ± 3.6 mo	fESWT	1, 12, 22 wk	(1) VISA (2) VAS during ADL, sports, during 1 and 10 single-legged decline squats, after 3 maximum single-legged jumps, and after the triple-hop test (3) Improvement ratio	I
		31	25.7 ± 4.5	21/10	8.1 ± 3.8 mo	Control			
Steunebrink et al., 2013[42]	No	16	31.9 ± 9.6	11/5	47 ± 39 wk	TGT	6, 12, 24 wk	(1) VISA (2) VAS (3) Satisfaction rate	I
		17	33.8 ± 10.5	14/3	49 ± 36 wk	Control			
van der Worp et al., 2014[44]	Yes	21	28.8 ± 10.3	16/5	32.3 ± 28.7 mo	fESWT	7, 14 wk	(1) VISA (2) VAS during ADL, sport, 1 single-leg decline squat, 10 single-leg decline squats	I
		22	33.4 ± 10.7	16/6	38.6 ± 56.9 mo	rESWT			
Vetrano et al., 2013[45]	Yes	23	26.9 ± 9.1	20/3	18.9 ± 19.1 mo	LR-PRP	2, 6, 12 mo	(1) VISA (2) VAS (3) Modified Blazina scale	I
		23	26.8 ± 8.5	17/6	17.6 ± 20.2 mo	fESWT			
Dragoo et al., 2014[40]	Yes	9	28 ± 8	8/1	Unknown	LR-PRP	12, 26 wk	(1) VISA (2) Tegner (3) Lysholm (4) VAS (5) SF-12	I
		12	40 ± 14	12/0	Unknown	Dry needling			
Resteghini et al., 2016[41]	Yes	11	38.9 ± 8.9	10/1	16.7 ± 9.7 mo	ABI	1, 3, 12 mo	(1) VAS (2) VISA (3) SF-MPQ	I
		11	42.5 ± 12.9	8/3	19.2 ± 12.2 mo	Control			
Lee et al., 2018[4]	Yes	16	21.1 ± 2.2	16/0	35.6 ± 22.4 mo	fESWT	12 wk	(1) VISA (2) VAS during activity (3) Tendon force and mechanical properties	I
		14	24.1 ± 4.6	14/0	31.5 ± 30.0 mo	Control			
Thijs et al., 2017[43]	No	22	30.5 ± 8.0	14/8	65.1 ± 72.7 wk	fESWT	6 wk, 12 wk, 24 wk	(1) VISA (2) NRS during 10 decline squats, 3 single-leg jumps, and 3 maximal vertical jumps (3) Satisfaction ratio	I
		30	27.3 ± 5.2	24/6	99.4 ± 126.3 wk	Control			

ABI, autologous blood injection; ADL, activities of daily living; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; NRS, Numerical Rating Scale; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tenocyte-like cell; SF-12, Short Form−12; SF-MPQ, Short-Form—McGill Pain Questionnaire; TGT, topical glyceryl trinitrate; VAS, visual analog scale; VISA, Victorian Institute of Sports Assessment score.

5. Details of interventions and treatment strategies.
6. Outcome measures.
7. Risk of bias.

If any unclear or missing information were encountered, we contacted the authors of the individual papers for assistance. Any differences in opinion were resolved through discussion with the corresponding authors.

Assessment of Risk of Bias in Included Studies

We used the PEDro scale to evaluate the quality of the included studies. The PEDro scale contains 11 items that result in a score of 10. It also includes additional questions regarding the follow-up of study subjects and between-group statistical comparisons. The risk of bias of the included studies is summarized in Appendix 2.

Measures of Treatment Effect

Because VISA and pain scores (VAS or NRS) are numerical variables, we displayed these outcome measures as the mean difference (MD) with a 95% confidence interval (CI).

Unit of Analysis Issues

The unit of analysis was knees affected by PT according to the intervention group to which they were randomly assigned.

Dealing with Missing Data

We used data from intention-to-treat analysis[25] whenever possible; otherwise, we used the data available from the included studies. For numerical variables, the median value was substituted for the mean value if the latter was unavailable. Standard deviations (SDs) were input from *P* values according to guidance given in the Cochrane Handbook for Systematic Reviews of Intervention.[26] If only means and SDs for baseline and follow-up measurements for each group were reported, we calculated the changes in the means and SDs for each group,[27,28] as per the following mathematical formula:

$$\text{Change in mean} = Mean_{post} - Mean_{pre}$$

$$\text{Change in SD} = \sqrt{SD_{pre}^2 + SD_{post}^2 - 2 \times r \times SD_{pre} \times SD_{post}}$$

$Mean_{pre}$ and SD_{pre} are the mean and SD for the baseline measurement, and $Mean_{post}$ and SD_{post} are the mean and SD for the follow-up measurement; r is the correlation between the matched pairs of baseline and follow-up measurements, and was set at $r = 0.5$ for each group.

Data Synthesis

Data were extracted into a spreadsheet software (Excel version 2013, Microsoft, Redmond, WA) for

