Biomedicine & Pharmacotherapy 180 (2024) 117507

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Effectiveness of platelet derivatives in neuropathic pain management: A systematic review

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ARTICLE INFO

Keywords:
Platelet-rich plasma
Neuropathic pain

ABSTRACT

Background: Neuropathic pain (NP) has a considerable impact on the global economic burden and seriously impairs patients' quality of life. Currently there is no evidence-based "effective" treatment and new treatments are needed. Recently, platelet rich plasma (PRP) has emerged as an alternative treatment. Therefore, a systematic review has been conducted to present an evidence-based assessment of the use of PRP in the treatment of NP.
Methods: Randomized studies that investigated the effect of PRP injection on patients with NP compared to alternative treatments or placebo were included. An encompassing search of specific databases, from their inception to April 2024, was performed. The databases were as follows: PubMed, Web of Sciences (MEDLINE) and Cochrane Library. The Cochrane Risk-of-Bias 2 tool was used to assess study methodological quality.
Results: A total of 12 randomized studies with 754 patients with different NP conditions were included in this systematic review. According to the results from the qualitative analysis, PRP injection exerted a positive effect on improving pain intensity on most of the trials (8 out of 12). In the remaining studies, no differences were found. A high safety profile was reported with no serious adverse effects in the analysed patients.
Conclusion: PRP treatment might be an effective therapeutic approach for patients with different neuropathic pain conditions. The efficacy of PRP was not dependant on the aetiology of the underlying disorder; nevertheless, interpretations of the results should be performed cautiously, as for the under-representation of NP conditions.

1. Introduction

Nociceptive pain is the protective physiological reaction to noxious stimuli whose purpose is to avoid potential injury and preserve body integrity [1,2]. On the contrary, neuropathic pain (NP) does not offer any such benefit, losing all its usefulness. The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory nervous system [3]. NP has a considerable impact on the global economic burden and seriously impairs patients' quality of life by causing anxiety, depression, sleep and psychological disorders, as well as physical disability and social dysfunction [4,5]. With the ageing of the global population, NP prevalence is likely to increase.

NP has a complex pathophysiological profile and is beginning to be considered as a distinct clinical multi-aetiology entity [5,6]. NP conditions include, but are not limited to, metabolic diseases, viral infections, nerve compression, nerve trauma, autoimmune diseases, vascular diseases or cancer [7–9]. Despite obvious differences in aetiology, many of these conditions share clinical features including positive symptoms that could be spontaneous (paresthesia and dysesthesia) or stimulus-evoked (hyperalgesia and allodynia), and negative symptoms (sensory deficits) [1,6,10,11]. Therefore, disease-based classification is often insufficient [12]. An important feature of NP is pain in the absence of an identifiable stimulus [13].

Multiple mechanisms are responsible for NP. They involve ectopic activity within the nociceptive pathways as wells as peripheral and central sensitization. Voltage-gated sodium channels contribute largely to ectopic generations of action potentials. Peripheral nociceptor hyperactivity leads to dramatic secondary changes in the spinal cord dorsal horn causing central sensitization that refers to the increasing responsiveness in the central nervous system due to repeated painful inputs [6,9,11,12,14]. Immune system also has an important role. Central sensitization is also driven by neuroinflammation. Nerve damage induces activation of glial cells, such as microglia and astrocytes, in the spinal

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https://doi.org/10.1016/j.biopha.2024.117507
Received 4 July 2024; Received in revised form 28 August 2024; Accepted 25 September 2024
Available online 8 October 2024

cord and brain, increasing the release of pro-inflammatory cytokines and chemokines. In turn, the signal regulation of neurons enhances, thus further promoting central sensitization [9, 15–17].

NP treatment include medications, interventional techniques and psychological approach [10]. Oral medications are often recommended as first-line treatment for NP conditions. In 2015, the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP has provided some recommendations based on a systematic review and meta-analyses of 229 randomized double-blind studies of oral and topical pharmacotherapy for neuropathic pain. The analysis revealed a strong GRADE recommendation for use and proposal as first line drugs for tricyclic antidepressants (TCA), serotonin-noradrenaline reuptake inhibitor (SNRI) antidepressants, gabapentin, pregabalin, and gabapentin ER/enacarbil in neuropathic pain [5]. Subsequently, Di Stefano et al. [18] conducted another systematic review and meta-analysis. They updated previous knowledge by demonstrating small effect sizes and/or large numbers needed to treat (NNTs) for all compounds used to treat neuropathic pain. The modest efficacy, even for first-line drugs, would suggest the need for novel drug options. Moreover, side effects related to these drugs are common [6,9,13,16]. Therefore, there is still a lack of effective and safe treatments. This has led to attempts to research into new solutions, and this is where regenerative medicine tools may come to the rescue.

In this context, platelet rich plasma (PRP) has been widely applied in different medical fields including dentistry, orthopedic, ophthalmology, dermatology, and gynecology [19–22]. Recently, the use of PRP has gained increasing interest in the field of NP management [23–29]. Based on the consideration that NP is tightly associated with neuroinflammation, the main rationale for using PRP lies in its anti-inflammatory effect [30–33]. Thus, this systematic review was aim at investigating the efficacy and safety of PRP injection for neuropathic pain treatment, through an analysis of the available randomized studies.

2. Material and methods

2.1. Protocol registration and reporting format

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol has been registered in the Open Science Framework (OSF) database with registration doi: https://doi.org/10.17605/OSF.IO/6UWCZ.

2.2. Focus question

This review aimed to answer the following question:

Does PRP injection improve pain intensity in patients with neuropathic pain?

2.3. PICO strategy

The following strategy was constructed according to PICO study design:

- The participants were patients with neuropathic pain.
- The intervention was PRP injection.
- The comparison was alternative treatments or placebo.
- The main outcomes were pain intensity and adverse effects. Other clinical variables such as quality of life, nerve repair, wound healing, symptom severity and functional status and screening and diagnosis of neuropathy were also evaluated.

2.4. Search strategy

The following databases were used for the systematic search from inception to April 2024: PubMed, Web of Sciences (MEDLINE) and Cochrane Library. The following terms were used in the search strategy: ((neuropathic pain) AND ((platelet rich plasma) OR (platelet lysate) OR (platelet rich fibrin))).

2.5. Selection criteria

The inclusion criteria were: (a) patients with neuropathic pain according to the IASP definition [3], (b) intervention of PRP or PRP derivatives for the treatment of neuropathic pain, and (c) randomized studies involving at least 10 patients. The following studies were excluded: (a) articles not published in English or Spanish, (b) reviews, perspectives, letters, case reports, (c) *in vitro* or animals' studies, (d) retrospective studies, (e) duplicates, (f) no completed, recruiting, or cancelled studies, and (g) articles for which the full text was not available.

