Platelet-Rich Plasma Versus Corticosteroids for the Treatment of Plantar Fasciitis: A Systematic Review and Meta-analysis

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Abstract

Background: Plantar fasciitis is a common cause of heel pain. Corticosteroid injections are commonly used and proven to be effective, and lately platelet-rich plasma (PRP) has been used with mixed results.

Purpose: To perform a systematic review and meta-analysis comparing intralesional injections of PRP and steroid infiltration.

Study Design: Systematic review and meta-analysis.

Methods: A systematic review of Medline, Embase, Scopus, and Google Scholar including all level 1 and 2 studies from 2010 to 2019 was perfomed. American Orthopaedic Foot and Ankle Society and visual analog scale for pain scores were used as outcome variables. Publication bias and risk of bias was assessed with the Cochrane Collaboration tools. The Grading of Recommendations, Assessment, Development and Evaluations system was used to assess the quality of the body of evidence. Heterogeneity was assessed with χ^2 and I^2 statistics.

Results: Fifteen studies were included in the analysis. Nine studies had a high risk of bias. There was 1 study with high quality, 9 with moderate, 2 studies with low, and 3 with very low quality. The pooled estimate for the American Orthopaedic Foot and Ankle Society score demonstrated nonsignificant differences at 1 month (P = .4) and 3 months (P = .076). At 6 months (P = .009) and 12 months (P = .009), it indicated significant differences in favor of PRP. The pooled estimate for visual analog scale demonstrated nonsignificant differences at 1 month (P = .653). At 3 months (P = .0001), 6 months (P = .002), and 12 months (P = .019), it yielded significant differences in favor of PRP.

Conclusion: The results of this systematic review and meta-analysis suggest that PRP is superior to corticosteroid injections for pain control at 3 months and lasts up to 1 year. In the short term, there is no advantage of corticosteroid infiltration. However, the low study quality, high risk of bias, and different protocols for PRP preparation reduce the internal and external validity of these findings, and these results must be viewed with caution.

Keywords: heel pain, plantar fasciitis, PRP, platelet-rich plasma, meta-analysis, systematic review, autologous conditioned plasma (ACP)

There is no current consensus with regard to the most appropriate treatment of plantar fasciitis.[45] This condition is caused by degenerative changes resulting in repetitive microtears of the plantar fascia, which are in turn caused by biomechanical overuse from prolonged standing or running.[5,6,12,18,45] The estimated prevalence of heel pain in the general population ranges from 3% to 7%,[22,36] and it has been reported to account for about 8% of all running-related injuries.[43]

Several nonoperative treatments have been employed, such as stretching, physical therapy, nonsteroidal anti-inflammatory drugs, extracorporeal shock wave therapy, needling and night splints, relative rest, Achilles tendon and plantar fascia stretching exercises, and heel cushions, and all have demonstrated significant benefits within 12 months of treatment.[10]

Various invasive procedures are commonly used to improve the clinical outcomes of plantar fasciitis.[18,24,39] For example, infiltration with corticosteroids is effective but provides only short-term pain relief with disappointing long-term results.[39,42] This procedure is also associated with complications, including localized infection, fat pad atrophy, and plantar fascia rupture.[24,42] Furthermore, the evidence from histopathologic studies has failed to demonstrate any inflammatory process in plantar fasciitis, calling into question the rationale for the use of corticosteroids.[26,52]

In recent years, platelet-rich plasma (PRP) has been investigated as a treatment option for plantar fasciitis. PRP is a bioactive concentrate of various growth factors and cytokines that modulate cell proliferation and differentiation, angiogenesis, and chemotaxis.[12,24] When it is injected into injured tissue, the presumed mode of PRP action is to promote collagen synthesis and enhance tendon and tissue healing.[13,39] Not surprising, long-term pain relief has been reported by a few authors, suggesting that PRP treatment augments a natural healing response.[13,39] In theory, this makes PRP an ideal treatment option, and in fact, several studies have demonstrated very positive treatment outcome effects.[21,24,29,32] However, recent studies have reported conflicting results when PRP injections were compared with steroid injection and other treatment methods, and in some instances they were unable to demonstrate superiority of the PRP treatment.[17-19,27,39,40,47,50]

The purpose of this study was to perform a meta-analysis comparing injection of PRP with corticosteroid injections.

Methods

The guidelines described in the *Cochrane Handbook*[14] were used to conduct this research. The study was designed and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[30]

Eligibility Criteria

All level 1 and level 2 studies were included that compared intralesional infiltration of corticosteroids and PRP in patients with plantar fasciitis from 2010 through 2019. A minimum follow-up of 3 months was required for inclusion, but longer-term follow-up

studies were eligible if the authors reported 3 months of follow-up data. Studies comparing PRP with normal saline or other analgesics were not considered for inclusion, unless they included a treatment group with corticosteroid infiltration; for these studies, the data were extracted only for the treatment arms of interest. Retrospective studies and level 4 case series were excluded. To be included in the meta-analysis, studies had to have at least 1 outcome measure—either the American Orthopaedic Foot and Ankle Society (AOFAS) score or visual analog scale (VAS) for pain—and complete documentation of all data in the tables, main text, or supplementary documentation outlining demographic information and treatment details. The reason for the selection of the short-term follow-up was that injection therapy in general has only short-term effects.[32] Moreover, growth factors and cytokines are released within 1 hour, which reduces the likelihood of long-term effects.[12] However, if the studies included longer-term data, pooling was performed, and these data were meta-analyzed.

Abstracts or conference proceedings, case reports, and in vitro and in vivo basic science studies were excluded. It is acknowledged that the omission of these "gray" data sources can result in publication bias.

Literature Research

A systematic review of the literature was performed to identify all publications in English and German reporting on injections for the treatment of plantar fasciitis. The databases Medline, Embase, Scopus, and Google Scholar were systemically searched with the following terms and Boolean operators: "PRP" AND/OR "platelet plasma" AND/OR "cortisone" AND/OR "corticosteroid"; AND/OR "injection" AND/OR "infiltration" AND/OR "heel pain" AND/OR "plantar fasciitis." Two reviewers conducted independent title and abstract screening. Disagreements between reviewers were resolved by consensus, and if no consensus was reached, they were carried forward to the full-text review. All eligible articles were manually cross-referenced to ensure that other potential studies were included.