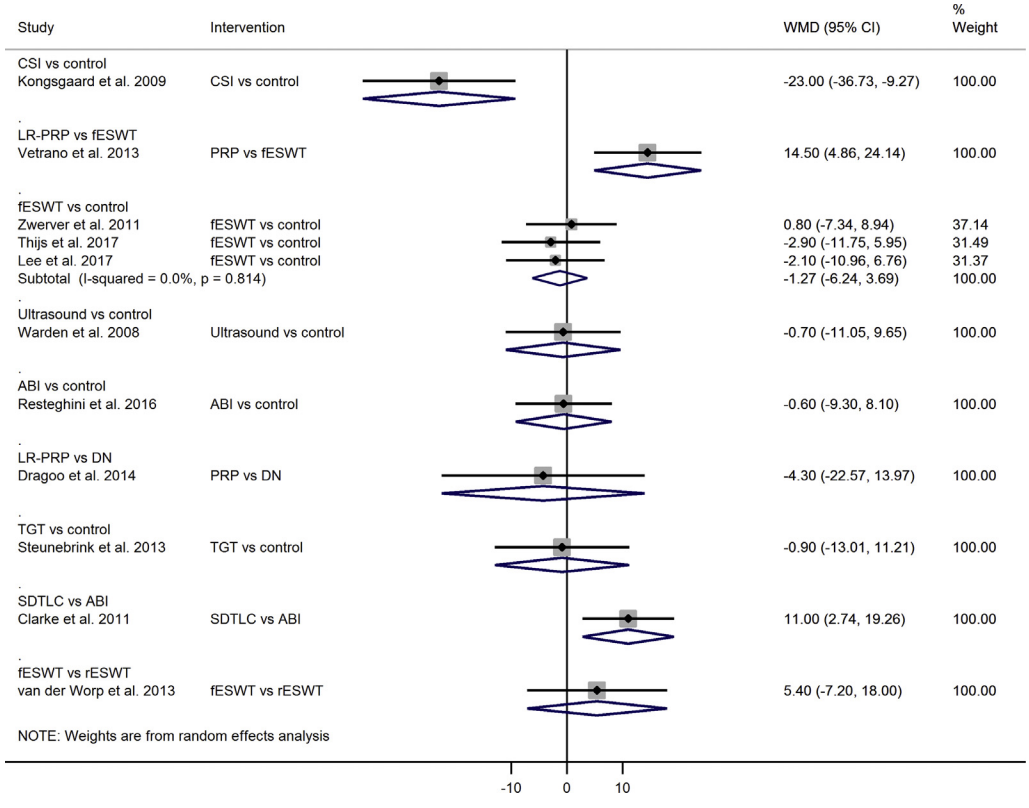

Fig 2. Forest plot of the traditional pairwise meta-analysis for improvement on the VISA scale for patellar tendinopathy. (ABI, autologous blood injection; CI, confidence interval; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; PRP, platelet-rich plasma; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; WMD, weighted mean difference.)

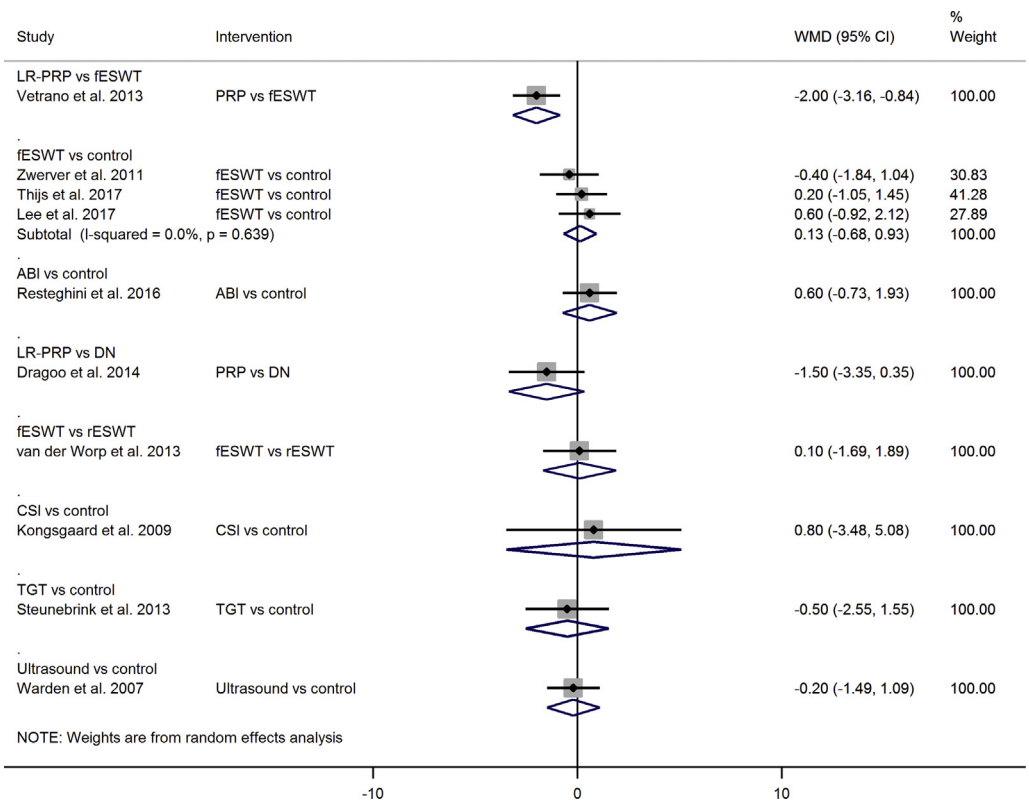

Fig 3. Forest plot of the traditional pairwise meta-analysis for change in pain score for patellar tendinopathy. (ABI, autologous blood injection; CI, confidence interval; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; PRP, platelet-rich plasma; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; WMD, weighted mean difference.)

preliminary management and were later imported into the statistical software STATA (StataCorp. 2013. Stata Statistical Software: Release 13; StataCorp LP College Station, TX). Traditional pairwise meta-analysis for direct comparisons and network meta-analysis to combine direct and indirect evidence were undertaken. We used random-effects models for meta-analysis throughout this systematic review due to various participant groups and treatment regimens. In the traditional pairwise meta-analysis, I^2 and the Cochrane Q test were calculated for evaluation of heterogeneity. Subgroup analysis, meta-regression, or sensitivity analysis was performed when substantial heterogeneity was recognized. Network meta-analysis compares multiple treatments by combining both direct and indirect evidence,[29,30] yielding more precise and robust estimates under certain assumptions.[31,32] The assumption of transitivity can be thought of as any participant in the network could have been given any of the treatments in the network. We used the frequentist