2.6. Data extraction

Firstly, articles were screened based on the tittle and the abstracts to determine their suitability. Studies that passed this initial evaluation were retrieved for full-text review. For data extraction, an evidence table was created with Microsoft Excel. The following data were included: (a) study characteristics (primary author, year of publication and country), (b) study type, (c) registration number, (d) masking, (e) intervention groups, (f) sample size, (g) neuropathic pain condition, (h) patient characteristics (age and sex), (i) PRP characteristics (type, anticoagulant, centrifugation, presence of leukocyte, platelet concentration, PRP activation, volume, method and site of application, number of doses and frequency), (j) outcome measurements (primary, secondary and follow-up), (k) final outcomes, and (l) adverse events.

2.7. Risk of bias assessment

Studies were evaluated with the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [34]. The assessment involves five domains and the response options for each risk of bias judgement are: low risk of bias, some concerns and high risk of bias.

3. Results

Due to the high heterogeneity of the clinical studies, in terms of pathologies, treatment, follow-up period and methodologic diversity, a meta-analysis and an overall quality of evidence using GRADE approach could not be conducted.

3.1. Study selection

The search strategy yielded a total of 1085 articles from the three databases to which 14 articles were added form other sources. Forty-one studies passed the initial title and abstract evaluation. After an exhaustive full-text screening, 12 studies [35–46] with 754 patients with NP of different aetiology were finally included in this systematic review. Flow chart of the selected studies is depicted in Fig. 1 and detailed information is shown in Tables 1 and 2.

3.2. Study characteristics

All the included articles were single-center randomized studies. Different types of NP conditions were included: carpal tunnel syndrome [35–40], diabetic peripheral neuropathy [41,42], herpes zoster neuralgia [43], leprosy peripheral neuropathy [44], piriformis syndrome [45] and radicular pain due to lumbar disc herniation [46]. Three randomized studies [38–40] compared PRP injections with first-line oral drugs for NP conditions. Placebo injections (saline) were the counter-group in other 3 RCTs [32,37,42]. Anjayani et al. [41] used PPP injection as the alternative treatment to compare PRP with. Although the authors referred to it as a placebo, PPP contains biologically active plasma

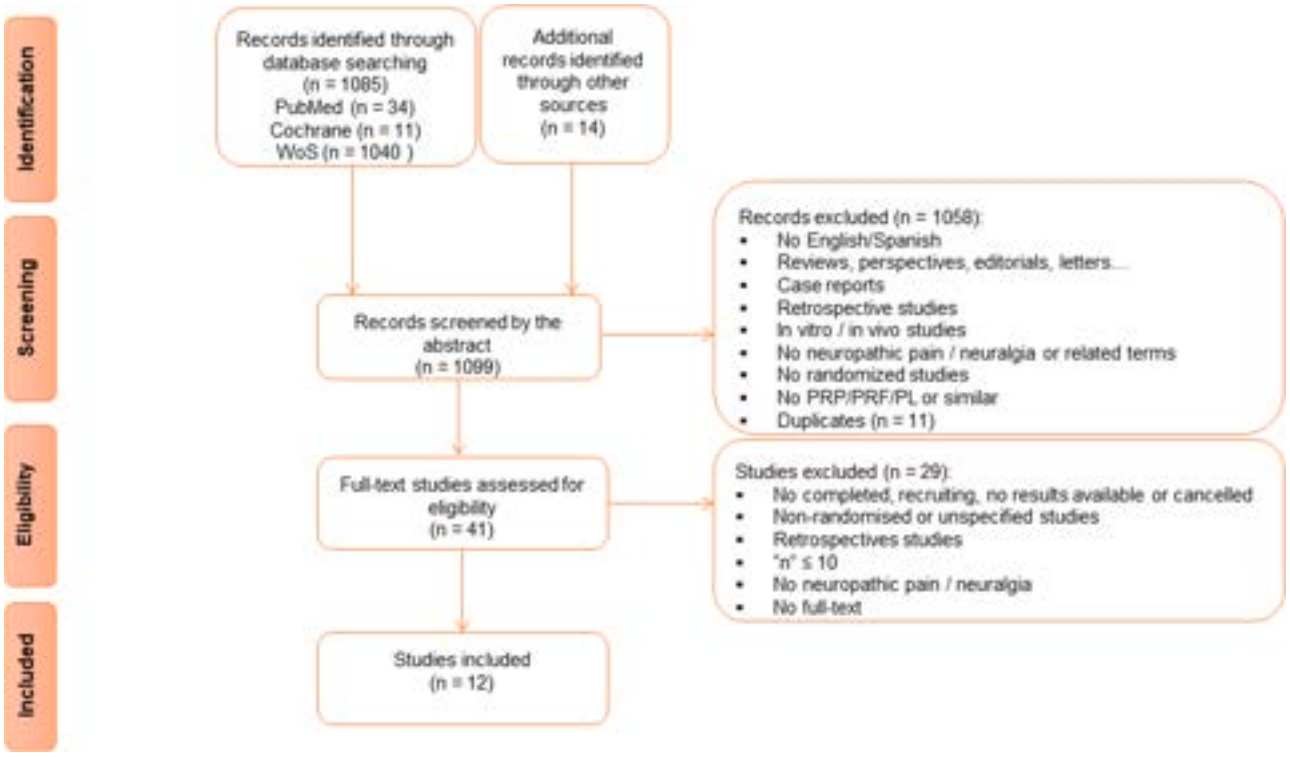

Fig. 1. Flow diagram of the study selection process.

proteins and therefore this designation would not be correct. Trull-Ahuir et al. [36] also compared the effects of administering PRP versus PPP. Finally, conservative treatment (wrist splint) [33,35] or steroid injection [34,43] were also used as controls. Sample size was only calculated in 7 out of the 12 studies [36, 38–40, 42, 44, 46] with a statistical power of 80–90 % at a 5 % significance level, except for Anjayani et al. [44] who did not specify this latter value. The control group in the Raeissadat et al. [36] trial did not meet the calculated sample size, while the remaining studies did.