Data Extraction and Quality Assessment

An electronic data extraction form was used to obtain the following data from each article: age, sex, level of evidence, length of follow-up, disease duration, PRP and steroid preparation and injection technique, outcome scores, country, and sample size. The senior author independently completed data extraction, and a second reviewer verified the data.

Risk of bias was assessed with the Cochrane Collaboration Risk of Bias Tool.[14] The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used by the senior author (E.H.) to assess the quality of the body of evidence for each outcome measure; a second reviewer (K.T.) verified the assessments.[14] The recommendations from the *Cochrane Handbook* were followed, and studies were downgraded if there were limitations in the design, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high probability of publication bias. All institutional and author information was concealed to the second reviewer to reduce reviewer bias. Any disagreement between reviewers was resolved by consensus and/or arbitration between the senior authors (E.H., K.T.).

Statistical Analysis

Interobserver differences for study eligibility and risk of bias were measured with Cohen kappa coefficient. Heterogeneity of the data was assessed with χ^2 and I^2 statistics. Outcomes

were pooled with a random effects model if the I^2 statistic was >50%; however, if it was <25%, then a fixed effect model was utilized. Similar improvements in outcome scores were calculated from baseline scores and pooled. Subgroup analysis for AOFAS and VAS for the same time period and different follow-up intervals was performed if >3 studies utilized these scores. If standard deviations were not reported, the standard deviation was calculated per the following formula: SD = maximum – minimum / 4. Hozo et al[15] showed that this formula reliably provides a good estimate of the standard deviation. All tests of significance were 2-tailed, and an α of <.05 was considered significant. Publication bias was assessed with funnel plots and the Egger test. Funnel and forest plots and all statistical analyses were performed with STATA SE (v 12.0; StataCorp) for Windows and the Comprehensive Meta-analysis software package (Version 3; Biostat Inc).

Results

Study Selection and Characteristics

The initial literature search identified 1496 studies for consideration. Of those, 714 were excluded for duplication, and the remaining 763 were checked for eligibility. Another 471 studies were excluded due to not fitting the eligibility criteria, and after abstract review, the full text of 22 studies was examined. Only 15 studies ultimately met all of the eligibility criteria and were included in the analysis (Figure 1).††

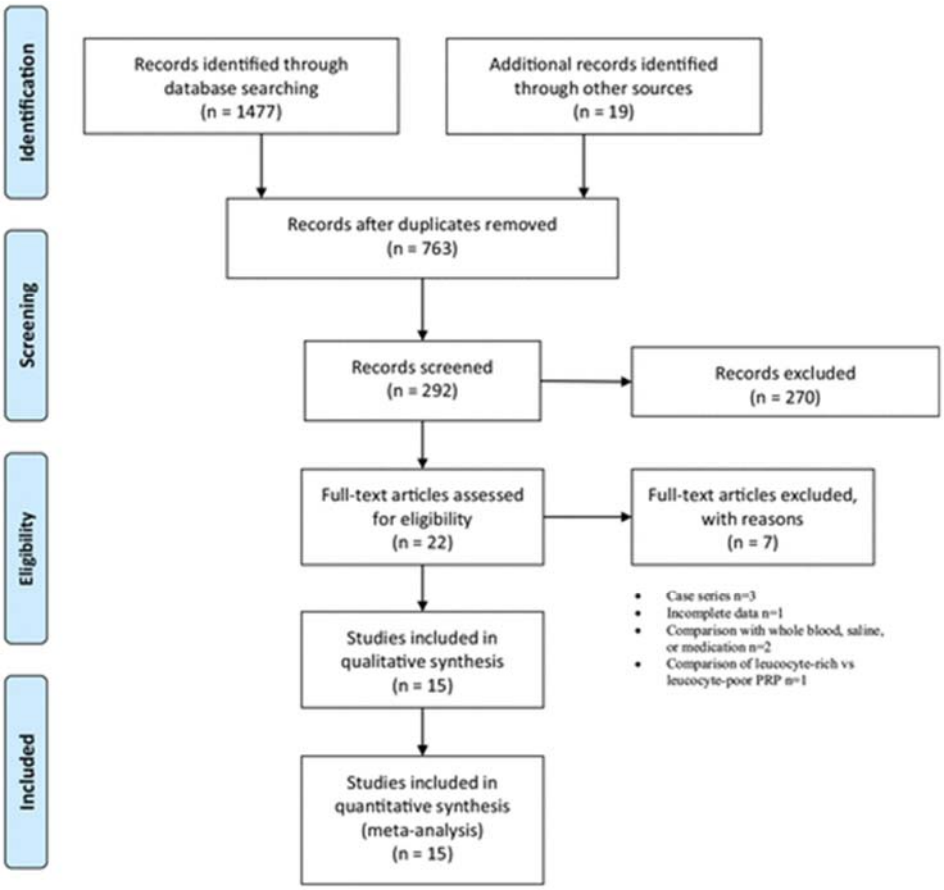

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. From the initial 1496 records, 15 studies were included. PRP, platelet-rich plasma.

TABLE 1
Summary of the Study Characteristics[a]