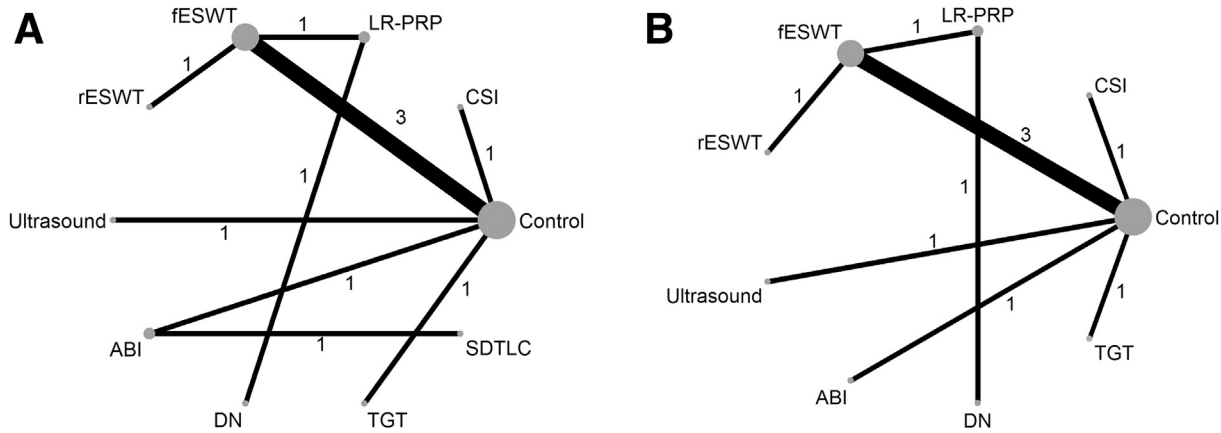

Fig 4. Network plot of the treatments for (A) improvement on the VISA scale and (B) change in pain score for patellar tendinopathy. (ABI, autologous blood injection; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.)

Table 2. Summary of Pairwise and Network Meta-Analyses of Treatment Effectiveness in Terms of Improvement on the VISA Scale

Effect Expressed as Improvement on VISA Scale With 95% CI											
Pairwise Meta-Analysis (B vs A)		B Control	CSI	LR-PRP	fESWT	rESWT	Ultrasound	ABI	DN	TGT	SDTLC
Network meta-analysis (A vs B)	A Control		−23.00 (−36.73 to −9.27)	—	−1.27 (−6.24 to 3.69)	—	−0.70 (−11.05 to 9.65)	−0.60 (−9.30 to 8.10)	—	−0.90 (−13.01 to 11.21)	—
	CSI	−23.00 (−36.73 to −9.27)		—	—	—	—	—	—	—	—
	LR-PRP	13.22 (2.37 to 24.07)	36.22 (18.72 to 53.72)		−14.50 (−24.14 to −4.86)	—	—	—	4.30 (−13.97 to 22.57)	—	—
	fESWT	−1.28 (−6.25 to 3.68)	21.72 (7.12 to 36.32)	−14.50 (−24.15 to −4.85)		−5.40 (−18.00 to 7.20)	—	—	—	—	—
	rESWT	−6.68 (−20.20 to 6.84)	16.32 (−2.95 to 35.59)	−19.90 (−35.75 to −4.05)	−5.40 (−17.98 to 7.18)		—	—	—	—	—
	Ultrasound	−0.70 (−11.23 to 9.83)	22.30 (4.99 to 39.61)	−13.92 (−29.04 to 1.21)	0.58 (−11.06 to 12.23)	5.98 (−11.16 to 23.12)		—	—	—	—
	ABI	−0.60 (−9.30 to 8.10)	22.40 (6.14 to 38.65)	−13.82 (−27.72 to 0.09)	0.68 (−9.33 to 10.70)	6.08 (−10.00 to 22.16)	0.10 (−13.56 to 13.76)		—	—	11.00 (2.74 to 19.26)
	DN	17.51 (−2.57 to 37.60)	40.51 (16.19 to 64.84)	4.30 (−12.60 to 21.20)	18.80 (−0.66 to 38.26)	24.20 (1.03 to 47.37)	18.21 (−4.46 to 40.89)	18.11 (−3.77 to 40.00)		—	—
	TGT	−0.90 (−13.07 to 11.27)	22.10 (3.75 to 40.45)	−14.12 (−30.42 to 2.19)	0.38 (−12.76 to 13.52)	5.78 (−12.41 to 23.97)	−0.20 (−16.29 to 15.89)	−0.30 (−15.26 to 14.66)	−18.41 (−41.90 to 5.07)		—
	SDTLC	10.40 (−1.59 to 22.39)	33.40 (15.17 to 51.63)	−2.82 (−18.99 to 13.35)	11.68 (−1.29 to 24.66)	17.08 (−0.99 to 35.15)	11.10 (−4.86 to 27.06)	11.00 (2.75 to 19.25)	−7.12 (−30.50 to 16.27)	11.30 (−5.78 to 28.38)	

NOTE. Effect expressed as MD with 95% CI for network meta-analysis or pairwise meta-analysis.

ABI, autologous blood injection; CI, confidence interval; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shock wave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; MD, mean difference; rESWT, radial extracorporeal shock wave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.