There was a great variability in the PRP obtaining protocols and in its composition along with a serious lack of information (Table 3). Seven studies detailed the type of anticoagulant used [36–38, 40, 42, 44, 46], and citrate was the one of choice in different presentations. PRP was obtained by double centrifugation in most of the studies [35–37,41,42, 44,46], despite the conditions, such as centrifugal force, speed and time, were completely varied among studies. Regarding cell composition, only 2 articles [36,38] did detail both platelet and leukocyte concentration. Trull-Ahuir et al. [39] described platelet concentration but not leukocyte concentration; however, authors presumed a leukocyte content due to the results usually reported for their commercial PRP obtaining device. The remaining studies did not specify whether leukocytes were included in the PRP, except Chen et al. [40] who used a leukocyte-poor PRP. No information concerning PRP activation was available for 7 articles [35, 36,39,40,44–46]. When information was provided, calcium chloride [37,42], autologous thrombin [38] and spin [41] were used. Zhou et al. [43] evaluated a freshly PRP. The application volume varied from 1 mL to 4 mL in a single dose, except in the case of Anwar et al. [41] who administered 3 PRP injections once a month. Most of the studies performed the PRP injections under ultrasound guidance [35,37,38,40–43, 45,46]. Trull-Ahuir et al. [39] irrigated with PRP by a cannula insertion. On the other hand, Anjayani et al. [44] performed the injection by palpation and Raeissadat et al. [36] did not specify the application method. Reported follow-up differed considerably among the studies, ranging from 1 week to 1 year, with different intermediate periods.

Moreover, overall positive effects were reported for PRP treatment in 9 out of 12 studies. Only Raeissadat et al. [36], Trull-Ahuir et al. [39] and Xu et al. [46] detected no differences compared to the control (Table 4).

3.3. Risk of bias assessment

The risk-of-bias judgement was detailed in Fig. 2. The item of randomization process was judged low in 4 studies [36,37,39,46] that provided both random sequence generation and allocation concealment description. The risk-of-bias judgement was considered as "some concerns" when the allocation sequence concealment [38,40,42,43,45] or the random sequence generation [35] methods were not described. Anwar et al. [41] and Anjayani et al. [44] did not disclose how randomization was conducted except for a statement that the study was randomized, therefore, they were also judged to be a risk of "some concerns". Three trials were judged as low risk regarding deviations from the intended interventions as both participants and the physicians delivering the interventions were blinded. High risk was assigned when there was no masking [36], no blinding was specified [41,43] or neither the patients no the researchers conducting the intervention were blinded [38,42,45,46]. "Some concerns" were considered when the personnel in charge of the interventions were not blinded but patients were [35,37]. The design of some studies and the type of intervention groups being compared [36, 38, 41–43] makes blinding of patients and intervening physicians unfeasible. Five studies [35,36,38,39,45] reported no loss to follow-up, thus considering to be at low risk of bias from missing outcome data. The same judgement was made for three trials [40,42,46] that registered lost to follow-up, but balanced were kept across intervention groups and they still met the sample size criterion. Three studies [41,43,44] had no description of the loss to follow-up and Senna et al. [37] did report lost to follow-up that despite being balanced, there was uncertainty as to whether they would meet the minimum sample size. In all these studies the risk-of-bias judgement was considered as "some concerns". Raeissadat et al. [36] conducted a non-blinded trial, therefore the risk of measurement of the outcome bias was also judged as high. The same high-risk assessment was made when authors did not specify the type of masking [41,43] or when they specified that a

Table 1
General information of the included studies in this systematic review. The data in this table come from the scientific articles themselves, as they are considered to be definitive in the event of discrepancies with what was described in the register. * The trial has been retrospectively registered. ** Authors do not specify units of measurement. *** Standard error. **** Authors stated a prospective, randomized, double-blinded, controlled trial. However, according to the information provided in the manuscript authors conducted a triple-blinded study, as patient, injector and outcome assessor were blinded. *****Too extensive to be specified in this table; check the article directly. ****** Duration of condition was reported in days.

Ref.	Country	Study type	Registration number	Masking	Intervention	Comparator	Neuropathic pain condition	Length of condition (months ± SD)
Malahias 2017 [35]	Greece	RCT	NS	Double-blind (at the follow-up level)	PRP injection	Placebo injection (normal saline)	CTS (mild to moderate)	At least three
Raeissadat 2018 [36]	Iran	RCT	IRCT2017041513442N13*	None	PRP injection + splint	Control (wrist splint)	CTS (mild to moderate)	PRP+splint (13.74 ± 11.5) ** splint (14.13 ± 8.55)**
Senna 2019 [37]	Egypt	RCT	NCT03863873	Double (participant, and outcomes assessor)	PRP injection	Corticosteroid injection	CTS (mild to moderate)	At least three
Wu 2017 [38]	Taiwan	RCT	NCT02539186	Single (Outcomes assessor)	PRP injection	Control: splint	CTS (mild to moderate)	PRP (34.43 ± 5.67)*** splint (30.70 ± 6.03)***
Trull-Ahuir 2020 [39]	Spain	RCT	NCT03548259	Triple (participant, surgeon, outcomes assessor)	PRP injection	PPP injection	CTS (mild to extreme)	NS
Chen 2021 [40]	Taiwan	RCT	NCT03184688	Double****	PRP injection	Control: normal saline injection	CTS (moderate to severe)	PRP (35.3 ± 7.4)*** saline (36.2 ± 7.8)***
Anwar 2024 [41]	Pakistan	RCT	NS	NS	PRP injection	Control: pregabalin PO	DPN	NS
Hassanien 2020 [42]	Egypt	RCT	NCT03601494	Single (Outcomes assessor)	PRP injection in addition to medical treatment	Control: medical treatment (vit B complex, αlipoic acid, SSRI and pregabalin) PO	DPN	At least six
Zhou 2022 [43]	China	Randomized study	NS	NS	PRP injection on the basis of the control group	Control: drugs PO*****	HZN	PRP + drugs (14.6 ± 7.8) ****** drugs (15.2 ± 7.1)******
Anjayani 2014 [44]	Indonesia	RCT	NS	Double	PRP injection	PPP injection	LPN	NS
Öztürk 2022 [45]	Turkey	RCT	NS	Single (evaluator)	PRP injection	Control: saline injection	PS	PRP (4.4 ± 3.1) saline (4.5 ± 3.1)
Xu 2021 [46]	China	RCT	ChiCTR-INR−17011825	Single (Outcomes assessor)	PRP injection	Control: steroid injection	Radicular pain due to LDH	More than 3 months

CTS: carpal tunnel syndrome; DPN: peripheral neuropathy; HZN: herpes zoster neuralgia; LDH: lumbar disc herniation; LPN: leprosy peripheral neuropathy; N.S.: not specified; PO: "per os" oral administration; PPP: platelet-poor plasma; PRP: platelet-rich plasma; PS: piriformis syndrome; RCT: randomized controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitors.

double-blind trial was conducted, thus understanding that those who were blinded were the patients and those delivering the intervention, but not the outcome assessors. In the study by Malahias et al. [35], only part of the assessors was blinded, thus judging the risk to be of "some concerns". The remaining studies were blinded in the outcome assessment and thus considered low risk. The selection of the reported result was judged low risk of bias in all the studies as eligible reported results corresponded to all pre-specified analysis. Overall assessment was algorithmically scored as being at low risk of bias in only one study [39], and at high risk of bias in 8 studies [36, 38, 41–46], with domain two (deviations from the intended interventions) contributing the most to the bias. The remaining studies were algorithmically scored as having "some concerns".