First Author	LOE	Country	PRP; Steroid			Follow-up	Mean Disease Duration, mo	PRP Preparation	Steroid
			Patients, No.	Mean Age, y	Sex, Male: Female, No.				
Aksahin (2012)[3]	3	Turkey	30; 30	46.4; 45.7	12:18; 13:17	3 wk, 6 mo	8.6-9.4	25 mL, blood. 15 min at 1800 rpm. 10 min at 3500 rpm. Dose: 3 mL, PRP. 2 mL, 2% prilocaine. Blind injection.	2 mL, methylprednisolone (40 mg). 2 mL, 2% prilocaine. Blind injection.
Tiwari (2013)[44]	3	India	30; 30	All >18	14:16; 13:17	1, 3 mo	Not reported	30-50 mL, blood (PRP Fast System; BIO). 5 min at 3200 rpm. Dose: 5 mL, PRP. Blind injection.	1 mL, methylprednisolone (40 mg). Blind injection.
Monto (2014)[31]	2	US	20; 20	51; 59	8:12; 9:11	3, 6, 12, 24 mo	4	27 mL, blood. 12 min at 2400 rpm. Dose: 3 mL, PRP. Ultrasound guided.	40 mg, Depo-Medrol (Pharmacia & Upjohn Co). 6 mL, 0.5% bupivacaine. Ultrasound guided.
Say (2014)[35]	2	Turkey	25; 25	47; 48.6	5:20; 6:19	3 mo	3	30 mL, blood. 8 min at 1800 rpm. Dose: 2.5 mL, PRP. Blind injection.	1 mL, methylprednisolone (40 mg). 1 mL, prilocaine. Blind injection.
Jain (2015)[16]	3	UK	24; 22	55.6; 55.6	8:16; 8:14	3, 6, 12 mo	Not reported	27 mL, blood. 3 mL, sodium citrate (GPSIII; Biomet). 15 min at 3200 rpm. Dose: 2.5 mL, PRP. Blind injection.	40 mg, triamcinolone. 40 mg, levobupivacaine. Blind injection.
Sherpy (2016)[38]	1	Egypt	25; 25	37.5; 38.5	2:23; 0:25	6 wk, 3 mo	7.2-7.6	10 mL, blood. 15 min at 1800 rpm. 10 min at 3500 rpm. Dose: not reported. Blind injection.	40 mg, triamcinolone. 1 mL, mepivacaine. Blind injection.
Mahindra (2016)[27]	1	India	25; 25	30.7; 33.9	12:13; 11:14	3 wk, 3 mo	3	27 mL, blood. 3 mL, citrate dextrose. 12 min at 3200 rpm. Dose: 3 mL, PRP. Blind injection.	2 mL, methylprednisolone (40 mg). Blind injection.
Shetty (2014)[40]	3	India	30; 30	34; 39.2	11:19; 13:17	3 mo	>3	54 mL, blood. 6 mL, citrate dextrose. 14 min (rpm not reported). Dose: 8 mL, PRP. Blind injection.	40, mg triamcinolone. 3 mL, lignocaine (2%). Blind injection.
Acosta-Olivo (2017)[1]	1	Mexico	15; 15	44.8; 44.8	3:11; 3:11	1, 2, 3, 4 mo	>3	40 mL, blood. 3.8% sodium citrate. 10 min at 1800 rpm, then 12 min at 3400 rpm. Dose: 3 mL, PRP. Blind injection.	8 mg, dexamethasone. 2 mL, lignocaine. Blind injection.
Jain (2018)[17]	3	UK	24; 22	55.6; 55.6	8:16; 8:14	1, 3, 6 mo	Not reported	27 mL, blood. 3 mL, sodium citrate. 10 min at 1300 rpm. 10 min at 3500 rpm. Dose: 3 mL, PRP. Blind injection.	2 mL, methylprednisolone (40 mg). 2 mL, 2% lidocaine. Blind injection.
Ugurlar (2018)[45]	1	Turkey	39; 40	38.4; 40.1	19:20; 17:23	1, 3, 6, 12, 24, 36 mo	13.9-14.5	15 mL, blood. 5 min at 1500 rpm (ACP; Arthrex). Dose: 5 mL, PRP. Ultrasound guided.	1 mL, betamethasone (40 mg). 2 mL, bupivacaine (10 mg). Ultrasound guided.
Upadhyay (2018)[46]	2	India	70; 70	46; 21 to >60	41:99	1, 3, 6 mo	4	10 mL, blood. 15 min at 1500 rpm. Dose: 2 mL, PRP. Blind injection.	1 mL, methylprednisolone (40 mg). 3 mL, 1% lidocaine. Blind injection.
Jimenez-Perez (2019)[18]	3	Spain	20; 20	53.7; 55.1	5:15; 6:14	6, 12 mo	>6	20 mL, blood. 3.8% sodium citrate. 8 min at 1800. Dose: 4 mL, PRP. Ultrasound guided.	2 mL, methylprednisolone (40 mg). Ultrasound guided.
Shetty (2019)[39]	2	India	30; 30	44.6	41:49	3 wk; 3, 6, 12, 18 mo	6.8	Blood (mL not reported). Standard double centrifugation (settings not reported). Dose: 2 mL, PRP; 1 mL, 1% lidocaine. Blind injection.	2 mL, methylprednisolone (80 mg). 1 mL, 1% lidocaine. Blind injection.
Peerbooms (2019)[33]	1	the Netherlands	63; 52	50.7; 47.5	15:48; 18:34	6, 12 mo	>6	55 mL, blood. 5 mL, sodium citrate (GPSIII; Biomet). 15 min at 3200 rpm. Dose: 5 mL, PRP. Blind injection.	1 mL, triamcinolone (40 mg). Bupivacaine Blind injection.

[a]ACP, autologous conditioned plasma; PRP, platelet-rich plasma.

Overall agreement between the reviewers for final eligibility was excellent (kappa, 0.92; 95% CI, 0.88-0.95). All 15 studies were published in English between 2012 and 2019, with a cumulative 811 cases. A total of 457 patients were treated with PRP and 354 with corticosteroid infiltration. The study characteristics are summarized in Table 1.

Risk of Bias and Quality Assessment

The findings of the risk of bias assessment are summarized in Figure 2.