Table 3. Summary of Pairwise and Network Meta-Analyses of Treatment Effectiveness in Terms of the Change in Pain Score

Effect Expressed as Change of Pain Scores With 95% CI										
Pairwise Meta-Analysis (B vs A)										
		B Control	CSI	LR-PRP	fESWT	rESWT	Ultrasound	ABI	DN	TGT
Network meta-analysis (A vs B)	A Control		0.80 (−3.48 to 5.08)		0.13 (−0.68 to 0.93)		−0.20 (−1.49 to 1.09)	0.60 (−0.73 to 1.93)		−0.50 (−2.55 to 1.55)
	CSI	0.80 (−3.48 to 5.08)								
	LR-PRP	−1.87 (−3.28 to −0.46)	−2.67 (−7.18 to 1.84)		2.00 (0.84 to 3.16)				1.50 (−0.35 to 3.35)	
	fESWT	0.13 (−0.68 to 0.93)	−0.67 (−5.03 to 3.69)	2.00 (0.84 to 3.16)		−0.10 (−1.89 to 1.69)				
	rESWT	0.03 (−1.92 to 1.98)	−0.77 (−5.48 to 3.93)	1.90 (−0.22 to 4.02)	−0.10 (−1.88 to 1.68)					
	Ultrasound	−0.20 (−1.49 to 1.09)	−1.00 (−5.47 to 3.47)	1.67 (−0.24 to 3.58)	−0.33 (−1.85 to 1.19)	−0.23 (−2.57, 2.11)				
	ABI	0.60 (−0.73 to 1.93)	−0.20 (−4.68 to 4.28)	2.47 (0.53 to 4.41)	0.47 (−1.08 to 2.02)	0.57 (−1.79 to 2.93)	0.80 (−1.05 to 2.65)			
	DN	−0.37 (−2.71 to 1.97)	−1.17 (−6.05 to 3.71)	1.50 (−0.37 to 3.37)	−0.50 (−2.70 to 1.70)	−0.40 (−3.22 to 2.42)	−0.17 (−2.84 to 2.50)	−0.97 (−3.66 to 1.72)		
	TGT	−0.50 (−2.55 to 1.55)	−1.30 (−6.05, 3.45)	1.37 (−1.12 to 3.86)	−0.63 (−2.83 to 1.57)	−0.53 (−3.36 to 2.30)	−0.30 (−2.72 to 2.12)	−1.10 (−3.54 to 1.34)	−0.13 (−3.24 to 2.98)	

NOTE. Effect expressed as MD with 95% CI for network meta-analysis or pairwise meta-analysis.

ABI, autologous blood injection; CI, confidence interval; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shock wave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; MD, mean difference; rESWT, radial extracorporeal shock wave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.

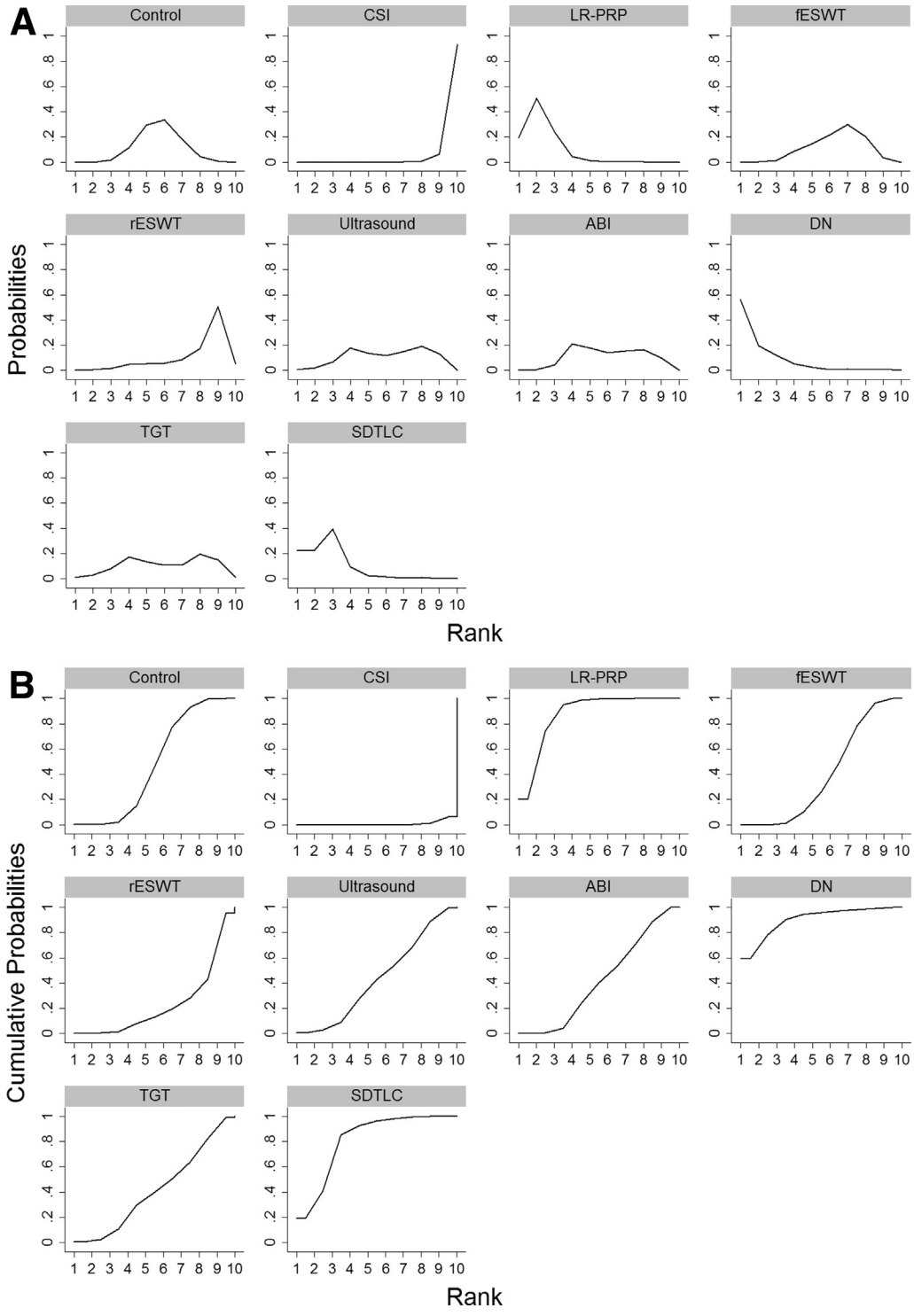

Fig 5. Ranking of treatment strategies based on (A) rank probabilities and (B) cumulative probabilities with regards to their effects on improvement on the VISA scale. (ABI, autologous blood injection; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.)

approach to network meta-analysis by specifying the consistency and inconsistency models as multivariate random-effects regression models.[33] We checked the inconsistency between direct and indirect comparisons using the design-by-treatment interaction models, loop inconsistency models, and node-splitting models.[34,35] For the ranking of treatments, we calculated the Surface Under the Cumulative Ranking curve (SUCRA), as described by Salanti et al.,[36] in which SUCRA is 1 when a treatment is always the best and 0 when a treatment is always the worst. All statistical analyses were performed using the *mvmeta* package for the statistical software STATA. The statistical significance level was set at 5%.