In terms of risk of bias, it should be noted that Raeissadat et al. [36] only included women in their study. Although CTS, the pathology they evaluated, is more prevalent in females than males, with a 3:1 female-to male ratio [47], including only one sex when the condition affects both sexes might represent a bias in the results.

3.4. Effects of interventions

The results described in this systematic review focused on the comparison between the two treatment groups, as considered to be the most clinically relevant (Fig. 3). Only in the case of pain intensity (the primary outcome) further comparison to baseline values was also performed. Table 4 provides an overall summary of the results based on both treatment groups and baseline values.

Table 2
Main characteristics of the selected studies. * The standard error was used instead of the standard deviation. ** It was not specified whether standard error or standard deviation was used. ***The same subjects were used for both treatments. Patients who were diagnosed with bilateral moderate-to-severe CTS were included. For each patient, one wrist was randomized into either the PRP or control group and the contralateral wrist of the same patient was allocated to another group. ****In these articles the authors have not specified whether or not there were dropouts, so these data should be taken with caution. Where there is no asterisk and the number of patients is the same at the beginning and at the end of the study, the authors have indeed specified that there were no dropouts. *****Median, 1st-3rd quartiles.

Ref.	Neuropathic pain condition	Initial sample size	Final sample size	Age (years ± SD)	Sex (F/M)	Primary outcome measure	Secondary outcome measure	Follow-up
Malahias 2017 [35]	CTS (mild to moderate)	TOTAL = 50 n = 26 (PRP) n = 24 (saline)		PRP (60.46 ± 14.390) saline (57.17 ± 16.137)	NS	Q-DASH	-VAS -DeltaCSA	Baseline and 4 and 12 weeks
Raeissadat 2018 [36]	CTS (mild to moderate)	TOTAL = 41 n = 21 (PRP+splint) n =20 (splint)		PRP+splint (51.20 ± 9.82) splint (47.23 ± 7.11)	PRP+splint (21/0) splint (20/0)	VAS (0−10)	-Electrophysiological parameters (PL/SNAP/OL/CMAP) -BCTQ	Baseline and 10 weeks
Senna 2019 [37]	CTS (mild to moderate)	TOTAL = 98 n = 49 (PRP) n = 49 (steroid)	TOTAL = 85 n = 43 (PRP) n = 42 (steroid)	PRP (38.3 ± 6.4) steroid (40.7 ± 9.4)	PRP (35/8) steroid (36/6)	-VAS (0−100) -Paresthesia -Phalen's test -Tinel's test	-BCTQ -electrodiagnostic testing -CSA of the median nerve	Baseline and 1 and 3 months
Wu 2017 [38]	CTS (mild to moderate)	TOTAL = 60 n = 30 (PRP) n = 30 (splint)		PRP (57.87 ± 1.51)* splint (54.27 ± 1.34)*	PRP (27/3) splint (25/5)	VAS (0−10)	-BCTQ -CSA of MN -Electrophysiological study -FP	Baseline and 1, 3 and 6 months
Trull-Ahuir 2020 [39]	CTS (mild to extreme)	TOTAL = 50 n = 25 (PRP) n = 25 (PPP)		PRP (46.1 ± 6.8) ** PPP (46.4 ± 10.6)**	PRP (19/6) PPP (18/7)	HGS	-WBFS -BCTSQ -SWAS - The time the patient took off work	Baseline and 6 weeks
Chen 2021 [40]	CTS (moderate to severe)	TOTAL = 26*** n = 26 (PRP) n = 26 (saline)	TOTAL = 24*** n = 24 (PRP) n = 24 (saline)	53.0 ± 2.0*	PRP and saline (21/3)	BCTQ	-CSA of median nerve -electrophysiological study	Baseline and 1, 3, 6, and 12 months
Anwar 2024 [41]	DPN	TOTAL = 60**** n = 30 (PRP) n = 30 (pregabalin)		PRP (55.17 ± 8.87) pregabalin (54.37 ± 8.90)	PRP (17/13) pregabalin (12/18)	- VAS - LANSS - SF−36 - SQS		Baseline and 1 year
Hassanien 2020 [42]	DPN	TOTAL = 68 n = 34 (PRP + drugs) n = 34 (drugs)	TOTAL = 60 n = 31 (PRP + drugs) n = 29 (drugs)	PRP + drugs (39.7 ± 13.5) drugs (32.6 ± 18.2)	PRP + drugs (17/14) drugs (16/13)	Pain VAS	- numbness VAS -mTCNS -nerve conduction	Baseline and 1, 3, and 6 months. Nerve conduction at baseline and 6 months
Zhou 2022 [43]	HZN	TOTAL = 80**** n = 40 (PRP + drugs) n = 40 (drugs)		PRP + drugs (64.6 ± 9.4) drugs (65.4 ± 8.9)	PRP + drugs (17/23) drugs (19/21)	-NRS (0−10) -Athens Insomnia Scale -wound healing -gabapentin dosage -adverse reactions -incidence of PHN		Baseline and 1 week, 1, 3 and 6 months. Incidence of PHN after 6 months
Anjayani 2014 [44]	LPN	TOTAL = 60**** n = 30 (PRP) n = 30 (PPP)		PRP (44.83 ± 10.63)** PPP (45 ± 11.15)**	PRP (20/10) PPP (19/11)	-VAS -TPDT		Baseline and 2 weeks
Öztürk 2022 [45]	PS	TOTAL = 60 n = 30 (PRP) n = 30 (saline)		PRP (40.2 ± 7.4) saline (40.8 ± 6.9)	PRP (18/12) saline (20/10)	-VAS (0−100) -ODI		Baseline, 1 week and 1 month
Xu 2021 [46]	Radicular pain due to LDH	TOTAL = 132 n = 64 (PRP) n = 68 (steroid)	TOTAL = 124 n = 61 (PRP) n = 63 (steroid)	PRP (56.0 (44.5–60.0)) steroid (56.0 (50.0–59.0)) *****	PRP (33/28) steroid (26/37)	-PPT -VAS -ODI -SF−36 (PF and BP)	-rate of F-wave -latency of F-wave	Baseline and 1 week, 1, 3, 6 months and 1 year. F-wave rate and latency only 1-year post operation