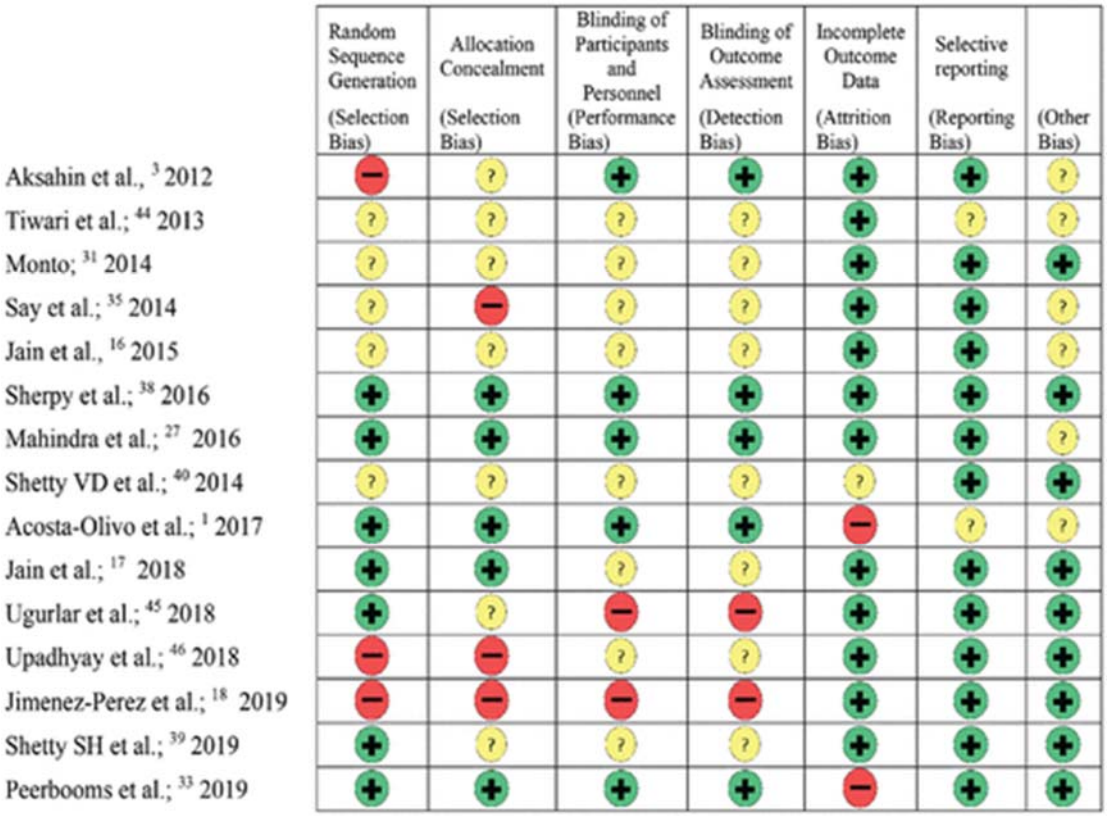

Figure 2. Risk of bias. (+) Indicates high risk of bias; (?) indicates unclear risk of bias; (−) indicates low risk of bias.

Nine studies had a high risk of bias.[1,3,18,33,35,44-46] These biases were related to poor or unclear randomization generation and allocation concealment. The *Cochrane Handbook*[14] clearly outlines that a high risk of bias reduces the confidence in the estimate of the effect, and as the proportion of studies with high risk is 60%, the risk of bias across all studies must be considered high and is sufficient to affect the interpretation of the overall results. Publication bias, or studies with positive findings being more likely to be published (and tending to be published faster) than studies with negative findings, was detected for VAS and AOFAS pooling at different time points. For VAS, the funnel plot was symmetric only at 6 months; however, Egger regression intercept (intercept, –19.87; $t = 4.35$; $P = .003$) suggests publication bias. Egger regression intercepts for VAS at 1 month (intercept, –14.741; $t = 0.46$; $P = .17$), 3 months (intercept, –6.11; $t = 0.46$; $P = .65$), and 12 months (intercept, –12.93; $t = 3.93$; $P = .081$) were negative, and despite the lack of statistical significance, this suggests funnel plot asymmetry and publication bias. The funnel plots for AOFAS at all time points were symmetrical, and Egger regression intercepts at 1 month (intercept, 52.31; $t =$

2.17; P = .11), 3 months (intercept, 5.65; t = 1.59; P = .17), 6 months (intercept, 15.3; t = 2.09; P = .1), and 12 months (intercept, 12.44; t = 1.98; P = .29) were positive and nonsignificant, strongly suggesting a higher level of test accuracy and a lack of publication bias (Appendix Figure A1, available in the online version of this article).

Ten studies were initially defined as high quality[‡‡] and the remaining 5 studies[3,16,35,40,44] as moderate quality (Table 2).[14] All but 2 studies[1,33] were downgraded for imprecision of results; all 13 of these studies failed to provide an a priori sample size calculation and report the 95% CIs. Five studies[3,16,18,40,44] were downgraded for limitations in the study design with regard to being quasi randomized control trials.

TABLE 2
Quality Assessment per the Cochrane GRADE System[a]

	Quality of Evidence				
First Author	Initial	Final	Limitations in Study Design	Imprecision of Results	Increased Quality of Evidence
Aksahin (2012)[3]	Moderate	Very low	Quasi RCT, automatic downgrade	No sample size calculation, 95% CI missing	
Tiwari (2013)[44]	Moderate	Very low	Quasi RCT, automatic downgrade	No sample size calculation, 95% CI missing	
Monto (2014)[31]	High	Moderate	High risk of bias	No sample size calculation, 95% CI missing	Large magnitude effect
Say (2014)[35]	Moderate	Moderate		No sample size calculation, 95% CI missing	Large magnitude effect
Jain (2015)[16]	Moderate	Very low	Quasi RCT, automatic downgrade; high risk of bias	No sample size calculation, 95% CI missing	
Sherpy (2016)[38]	High	Moderate		No sample size calculation, 95% CI missing	
Mahindra (2016)[27]	High	Moderate		No sample size calculation, 95% CI missing	
Shetty (2014)[40]	Moderate	Low	Quasi RCT, automatic downgrade; high risk of bias	No sample size calculation, 95% CI missing	Large magnitude effect
Acosta-Olivo (2017)[1]	High	High			
Jain (2018)[17]	High	Moderate		No sample size calculation, 95% CI missing	
Ugurlar (2018)[45]	High	Low	Moderate risk of bias	No sample size calculation, 95% CI missing	
Upadhyay (2018)[46]	High	Moderate	High risk of bias	No sample size calculation, 95% CI missing	Large magnitude effect
Jimenez-Perez (2019)[18]	High	Moderate	Quasi RCT, automatic downgrade; high risk of bias	No sample size calculation, 95% CI missing	Large magnitude effect
Shetty (2019)[39]	High	Moderate		No sample size calculation, 95% CI missing	
Peerbooms (2019)[33]	High	Moderate	Loss to follow-up 33%		

[a]Three aspects of the Cochrane assessment were negative across all studies: inconsistency of results, indirectness of evidence, and publication bias. RCT, randomized controlled trial.

The GRADE criteria were used to determine which studies should be downgraded.[14] Five studies[16,18,31,40,46] were downgraded because of a high risk of bias, and 1 study[45] was downgraded because of a moderate risk of bias. One study[33] reported a loss of follow-up of 33% and was downgraded because of limitations in the study design. In 5 studies,[18,31,35,40,46] a large magnitude effect was observed, and these studies were upgraded 1 level.[14] As a result, there was only 1 study with high-quality evidence,[1] 9 studies with moderate quality, [§§] 2 studies[40,45] with low quality, and 3 studies[3,16,44] with very low quality.