Assessment of Heterogeneity

We carefully examined the characteristics and designs of the included studies for clinical and methodologic heterogeneity. Differences in patients' ages, sex, and the duration of symptoms of PT could result in clinical heterogeneity, and the risk of bias and methodologic characteristics of included studies could contribute to methodologic heterogeneity. If substantial heterogeneity was recognized, we explored the causes of heterogeneity by subgroup analysis, sensitivity analysis, or meta-regression.

Assessment of Reporting Bias

Funnel plot asymmetry is the most common tool used for evaluating reporting bias[28,37]; however, there was no single reference line against which symmetry could be judged owing to the estimated effects for different comparisons, and a comparison-adjusted funnel plot was used instead.[38]

Results

Study Selection and Description

The details of the study selection process are presented in Figure 1. We identified 865 references through electronic searches and other sources. Following screening of titles and abstracts, 822 inappropriate references were excluded. After reading the full text, we finally retrieved 11 references for further evaluation.[4,11,15,19,39-45] These studies included 430 affected patellar tendons. Although 1 study[39] did not report the number of male and female participants, participants in other included studies were mostly male (295 males and 75 females). The average age of the participants was 21 to 42 years, and the duration of symptoms varied from 7 months to 4 years. Most studies assessed outcome measures from 3 to 12 months. All included studies compared the improvement on the VISA scale, whereas only 10 studies[4,11,15,19,40-45] compared the change in pain scores. The characteristics of the included studies are summarized in Table 1.

Quality of Studies

Appendix 2 shows the methodologic quality of the included studies. The eligibility criteria were specified in all studies. The allocation concealment methods were described in 6 studies.[11,19,40,42-44] The groups were similar at baseline with regards to the most important prognostic indicators in all studies except 2.[39,41] In terms of blind assessment, 8 studies[11,19,39-44] had blinding of all subjects, and 9 studies[4,11,19,39-44] had blinding of all assessors, whereas 4 studies[11,39,41,42] mentioned blinding of all therapists who administered treatment. Two studies[11,43] had a dropout rate greater than 15%. Intention-to-treat analysis was used in 9 studies.[11,19,39-45] The results of between-group statistical comparisons were reported for at least 1 key outcome in all but one of the included studies.[39] Both point measures and measures of variability for at least 1 key outcome were provided in all included studies.

Effects of Interventions

Pairwise Meta-Analysis (Direct Comparisons)

Figures 2 and 3 show the pooled estimates for each outcome measure.

Improvement on the VISA Scale. Eleven studies were included in the analysis of the improvement on the VISA scale for PT. The weighted MD of improvement on the VISA scale was −1.27 (95% CI −6.24 to 3.69, $I^2 = 0\%$) for focused ESWT versus control studies.[4,19,43] Other comparisons consisted of only one clinical trial, and the MD of improvement on the VISA scale was −23.00 (95% CI −36.73 to −9.27) for corticosteroid injection versus control study,[15] 14.50 (95% CI 4.86-24.14) for leukocyte-rich (LR)-PRP versus focused ESWT study,[45] −0.70 (95% CI −11.05 to 9.65) for ultrasound versus control study,[11] −0.60 (95% CI −9.30 to 8.10) for autologous blood injection (ABI) versus control study,[41] −4.30 (95% CI −22.57 to 13.97) for LR-PRP versus dry needling study,[40] −0.90 (95% CI −13.01 to 11.21) for topical glyceryl trinitrate (TGT) versus control study,[42] 11.00 (95% CI 2.74 to 19.26) for skin-derived tendon-like cells versus ABI study,[39] and 5.40 (95% CI −7.20 to 18.00) for focused ESWT versus radial ESWT study.[44]

Change in Pain Score. Ten studies were enrolled to analyze the change in pain score for PT. The weighted MD of the change in pain score was 0.13 (95% CI −0.68 to 0.93, $I^2 = 0\%$) for focused ESWT versus control studies.[4,19,43] Other comparisons were composed of only one clinical trial, and the MD of change in pain score was −2.00 (95% CI −3.16 to −0.84) for LR-PRP versus focused ESWT study,[45] 0.60 (95% CI −0.73 to 1.93) for ABI versus control study,[41] −1.50 (95% CI −3.35 to 0.35) for LR-PRP versus dry needling study,[40] 0.10 (95% CI −1.69 to 1.89) for focused ESWT versus radial ESWT study,[44] 0.80 (95% CI −3.48 to 5.08) for corticosteroid injection versus control study,[15] −0.50 (95% CI −2.55 to 1.55) for TGT versus control study,[42] and −0.20 (95% CI −1.49 to 1.09) for ultrasound versus control study.[11]

Network Meta-Analysis (Combination of Direct and Indirect Comparisons)

Figure 4 presents a network plot of treatments in terms of improvement on the VISA scale and change in pain score for PT. The area of each circle is proportional to the number of studies involving the specific treatment. Any 2 circles connected by lines represent direct comparisons in the studies, and the thickness of each