BCTQ: Boston Carpal Tunnel Syndrome Questionnaire; BCTSQ: Boston Carpal Tunnel Syndrome Questionnaire; BP: bodily pain; CMAP: compound muscle action potential; CSA: cross sectional area; CTS: carpal tunnel syndrome; DPN: peripheral neuropathy; FP: finger pinch; HGS: hand grip strength; HZN: herpes zoster neuralgia; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; LDH: lumbar disc herniation; LPN: leprosy peripheral neuropathy; MN: median nerve; mTCNS: modified Toronto clinical neuropathy score; N.S.: not specified; NRS: numerical rating scale; ODI: Oswestry disability index; OL: onset latency; PF: physical function; PHN: postherpetic neuralgia; PL: peak latency; PPP: platelet-poor plasma; PPT: pressure pain thresholds; PRP: platelet-rich plasma; PS: piriformis syndrome; SD: standard deviation; SF-36: short form 36 health survey; SNAP: sensory nerve action potential; SQS: sleep quality scale; SWAS: Southampton wound assessment scale; TPDT: two-point discrimination test; VAS: visual analogue scale; WBFS: Wong-Baker faces scale.

3.5. Effect of PRP on Pain intensity

The effect of PRP on changes in pain intensity was investigated in all the studies included in this systematic review. Pain assessment was carried out using different scales: visual analogue scale (VAS) [3–6,9,10,12–14], Wong baker faces pain rating scale (WBFS) [7] and numerical rating scale (NRS) [11]. In addition to the VAS, Anwar et al. [9] and Xu et al. [14] assessed pain intensity by Leeds Assessment Neuropathic Symptoms and Signs (LANSS) and pressure pain thresholds (PPTs), respectively. In the study by Chen et al. [8] the assessment of pain was carried out as part of the symptom severity and functional status through the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ).

Seven randomized studies, including 429 patients, reported significant reduction in pain intensity compared to control, placebo or alternative treatment [5,6,8–11,13] (Table 4 and Fig. 4B). This positive effect for PRP was found in the following conditions: diabetic peripheral

Table 3
Description of the obtaining and aplication process of the platelet-rich plasma from the selected studies.

Ref.	Type	Anticoagulant	Centrifugation (force / time)	Platelet concentration	Leukocytes	Activator	PRP application		
							Volume	Number of doses	Frequency
Malahias 2017 [35]	PRP	NS	Double	NS	NS	NS	2 mL	1	N/A
Raeissadat 2018 [36]	PRP (Rooyagen kit (made by Arya Mabna Tashkis Corporation)	ACD-A	1st: 1600 rpm / 12 min 2nd: 3500 rpm / 7 min	4–6 times that of the whole blood	Leukocyte-poor PRP (5–10 %)	NS	1 mL	1	N/A
Senna 2019 [37]	PRP (GD medical pharma, Dutch company)	Citrate	1st: 704 g / 3 min 2nd: 1252 g / 15 min	NS	NS	Calcium chloride	2 mL	1	N/A
Wu 2017 [38]	PRP (RegentKit-THT−1- RegenLab)	Citrate solution	3400 rpm / 15 min	Yes (2.7 ± 0.4 times the WB)	Yes (1.2 ± 0.4 times the WB)	Autologous thrombin	3 mL	1	N/A
Trull-Ahuir 2020 [39]	PRP (GPS III Mini Platelet Concentrate Separation Kit - Biomet Biologics Inc)	NS	NS	Yes (1021,488 ± 355,603 platelets/ µL - 3.91 ± 1.36)	NS	NS	3 mL	1	N/A
Chen 2021 [40]	Leukocyte-poor PRP (PLTenus plus – TCM Biotech International Corp.)	ACD-A	500–1200 g / 8 min	NS	Leukocyte poor	NS	3.5 mL	1	N/A
Anwar 2024 [41]	PRP	NS	Double	NS	NS	Spin	1.5 mL / each nerve	3	Once a month
Hassanien 2020 [42]	PRP	ACD	1st: 3500 rpm / 10 min 2nd: 4000 rpm / 7 min	NS	NS	Calcium chloride	1.5 mL / each nerve	1	N/A
Zhou 2022 [43]	PRP	NS	2500 ± 200 g / 10 min	NS	NS	Freshly PRP	1 mL / nerve segment	1	N/A
Anjayani 2014 [44]	PRP	Citrate dextrose	1st: 280 g / 7 min 2nd: 1290 g / 7 min	NS	NS	NS	1 mL	1	N/A
Öztürk 2022 [45]	PRP (T-Lab PRP kit)	NS	830 g / 5 min	NS	NS	NS	4 mL	1	N/A
Xu 2021 [46]	PRP	Sodium citrate	1st: 1600 rpm / 10 min 2nd: 3200 rpm / 10 min	NS	NS	NS	3 mL	1	N/A

ACD: acid citrate dextrose; N.S.: not specified; PRP: platelet-rich plasma; WB: whole blood.

neuropathy (DPN) [9,10], herpes zoster neuralgia (HZN) [11], piriformis syndrome (PS) [13] and in half of the trials concerning carpal tunnel syndrome (CTS) [5,6,8]. However, the time intervals over which this effect was observed differed. In the case of PS [42], the pain intensity improvement was provided in the early period of treatment (1 week), reaching similar score to the control after 1 month. Regarding CTS, Senna et al. [34] and Wu et al. [35] reported PRP positive effects in the final period post-treatment (3 and 6 months, respectively), thus suggesting better outcomes in long-term following. Whereas the therapeutic effect shown by Chen et al. [37] referred to all time points for the follow-up (1, 3, 6 and 12 months). In the remaining conditions [38–40], the significant improvements in pain severity scores were also reported in all time points. In the other half of CTS studies [3,4,7], no statistical differences were found compared to control, placebo or alternative treatment. Similar outcomes were reported in the treatment of lumbar pain herniation [43], intergroup differences were not found to be significant during the 1-year follow-up period.

On the other hand, the aim of Anjayani et al. study [12] was to stimulate the sensation of pain in patients with sensory loss because of leprosy peripheral neuropathy (LPN), unlike the other studies, where the objective was to reduce the pain intensity. Therefore, in this case, the significant VAS improving by PRP injection that stimulated the patients' pain sensation was also considered as a positive effect for this biological treatment on this condition. Nevertheless, comparison was only made with respect to baseline. In fact, when it comes to baseline comparison, PRP treatment showed a significant positive effect (pain reduction) in all studies except for Malahias et al. [3], who did not make this type of comparison (Fig. 4A).