The clinical outcomes for all studies are summarized in Table 3. Five studies[1,27,33,35,46] reported the 1-month results for the AOFAS score. The pooled estimate for these studies demonstrated nonsignificant differences between the groups (standard mean difference [SMD], 0.982; 95% CI, –1.302 to 3.265; P = .4; I^2 = 98%) (Figure 3).

TABLE 3
Clinical Outcomes for AOFAS and VAS[a]

	Mean ± SD or Mean (Range)	
First Author: LOE	PRP	Steroid
Aksahin (2012)[3]: 3		
VAS		
1 mo	5.6 ± 1.64	4.4 ± 2.09
6 mo	3.93 ± 2.02	3.4 ± 2.32
Tiwari (2013)[44]: 3		
VAS		
1 mo	2.1 ± 1	2.7 ± 0.75
3 mo	2.0 ± 0.45	2.8 ± 0.76
6 mo	2.0 ± 0.45	2.8 ± 0.76
Monto (2014)[31]: 2		
AOFAS		
3 mo	95 (88-100)	81 (56-90)
6 mo	94 (87-100)	74 (54-87)
12 mo	94 (86-100)	58 (45-77)
24 mo	92 (77-100)	56 (30-75)
Say (2014)[35]: 2		
VAS		
6 wk	2.4 ± 0.8	4 ± 1.1
6 mo	1 ± 0.8	2.6 ± 0.9
AOFAS		
6 wk	85.5 ± 4.2	75.3 ± 4.8
6 mo	80.3 ± 4.7	80.3 ± 4.7
Jain (2015)[16]: 3		
VAS		
3 mo	3.5 ± 3.3	2.83 ± 3.44
6 mo	3.7 ± 3.58	3.28 ± 3.55
12 mo	3.3 ± 3.69	5.33 ± 3.47
AOFAS		
3 mo	83.7 ± 15.33	86.37 ± 17.15
6 mo	88.53 ± 11.84	83.8 ± 18.3
12 mo	88.5 ± 13.42	75.07 ± 20.13
Sherpy (2016)[38]: 1		
VAS		
6 wk	1.5 (0-10)	4 (0-9)
3 mo	0	1 (0-9)
Mahindra (2016)[27]: 1		
VAS		
1 mo	3.76 ± 1.53	2.84 ± 1.46
3 mo	2.52 ± 1.71	3.64 ± 1.62
AOFAS		
1 mo	83.92 ± 12.12	86.6 ± 6.77
3 mo	88.24 ± 8.76	81.32 ± 6.39
Shetty (2014)[40]: 3		
VAS, 3 mo	1.8 ± 1.12	4.27 ± 1.41
AOFAS, 3 mo	83.1 ± 10.11	70.5 ± 9.19
Acosta-Olivo (2017)[1]: 1		
VAS		
1 mo	2.42 ± 1.45	2.21 ± 1.69
3 mo	0.62 ± 0.73	0.53 ± 1.06
AOFAS		
1 mo	85.9 ± 6.7	85.9 ± 6.7
3 mo	94.4 ± 5.7	96.8 ± 5.4
Jain (2018)[17]: 3		
VAS		
1 mo	6.5 ± 1.7	5.7 ± 2.7
3 mo	5.0 ± 2.5	4.3 ± 2.8
6 mo	3.0 ± 2.6	3.3 ± 2.8
Ugurlar (2018)[45]: 1		
VAS		
1 mo	33.4 ± 29.9	2.7 ± 9.4
3 mo	12.9 ± 11.1	26.1 ± 24.2
6 mo	12.8 ± 11.6	24.4 ± 23.9
12 mo	24.8 ± 22.9	30.8 ± 29.9
24 mo	29.3 ± 28.4	30.2 ± 29
36 mo	32.2 ± 30.9	32.0 ± 30.8
Upadhyay (2018)[46]: 2		
VAS		
1 mo	4.52 ± 0.78	2.46 ± 0.74
3 mo	3.06 ± 0.86	6.46 ± 0.9
6 mo	1.41 ± 0.49	6.88 ± 0.68
AOFAS		
1 mo	79.7 ± 6.4	88.4 ± 4.9
3 mo	85.0 ± 0	85.5 ± 3.6
6 mo	95 ± 0	56.8 ± 10
Jimenez-Perez (2019)[18]: 3		
VAS		
6 mo	2	5.3
12 mo	1.9	6.05
AOFAS, 6 mo	92.1	49.75
Shetty (2019)[39]: 2		
VAS		
1 mo	8	6
3 mo	5	5
6 mo	3	5
12 mo	2	4
18 mo	2	4
Peerbooms (2019)[33]: 1		
AOFAS		
1 mo	65 ± 5	73 ± 3
3 mo	68 ± 5	67 ± 4
6 mo	70 ± 4	68 ± 4
12 mo	80 ± 4	67 ± 6

[a]AOFAS, American Orthopaedic Foot and Ankle Society; LOE, level of evidence; PRP, platelet-rich plasma; VAS, visual analog scale.

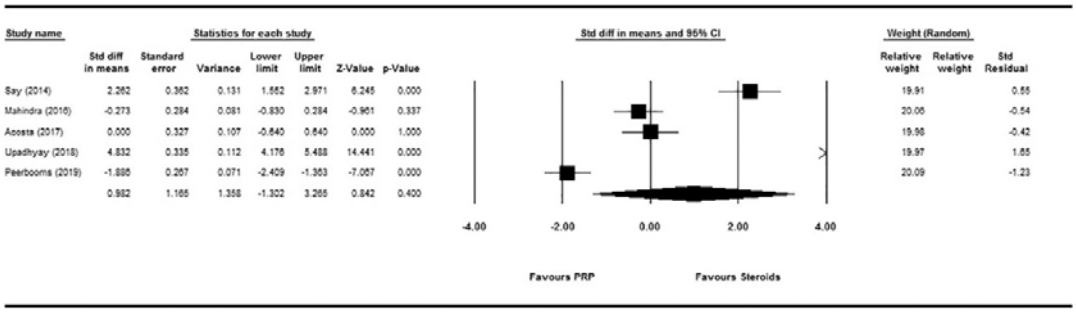

Figure 3. Forest plot for American Orthopaedic Foot and Ankle Society score at 1 month. The pooled estimate for all studies demonstrated no significant differences (P = .4).