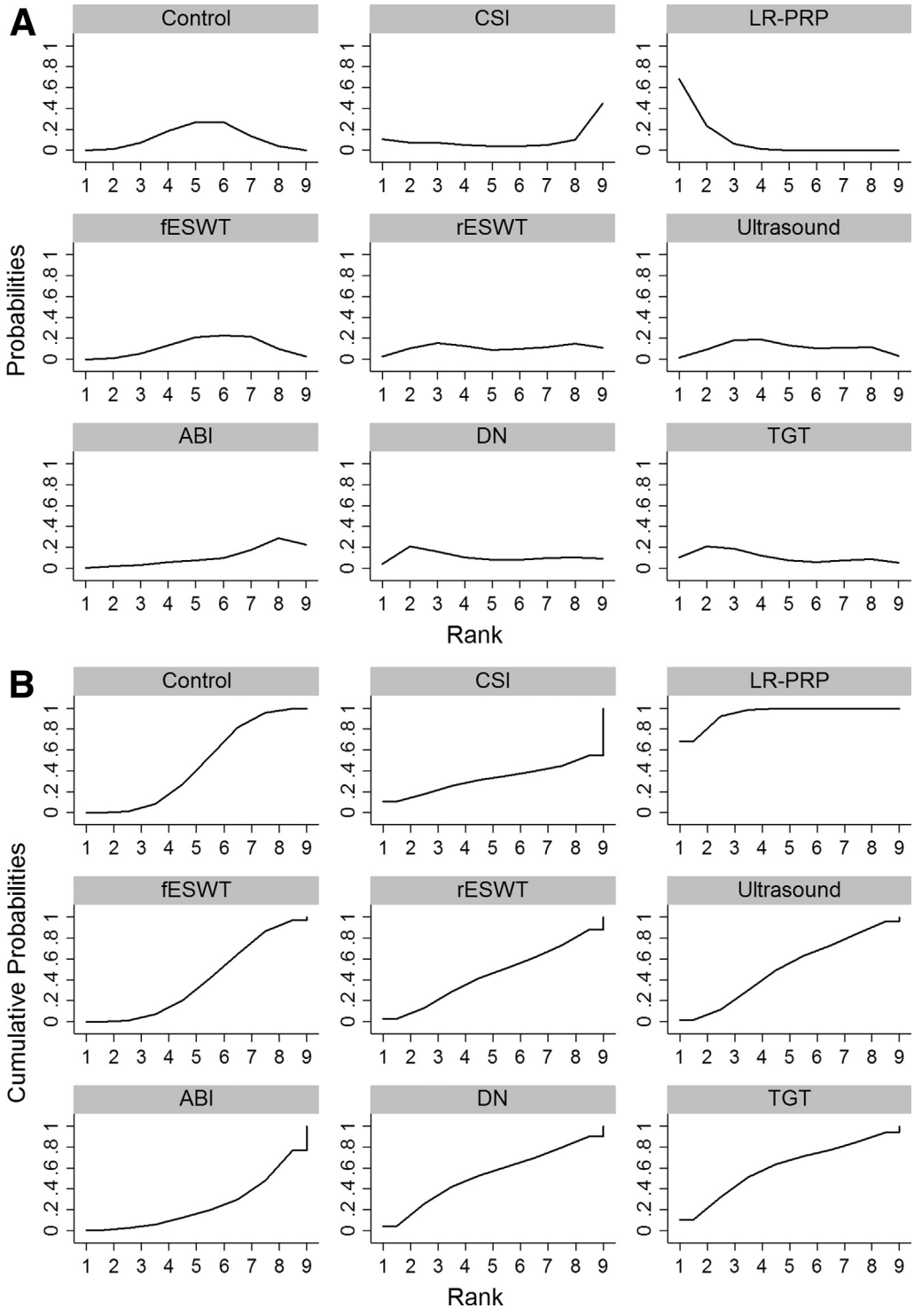

Fig 6. Ranking of treatment strategies based on (A) rank probabilities and (B) cumulative probabilities with regards to their effects on the change in pain score. (ABI, autologous blood injection; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shockwave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; rESWT, radial extracorporeal shockwave therapy; SDTLC, skin-derived tendon-like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.)

line is proportional to the number of comparisons included in the network meta-analysis.

The results of the network meta-analysis, including the summary MDs with 95% CIs, are reported in Table 2 and Table 3. The rank probabilities and cumulative probabilities are plotted in Figure 5 and Figure 6.

Improvement on the VISA Scale. Compared with the control group, the summary MD of improvement on the VISA scale for corticosteroid injection was −23.00 (95% CI −36.73 to −9.27), for LR-PRP was 13.22 (95% CI 2.37-24.07), for focused ESWT was −1.28 (95% CI −6.25 to 3.68), for radial ESWT was −6.68 (95% CI −20.20 to

6.84), for ultrasound was −0.70 (95% CI −11.23 to 9.83), for ABI was −0.60 (95% CI −9.30 to 8.10), for dry needling was 17.51 (95% CI −2.57 to 37.60), for TGT was −0.90 (95% CI −13.07 to 11.27), and for skin-derived tendon-like cells was 10.40 (95% CI −1.59 to 22.39). LR-PRP (SUCRA = 87.5%) or dry needling (SUCRA = 90.5%) was most likely to be ranked the best in terms of improvement on the VISA scale.

Change in Pain Score. Compared with the control group, the summary MD of the change in pain score for corticosteroid injection was 0.80 (95% CI −3.48 to 5.08), for LR-PRP was −1.87 (95% CI −3.28 to −0.46), for focused ESWT was 0.13 (95% CI −0.68 to 0.93), for radial ESWT was 0.03 (95% CI −1.92 to 1.98), for ultrasound was −0.20 (95% CI −1.49 to 1.09), for ABI was 0.60 (95% CI −0.73 to 1.93), for dry needling was −0.37 (95% CI −2.71 to 1.97), and for TGT was −0.50 (95% CI −2.55 to 1.55). The treatment most likely to be ranked the best in terms of change in pain score was LR-PRP (SUCRA = 94.9%).