3.6. *Effect of PRP on life quality*

Eight randomized studies [32,34,36,38–40,42,43] globally involving 569 patients assessed the effect of PRP on life quality in different NP conditions. This concept includes different outcomes. Anwar et al. [38] tested the effect of PRP in patients with diabetic peripheral neuropathy. Authors measured quality of life by Short Form 36 Health Survey (SF-36). They showed significant improvement in the patients receiving PRP compared to those taking oral pregabalin after 1 year. Xu et al. [43] also evaluated the effect of PRP treatment on the quality of life of patients with radicular pain due to lumbar disc herniation; however, in this case, no significant differences between the PRP group and the steroid group were reported. No significant differences were found in Trull-Ahuir et al. study [36] either. They tested PRP as an adjuvant treatment in patients with mild to severe CTS. They found no differences in the between-group (PRP and PPP) analysis for hand grip strength (HGS) and time to return to work.

Two studies [38,40] evaluated the PRP effect on sleep quality in patients with NP related to DPN [38] and HZN [40]. The PRP injection in the latter study was combined with the medication given to the control group. Although evaluated with two different scales, sleep quality scale

Table 4
Outcome and adverse effects of the selected studies. (✓) Significantly better than comparator treatment; (=) there was no significant difference between PRP and comparator treatment. *Overall significant results with respect to comparator treatment. **Patients treated with PRP regained their pre-surgery HGS significantly earlier than those in the PPP group compared to baseline, although no differences were found in the between-group analysis at 6-weeks follow-up. ***Compared to baseline values, as there was no statistical comparison between treatments. ****Similar effect as comparator treatment but PRP may be safer.

Ref.	Neuropathic pain condition	Outcomes	Effect of PRP*	Adverse effects
Malahias 2017 [35]	CTS (mild to moderate)	At 1st month no differences were found. At the final endpoint (12 weeks) the differences between both groups (PRP and placebo) for the Q-DASH score were statistically significant. Almost 77 % of patients receiving PRP appeared to have a more than 25 % Q-DASH score improvement, whereas only 33.3 % of the placebo-controlled group were found improved. No significant statistical difference in the success ratio of VAS between the two groups. Regarding individual DeltaCSA decrease, the difference between the 2 groups was found significant. Differences were also significant between both groups in the final DeltaCSA, thus suggesting a significant decrease of the CTS incidence.	Positive Pain intensity = Functional status and disability ✓ Screening and diagnosis of NP ✓	No serious side effects
Raeissadat 2018 [36]	CTS (mild to moderate)	The changes in neither of the evaluated outcome were found to significantly differ between the two groups (PRP + splint *vs.* splint), even when the analyses were adjusted for age of the patients. A single injection of PRP in the wrist did not add significantly to the benefit of wrist splinting at 10 weeks follow up.	No differences Pain intensity = Nerve repair = Symptom severity and functional status =	4 patients reported pruritus, 1 experienced pain in the fingers and 1 reported a burning sensation. The rest of patients [15] had no side effects after PRP injection.
Senna 2019 [37]	CTS (mild to moderate)	VAS-pain, positivity for Phalen's test, positivity for Tinel's test, BCTQ-SSS, BCTQ-FSS, motor conduction parameters, sensory conduction parameters and m-CSA were significantly improved along the study period in both groups (PRP and corticosteroid) with respect to baseline values. At 1 month follow-up, no statistically significant differences were found between both groups. At 3 months follow-up, a significant improvement was reported in the PRP group respect to steroid group, in all the evaluated parameters except for DML, distal CMAP amplitude, MN sensory conduction, and the m-CSA, that did not differ significantly between the two groups.	Positive Pain intensity ✓ Numbness ✓ Nerve repair ✓ Symptom severity and functional status ✓ Screening and diagnosis of NP =	No recorded side effects in all patients. Just increase pain sensation in PRP group in the first 48 h following injections, patients received paracetamol and local ice application.
Wu 2017 [38]	CTS (mild-to-moderate)	A significant improvement in all outcome measures (VAS, BCTQ, FP, SNCV, DML and CSA) was observed in the PRP and control groups at all follow-up assessments (1, 3 and 6 months) compared to baseline values (not including the 1st month FP in the control group). The differences in FP, SNCV and DML between the two groups were not statistically significant at all follow-up assessments.	Positive Pain intensity ✓ Nerve repair = Symptom severity and functional status ✓ Screening and diagnosis of NP ✓	No side-effects or nerve trauma were observed in either of the two groups.
Trull-Ahuir 2020 [39]	CTS (mild to extreme)	Pain, severity of symptoms, and functional status (WBFS, BCTSQs, and BCTSQf) significantly improved after surgery in both the PRP and PPP group compared to baseline values, except for the HGS parameter. In that case, only the patients in the PPP group showed significant differences in HGS. Thus, patients treated with PRP regained their pre-surgery HGS significantly earlier than those in the PPP group, although no differences were found in the between-group analysis at 6-weeks follow-up. PRP did not improve pain or the severity of symptoms or functional status more effectively than the control (PPP) at the 6-week follow-up. There was also no difference in wound healing (SWAS scores) or the time the patient needed to return to work.	No differences** Pain intensity = Quality of life = Wound healing = Symptom severity and functional status =	No surgical complications were reported in either the PRP or PPP groups.
Chen 2021 [40]	CTS (moderate-to-severe)	All outcome measures improved compared with baseline data in the PRP group, except for the 3rd month SNCV measurements. In the saline group, SSS and FSS improved significantly at each follow-up (1, 3, 6 and 12 months), but none of the CSA or electrophysiological parameters improved significantly other than the DML and CSA at 12 months. Furthermore, significant improvements were observed in the SSS scores and SNCV at all time points in the PRP group compared to the control group. Significant differences were only seen in the FSS scores and CSA at the 6- and 12-months follow-up and in the DML at the 6-month follow-up. A single dose of	Positive Pain intensity ✓ Nerve repair ✓ Symptom severity and functional status ✓ Screening and diagnosis of NP ✓	No mention of safety issues

(*continued on next page*)

Table 4 (*continued*)