Seven studies[1,16,27,31,33,40,46] reported the 3-month results for the AOFAS score. The pooled estimate (random effects model) for these studies demonstrated nonsignificant differences in favor of PRP (SMD, 0.532; 95% CI, –0.055 to 1.120; P = .076; I^2 = 88%) (Figure 4).

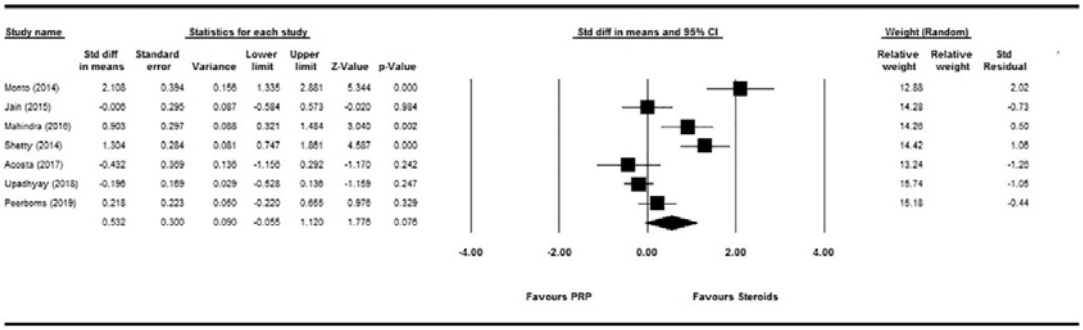

Figure 4. Forest plot for American Orthopaedic Foot and Ankle Society score at 3 months. The pooled estimate for all studies demonstrated no significant differences but favored platelet-rich plasma (PRP) (P = .076).

Six studies[16,18,31,33,35,46] reported the 6-month results for the AOFAS score. The pooled estimate (random effects model) for these studies demonstrated significant differences in favor of PRP (SMD, −2.510; 95% CI, [−4.397 to −0.622]; P = .009; I^2 = 97%) (Figure 5).

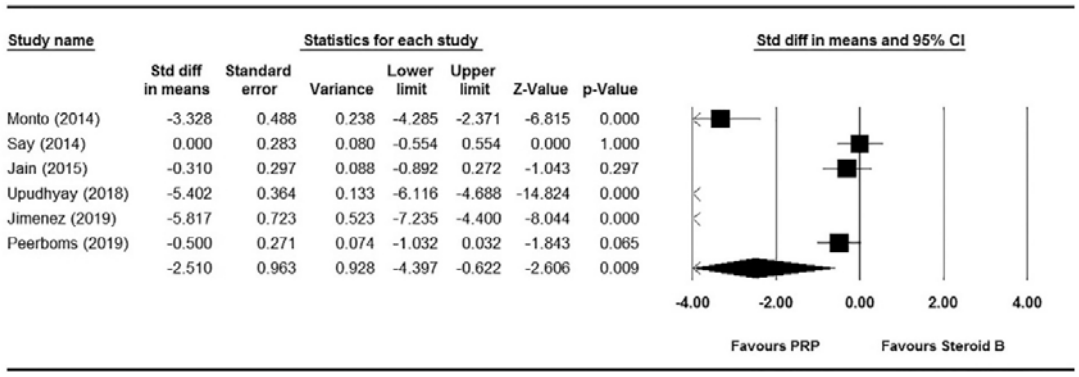

Figure 5. Forest plot for American Orthopaedic Foot and Ankle Society score at 6 months. The pooled estimate for all studies demonstrated significant differences in favor of platelet-rich plasma (PRP) (P = .009).

Three studies[16,31,33] reported the 12-month results for the AOFAS score. The pooled estimate (random effects model) for these studies also demonstrated significant differences in favor of PRP (SMD, −2.728; 95% CI, [−4.782 to −0.674]; P = .009; I^2 = 95%) (Figure 6).

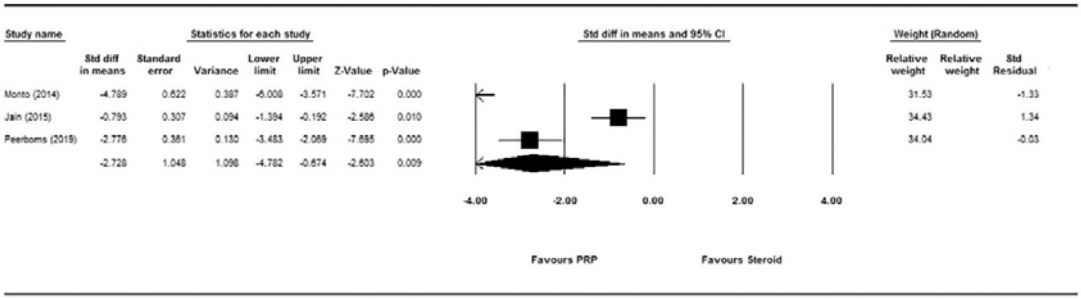

Figure 6. Forest plot for American Orthopaedic Foot and Ankle Society score at 12 months. The pooled estimate for all studies demonstrated significant differences in favor of platelet-rich plasma (PRP) (P = .009).

Ten studies[ll] reported the 1-month results for the VAS score. The pooled estimate (random effects model) for these studies demonstrated nonsignificant differences between the groups (SMD, −0.180; 95% CI, −0.606 to −0.966; P = .653; I^2 = 95%) (Figure 7).

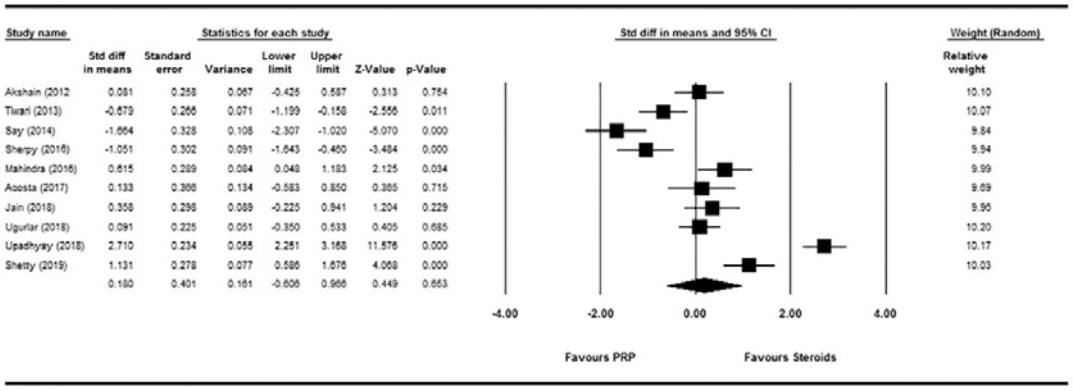

Figure 7. Forest plot for visual analog scale at 1 month. The pooled estimate for all studies demonstrated no significant differences (P = .653).