Inconsistency in these outcomes was evaluated using the design-by-treatment, loop inconsistency, and node-splitting models. As there was no loop in the network, there was no need to evaluate the inconsistency.

Reporting Bias

Appendix Figure 1 presents the comparison-adjusted funnel plots of improvement on the VISA scale and change in pain score. There was no significant funnel plot asymmetry. The Egger test found no evidence of small study bias.

Discussion

The network meta-analysis of improvement on the VISA scale showed that LR-PRP or dry needling was most likely to be ranked the best treatment, and the network meta-analysis of the change in pain score demonstrated that LR-PRP had the greatest probability to be ranked the best.

PT, also called jumper's knee, commonly affects the patellar tendon inserted on the inferior pole of the patella bone,[46,47] and its symptoms are not usually induced by an acute inflammatory process.[48,49] PT is instead a degenerative change in the patellar tendon resulting in knee pain and dysfunction, and the favored pathogenesis is chronic repetitive tendon overload that contributes to increased fibroblast production of prostaglandin E2 and leukotriene B4 or neovascularization.[50] In addition to activity modification or analgesics, eccentric exercise training is associated with improvement in knee pain or function.[7] Eccentric exercise training refers to muscle contractions as the muscle elongates, and is important for athletes to avoid sports injury.[51] Because the quadriceps muscles are embryologically related to the patellar tendons, the eccentric-specific strength of the quadriceps plays a significant role in protection of the patellar tendons during sports activities.[52]

ESWT has gained growing popularity for the treatment of orthopedic conditions, especially tendinopathies.[53] Published papers have reported various energy levels, numbers of treatment sessions, and numbers of impulses for ESWT in the treatment of tendinopathies, and there exist no guidelines with regards to the recommended dose of ESWT. It is being used more and more frequently in lower-limb tendinopathies, although the mechanism of pain reduction and functional improvement remains unclear. Possible mechanisms of ESWT include stimulation of healing, neovascularization, suppressive effects on nociceptors, and a hyperstimulation mechanism blocking the gate-control mechanism.[54-57] Recent evidence showed that there exists associations between tendon repair and increases in growth factors in patients receiving ESWT, and these growth factors are assumed to be responsible for the success of treatment.[58-60]

ABI and PRP represent one kind of regenerative medicine that has become popular in recent years. They are used in the treatment of many orthopedic conditions, including muscle or ligament injuries, tendinopathies and enthesopathies, osteoarthritis, and as an adjunct to surgical treatment.[61] Several randomized controlled trials compared ABI with PRP for chronic lateral epicondylitis,[62-65] and PRP reduced pain and improved function better than ABI did. However, there was no direct comparison of ABI versus PRP for PT in this systematic review. The primary effect of ABI or PRP in the treatment of PT is enhancement of tissue-healing. What differentiates ABI or PRP from ESWT for the treatment of PT is that high concentrations of growth factors are found within ABI or PRP,[45] whereas ESWT only triggers specific responses in the injured tissue to increase the concentrations of growth factors.

Dry needling involves repeated lancing of the area of abnormal tendons. It has been evaluated as a treatment option for chronic tendinosis, such as Achilles tendinosis, lateral epicondylitis, or patellar tendinosis.[66] It is performed to stimulate an inflammatory response within the tendon, resulting in focal disruption of the collagen fibers within the area of tendinosis and inciting internal hemorrhage. It is hypothesized that the inflammatory response induces the formation of granulation tissue, strengthening the tendon. However, as with the clinical response to ESWT, dry needling lacks high concentrations of growth factors to enhance the healing process of injured tissue.

Liddle and Rodriguez-Merchan[22] compared the effectiveness of PRP with alternative treatment options (eccentric exercise training, ESWT, and dry needling) in a pairwise meta-analysis. The results of the comparative studies were inconsistent, and superiority of PRP over

control treatments could not be conclusively demonstrated. This meta-analysis viewed eccentric exercise training, ESWT, and dry needling as the same comparator, but these 3 treatment options were actually different in clinical practice. This would lead to high heterogeneity in a meta-analysis. Dupley and Charalambous[21] performed a similar pairwise meta-analysis and compared PRP with controls (ESWT and dry needling). The results showed that PRP was statistically better than control with regards to VISA scale at long-term follow-up. Likewise, the results were also of high heterogeneity because of the same reasons encountered in Liddle and Rodriguez-Merchan.[22] In our network meta-analysis, we regarded nonsurgical treatments other than PRP as different treatment options. Besides, we also included studies without PRP to make the multiple comparisons of nonsurgical treatment options for PT more complete.

Our study depicted a practical and complete picture of the success of various treatments for PT in terms of major outcomes. The statistical model of network meta-analysis provided results including both direct and indirect comparisons. We also presented the probabilities of ranking for the treatment strategies and calculated the SUCRA for ranking purposes: this could help physicians to make better clinical decisions.

Limitations

Our study nevertheless had some limitations. First, the dose of each treatment was not standardized in the related studies. The dose−response effect should not be ignored when performing meta-analyses, and meta-regression could be considered with sufficient available data. Second, all participants received eccentric exercise training in the control groups. Although the exercise protocols (such as frequency, intensity, types of exercise, time) are similar in most studies, some differences may exist in these exercise programs, calling into question the assumption of transitivity. This is a common problem when studies involving exercise training were compared, and the differences in treatment effect should be interpreted with caution. Third, the included participants were mostly male, and the results might be biased by the sex difference. Future studies could focus on the effects of treatment for PT in female athletes relative to male athletes. Fourth, number of knees rather than patients were used as a unit of analysis in our systematic review, and this kind of non-independence of the data might bias the analysis. Fortunately, the number of knees did not far exceed patients in our systematic review, so the analysis would not be overly biased. Fifth, adverse events after each treatment were not analyzed due to the paucity of the data retrieved from these studies. Patient safety is an extremely important issue in clinical decisions, and it is essential to compare the rates of adverse events for each treatment strategy. Finally, we did not find any related literature with follow-up of greater than 2 years. The follow-up time of the included studies was quite short, which limited the results to the short-term effectiveness.