Ref.	Neuropathic pain condition	Outcomes	Effect of PRP*	Adverse effects
		ultrasound-guided perineural PRP injection can provide therapeutic effect for 1-year postinjection.		
Anwar 2024 [41]	DPN	Significant differences were reported in the PRP group with respect to baseline values for all outcome variables (VAS, LANSS, SF−36 and SQS). No such data were provided for the control group. When comparing both treatments, a significant improvement in PRP group as compared to control group was reported for all the outcomes.	Positive Pain intensity ✓ Quality of life ✓ Sleep quality ✓	No mention of safety issues
Hassanien 2020 [42]	DPN	Pain and numbness VAS scales were significantly lower in the intervention group (PRP + medical treatment) in comparison with the control group (medical treatment) during the whole follow-up period (1, 3 and 6 months). These scales showed significant decreased during the whole follow-up period in comparison to the basal value in the intervention group. In the control group, both scales were significantly higher than their basal values by the sixth month. mTCNS significantly improved (decreased) in PRP group in comparison with control group, for the whole follow-up period. The PRP group showed significantly lower post-interventional mTCNS values during the whole 6 months in comparison with their basal values, not so the control group. Nerve conduction study showed significantly improvement between both treatments at the performing time (6 months) except for DML in ulnar nerve and deep peroneal nerve. Significant improvement in comparison with baseline values for all the nerve conduction outcome was only observed in PRP group.	Positive Pain intensity ✓ Numbness ✓ DPN progress ✓ Nerve repair ✓	Post-PRP injection complications in the form of pain and/or paresthesia were noticed in 3 patients, who responded to short-term (3 days) vitamin B complex and/or paracetamol.
Zhou 2022 [43]	HZN	NRS scores and the sleep conditions of the two groups (PRP + drugs *vs.* drugs) showed a significant improvement compared to baseline at each time point (1 week, 1, 3 and 6 months). NRS scores, the sleep conditions and gabapentin dosage of the PRP group were significantly improved than that of the control group at each time point. The time of herpes dry-up, scab crusting and shedding of patients in the PRP group was significantly shorter than that in the control group. Six months post-treatment, the incidence of PHN was significantly decreased in the PRP group (5 %) compared to control group (37.5 %).	Positive Pain intensity ✓ Sleep quality ✓ Gabapentin dosage ✓ Wound healing ✓ PHN incidence ✓	The incidence of dizziness, lethargy, and ataxia in the observation group was lower than that in the control group ($p < 0.05$). No complications such as bleeding at the puncture site, pneumothorax, and infection in the observation group.
Anjayani 2014 [44]	LPN	The TPDT of the PRP group showed a significant reduction compared with the baseline, which was not observed with the PPP group. PRP injection significantly stimulated the patients' pain sensation (VAS) in week 2. PPP group showed no significant improvement.	Positive*** Pain intensity*** ✓ Nerve repair*** ✓	No mention of safety issues
Öztürk 2022 [45]	PS	VAS and ODI scores improved significantly in both groups (PRP and saline) at 1 week and 1 month after the intervention compared to baseline values. Significant differences between the two groups were only observed at 1 week of treatment.	Positive Pain intensity ✓ Functional status and disability ✓	No side effects were observed in any patient.
Xu 2021 [46]	Radicular pain due to LDH	VAS, PPT, ODI and PF of SF−36 scores of the two groups (PRP and steroid) showed a significant improvement compared to baseline at the following time points (1, 3 and 6 months and 1 year) week, 1, 3 and 6 months). The significant differences for BP of SF−36 were reported at 3 and 6 months and 1-year post-treatment in both groups. F-wave rate and latency were obtained only 1-year post-operation and significant differences were also detected in the two groups compared to baseline values. Nevertheless, no significant difference was found between the PRP group and the steroid group in any of the outcomes.	No differences**** Pain intensity = Quality of life = Nerve repair = Functional status and disability =	No complications or adverse effects were reported in any patient.

BCTQ: Boston Carpal Tunnel Syndrome Questionnaire; BCTSQf: Boston Carpal Tunnel Syndrome Questionnaire functional status; BCTSQs: Boston Carpal Tunnel Syndrome Questionnaire symptomology; BP: bodily pain; CMAP: compound muscle action potential; CSA: cross sectional area; CTS: carpal tunnel syndrome; DML: distal motor latency; DPN: peripheral neuropathy; FP: finger pinch; FSS: functional status scale; HZN: herpes zoster neuralgia; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; LDH: lumbar disc herniation; LPN: leprosy peripheral neuropathy; MN: median nerve; mTCNS: modified Toronto clinical neuropathy score; NRS: numerical rating scale; ODI: Oswestry disability index; PHN: postherpetic neuralgia; PPP: platelet-poor plasma; PRP: platelet-rich plasma; PS: piriformis syndrome; SF-36: short form 36 health survey; SNCV: sensory nerve conduction velocity; SQS: sleep quality scale; SSS: symptom severity scale; SWAS: Southampton wound assessment scale; TPDT: two-point discrimination test; VAS: visual analogue scale; WBFS: Wong-Baker faces scale.