Ten studies[1,16,17,27,38-40,44-46] reported the 3-month results for the VAS score. The pooled estimate (fixed effects model) for these studies demonstrated significant differences in favor of PRP (SMD, −0.843; 95% CI, −1.021 to −0.665; P = .0001; I^2 = 11%) (Figure 8).

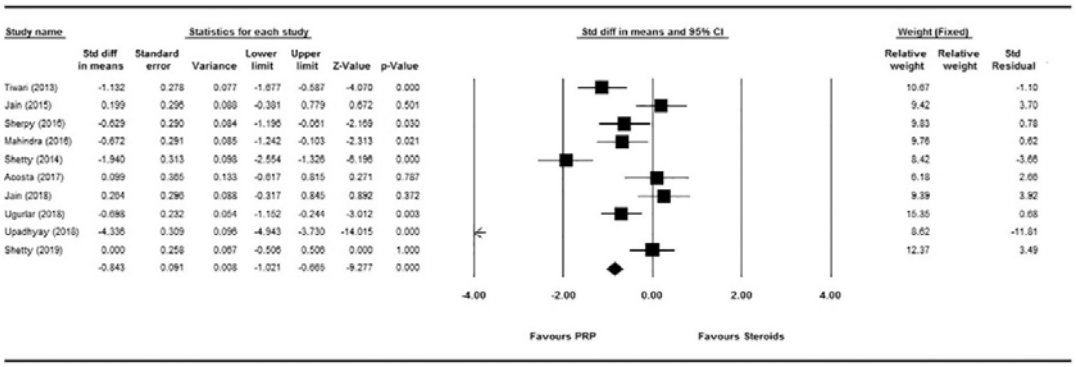

Figure 8. Forest plot for visual analog scale at 3 months. The pooled estimate for all studies demonstrated significant differences in favor of platelet-rich plasma (PRP) (*P* = .0001).

Nine studies[3,16-18,35,39,44-46] reported the 6-month results for the VAS score. The pooled estimate (random effects model) for these studies also demonstrated significant differences in favor of PRP (SMD, −1.983; 95% CI, −3.228 to −0.738; *P* = .002; I^2 = 97%) (Figure 9).

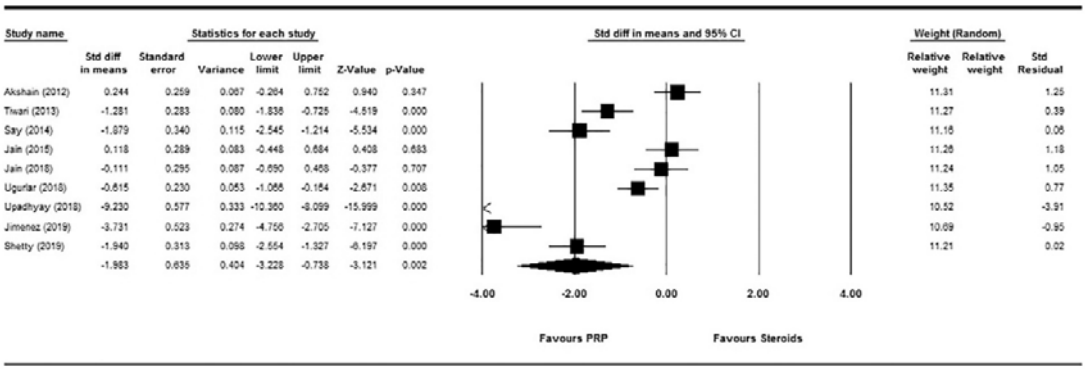

Figure 9. Forest plot for visual analog scale at 6 months. The pooled estimate for all studies demonstrated significant differences in favor of platelet-rich plasma (PRP) (*P* = .002).

Four studies[16,18,39,45] reported the 12-month results for the VAS score. The pooled estimate (random effects model) for these studies again demonstrated significant differences in favor of PRP (SMD, −1.708; 95% CI, −3.133 to −0.283; *P* = .019; I^2 = 95%) (Figure 10).

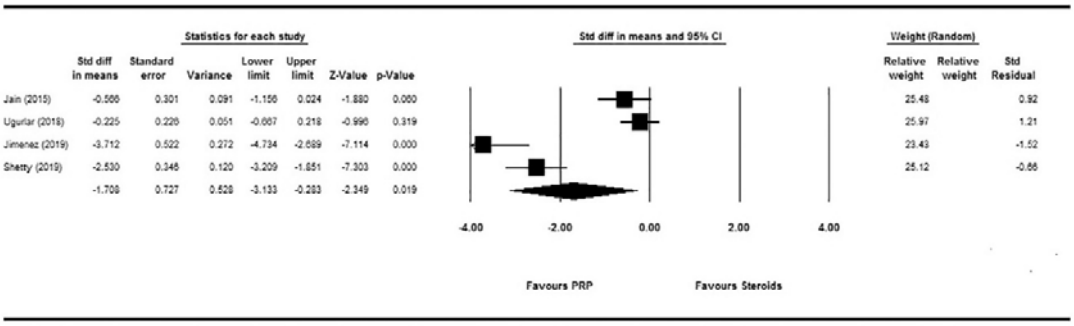

Figure 10. Forest plot for visual analog scale at 12 months. The pooled estimate for all studies demonstrated significant differences in favor of platelet-rich plasma (PRP) (*P* = .019).

Discussion

The results of this meta-analysis suggest that PRP has no advantage over steroid injections within the first month of treatment but is superior to steroids with regard to pain (VAS) between 3 and 12 months and function (AOFAS) between 6 and 12 months after an injection. However, the AOFAS scoring system includes elements of pain assessment, which contribute to 40% of the final score.[34] Functional assessment includes activity limitations, walking distance, walking surfaces, gait abnormality, motion, stability, and alignment. When the effect of injection therapy on the reduction of symptoms in patients with plantar fasciitis is being assessed, it is unlikely that walking surfaces, gait abnormality, motion, stability, or alignment has a large influence on the final outcome score. Yoo et al[51] could not demonstrate any significant changes in gait and pain relief, whereas Chang et al[8] reported that patients

compensate by increasing medial forefoot pressure and decreasing propulsive ground-reaction forces during the initial stance. These facts suggest that the AOFAS might be mainly assessing pain and not really functional outcomes and, in that sense, is very similar to the VAS.