Conclusions

The network meta-analysis demonstrated that LR-PRP has the greatest functional improvement and pain reduction for PT compared with other treatment options. However, the treatment effect estimates can be biased by the possible intransitivity and should not be overestimated.

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Appendix 1

Search strategy

The Central Register of Controlled Trials (CENTRAL) (Wiley)

#1. random*:ab,ti
#2. placebo*
#3. (double next/1 blind*):ab,ti
#4. (single next/1 blind*):ab,ti
#5. #1 or #2 or #3 or #4
#6. mh 'patellar tendinopathy'
#7. (patella$ next/3 tend$):ab,ti
#8. pt:ab,ti
#9. #6 or #7 or #8
#10. #5 and #9

MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt
3. randomized.ab.
4. placebo.ab.
5. therapy.fs.
6. randomly.ab.
7. trial.ab.
8. group.ab.
9. or/1−8
10. humans.sh.
11. 9 and 10
12. patella*.mp
13. tendinopathy/ or tendinosis/ or tendinitis/
14. 12 and 13
15. 11 and 14

EMBASE

#1. random*:ab,ti
#2. placebo*
#3. (double next/1 blind*):ab,ti
#4. (single next/1 blind*):ab,ti
#5. #1 or #2 or #3 or #4
#6. 'patellar tendinopathy'/exp
#7. (patella$ next/3 tend$):ab,ti
#8. pt:ab,ti
#9. #6 or #7 or #8
#10. #5 and #9

Web of Science

#1 TS = (random* OR rct* OR crossover OR masked OR blind* OR placebo*)
#2 TS = (patellar tendinopathy OR patellar tendinosis OR patellar tendinitis OR patellar tendon pain)
#3 #2 AND #1

PEDro

'patellar tendinopathy'

SportDiscus

(SU (patellar tendinopathy) OR TI (patellar tendinopathy) OR AB (patellar tendinopathy) OR SU (patellar tendinitis) OR TI (patellar tendinitis) OR AB (patellar tendinitis) OR SU (patellar tendinosis) OR TI (patellar tendinosis) OR AB (patellar tendinosis) OR SU (PT) OR TI (PT) OR AB (PT))

World Health Organization International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/Default.aspx)

#1 Patellar tendinopathy

Appendix 2. Methodologic Quality Assessment of the Included Studies (PEDro Scale)

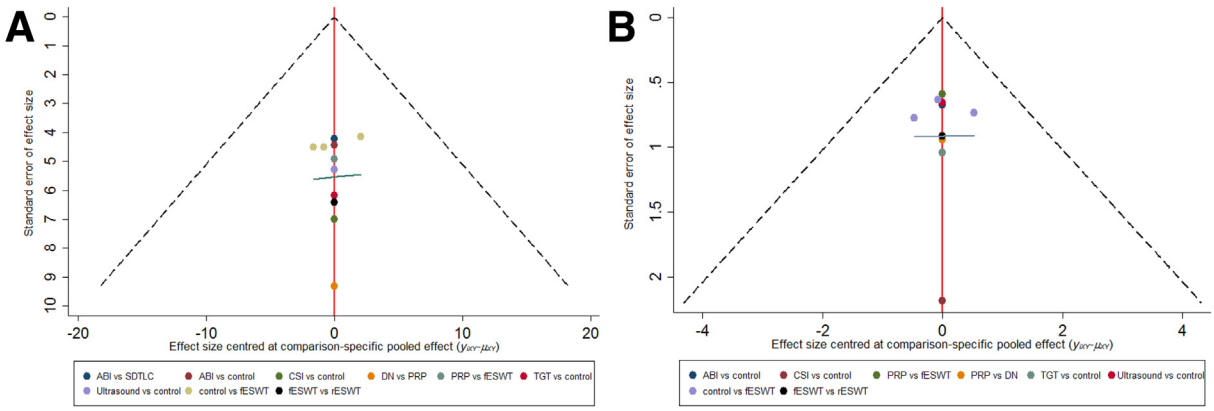
Study	1*	2	3	4	5	6	7	8	9	10	11	Total
Zwerver et al., 2011[19]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Thijs et al., 2017[43]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	8
Lee et al., 2018[4]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	5
Dragoo et al., 2014[40]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Resteghini et al., 2016[41]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	8
Vetrano et al., 2013[45]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7
Kongsgaard et al., 2009[15]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Warden et al., 2008[11]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Steunebrink et al., 2013[42]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Clarke et al., 2011[39]	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	7
van der Worp et al., 2014[44]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9

NOTE. The following is the website address for the PEDro Scale: https://www.pedro.org.au/english/downloads/pedro-scale/.

N, no; PEDro, Physiotherapy Evidence Database; Y, yes.

*Item 1 influences external validity; hence, it is not used to calculate the PEDro score. The 11-item scale gives a score out of 10. The 11 items of the PEDro scale are as follows:

1. Eligibility criteria were specified.
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least 1 key outcome.
8. Measures of at least 1 key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least 1 key outcome was analyzed by "intention to treat."
10. The results of between-group statistical comparisons are reported for at least 1 key outcome.
11. The study provides both point measures and measures of variability for at least 1 key outcome.



Appendix Figure 1. Comparison-adjusted funnel plots to assess reporting bias for (A) improvement on the VISA scale, and (B) change in pain score. (ABI, autologous blood injection; CSI, corticosteroid injection; DN, dry needling; fESWT, focused extracorporeal shock wave therapy; LR-PRP, leukocyte-rich platelet-rich plasma; rESWT, radial extracorporeal shock wave therapy; SDTLC, skin–derived tendon–like cells; TGT, topical glyceryl trinitrate; VISA, Victorian Institute of Sport Assessment.)