Ling and Wang[24] already completed a meta-analysis comparing the effects of PRP with other treatment modalities. Ten randomized controlled trials were included in their study, of which 5 were in our meta-analysis, and they demonstrated that PRP was as effective as other treatments in reducing pain and improving function.[24] Preceding this, Yang et al[50] completed a meta-analysis including 9 randomized controlled trials, of which 7 were in our meta-analysis, and they concluded that there is limited evidence to support the superiority of PRP over steroid treatment. Singh et al[41] published a systematic review and meta-analysis of 10 studies published between 2011 and 2016 comparing PRP with corticosteroid injections, of which 8 studies were in our meta-analysis, and their study demonstrated that PRP was associated with improvement of pain at 3 months. However, since the publication of these earlier meta-analyses, 6 more randomized controlled trials[17,18,33,39,45,46] have been added to the body of literature. When these 6 studies are added to the previous publications, meta-analysis now supports the superiority of PRP over corticosteroids but only for treatment effects >3 months.

Unfortunately, 9 publications included in this investigation had a high risk of bias[1,3,18,31,35,40,44-46] and made up 60% of the analyzed studies. This clearly reduces confidence in the effect estimate and most likely affects the intrinsic validity. With the exception of Acosta-Olivo et al,[1] all other studies were downgraded to moderate, low, or very low quality of evidence. Specifically, 60% of the studies[¶¶] were downgraded to moderate quality, and 33% were downgraded to low or very low quality.[3,16,40,44,45] According to the GRADE system, the results are to be viewed with caution, as there is only moderate and limited confidence in the effect estimate, and there is a possibility that the true effect is potentially substantially different.[14] Regrettably, these concerns are confirmed by the wide 95% CIs for all comparisons, except AOFAS and VAS at 3 months. Nevertheless, the narrow confidence intervals here strongly suggest that the true effect lies close to the estimate of the effect and strongly supports the superiority of PRP over corticosteroid injections.

It is well-demonstrated that corticosteroid injections for plantar fasciitis have only short-term effects, lasting up to 3 months.[3,49] It is therefore not surprising that this meta- analysis also found that the treatment effect of steroids are substantially reduced at 6 and 12 months, given that all studies utilized a single-injection protocol for corticosteroid and PRP. In contrast, the prolonged effect of PRP cannot be fully explained with the current available evidence—especially since studies have reported that 70% of the growth factors are released from the platelets within 10 minutes and 100% within 1 hour,[10] and the half-life of most plasma and platelet released cytokines is <2 hours.[54] Moreover, several studies have suggested that the inhibition of catabolic and inflammatory cytokines, such as IL-1β and TNF-α, fibroblast growth factor, and transforming growth factor β, are the main molecular effects of PRP applications.[7,9,20,37] Furthermore, the principal action of these proteins is to act as signaling molecules, mediating cell responses by binding to specific cell receptors to initiate the healing process.[53,54] As such, PRP may have a profound influence locally by downregulating proinflammatory cytokine receptors and upregulating endogenous anti-inflammatory cytokines, effectively reducing pain over a prolonged period[53] and aiding in the tissue-healing process. This could be an indication that prolonged growth factor activity is not required and that it is needed only for the first several hours to activate specific molecular pathways.

Unfortunately, PRP preparation and isolation methods are highly inconsistent, and this lack of standardization most likely has a profound effect on treatment efficacy.[4] Therefore, it is not surprising that the results of PRP treatment are conflicting, because currently there is no clear standard regarding how to prepare and evaluate PRP or how to report efficacy for treatment.[4] The "quality" of PRP is also highly dependent on several other physiological factors: circadian patterns, food or fasting states, physical exercise and stress, and medication may all influence the behavior of PRP.[28,54] These facts are reflected in the studies of this meta-analysis, all of which had different protocols for PRP production. For example, the amounts of blood drawn ranged from 10 to 55 mL, centrifugation speeds ranged from 1500 to 3500 rpm, and 4 studies used 2 consecutive centrifugations. In addition, several preparations and protocols for corticosteroid injections were used among studies. These factors introduced within- and between-study biases, further reducing the value of the results.

The limitations of this meta-analysis are directly related to those of the included studies and have already been highlighted. The high risk of bias, moderate to low study quality, publication bias, discrepancies in the preparation protocols for PRP, and differences in the dosage and preparations for the corticosteroid arm all substantially decrease the external validity and therefore reduce the value of any meta-analysis. Three studies did not report the duration of symptoms and possibly introduced reporting bias.[16,17,44] The total number of patients in these 3 studies was 152 and constituted 19% of the pooled cases. If the patients in these 3 studies had chronic cases with a considerably longer mean duration of symptoms as compared with the other studies, there is the possibility of reporting bias. However, the direction and size of treatment effects were similar to the other studies, making selection and reporting bias unlikely. The AOFAS score has been criticized for the lack of validation, and a position statement by the AOFAS has not recommended the use of this clinical scoring system.[34] Interestingly, the AOFAS rating system was successfully translated into several languages and found to be reliable and valid.[2,11,23,48] The main criticism is that 40 of the 100 points are subjectively assessed by staff, posing a significant risk for researcher bias.[25]

Conclusion

The results of this systematic review and meta-analysis suggest that PRP is superior to corticosteroid injections for pain control at 3 months and lasts up to 1 year. In the short term, there is no advantage of corticosteroid infiltration. However, the low study quality, high risk of bias, and different protocols for PRP preparation all reduce the internal and external validity of these findings, and these results must be viewed with caution.

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††References 1, 3, 16-18, 27, 31, 33, 35, 38-40, 44-46.

‡‡References 1, 17, 18, 27, 31, 33, 38, 39, 45, 46.

§§References 17, 18, 27, 31, 33, 35, 38, 39, 46.

‖References 1, 3, 17, 27, 35, 38, 39, 44-46.

¶¶References 17, 18, 27, 31, 33, 35, 38, 39, 46.

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