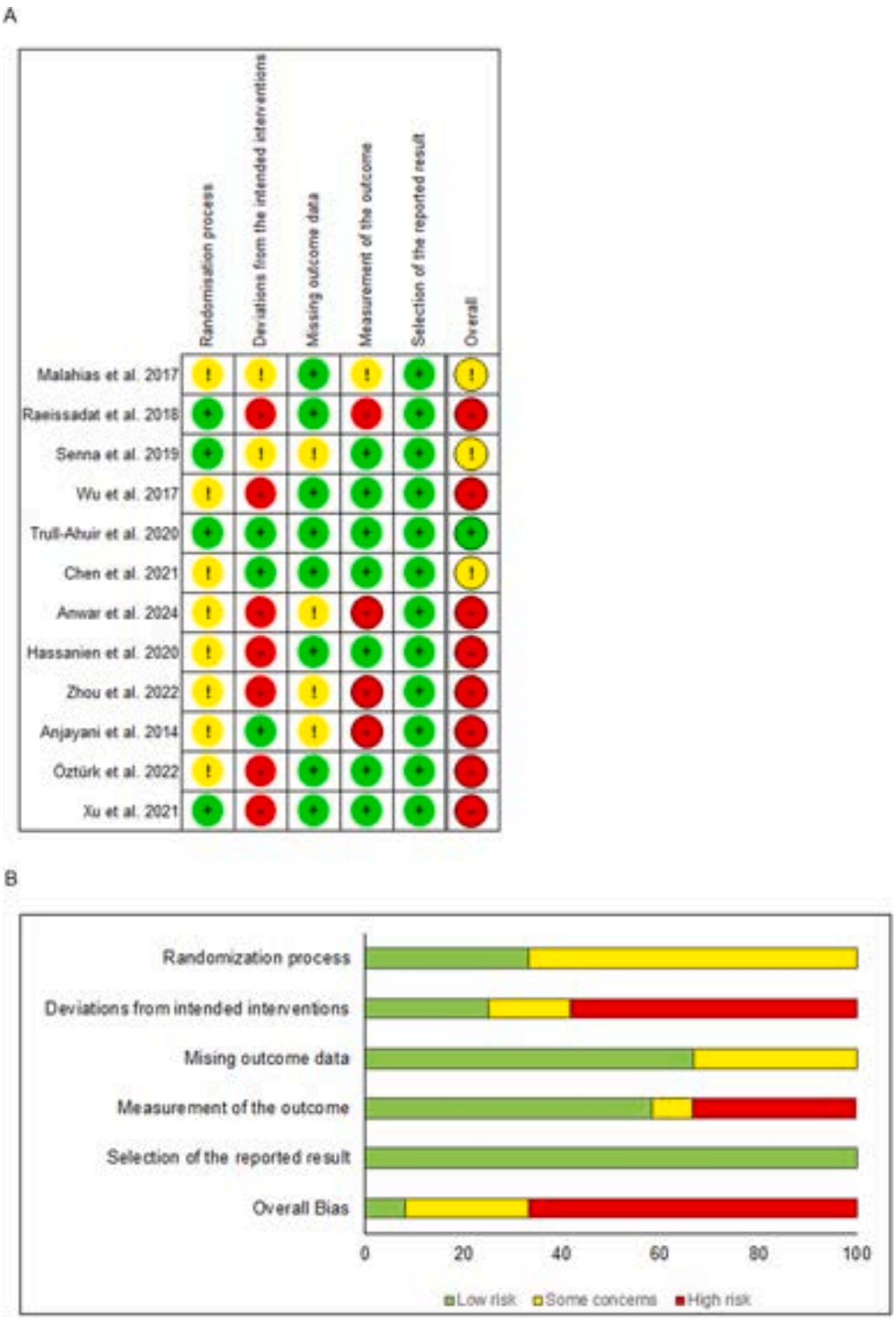

Fig. 2. Risk of bias assessment using RoB 2 tool. A) Risk of bias for each included study. B) Risk of bias summary across all included studies.

(SQS) [38] and Athens insomnia scale [40], significant sleep condition improvement was reported in both cases in the patients receiving PRP injection compared to control consisting in oral drugs. Differences were observed throughout the entire follow-up periods, 1 year [41] and 1 week, 1, 3 and 6 months [43].

Hassanien et al. [39] documented significant decrease in numbness scale in the PRP group (injection along with medical treatment) compared to the medical control group during the whole study period (6 months) in patients suffering from DPN. In line with this, Senna et al. [34] conducted their trial in CTS and they showed that the frequency of the Phalen's test and Tinel's test positivity and the frequency of paraesthesia were significantly lower in the PRP group compared to corticosteroid injection. This effect was showed in third month follow-up.

Finally, functional status and disability was determined in three studies concerning three different conditions: PS [42], radicular pain

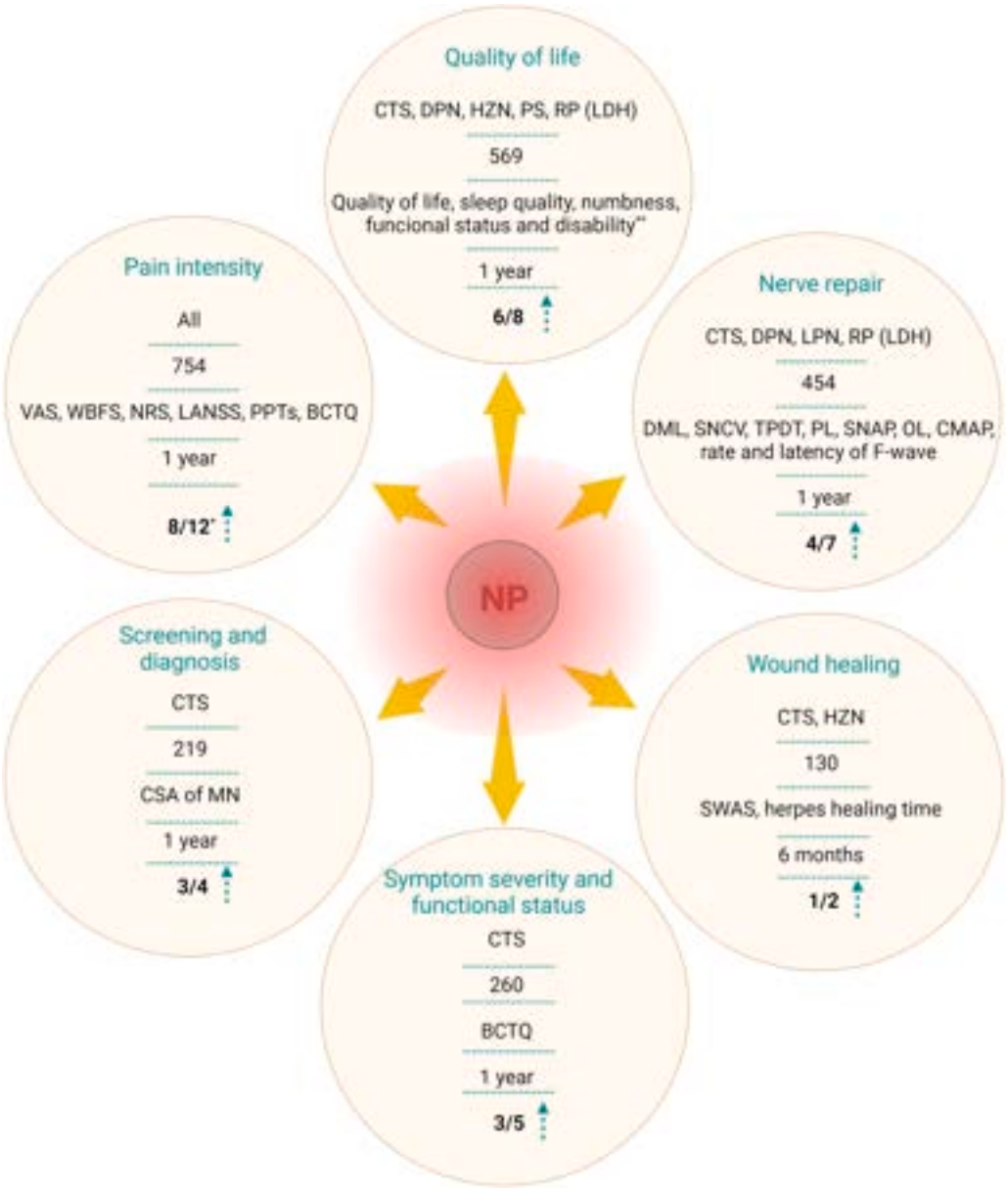

Fig. 3. Overall summary of NP related outcomes. In each panel, the following information is shown for each variable: NP conditions / sample size / scales / maximum follow-up period for that outcome / ratio of articles where the PRP had a positive effect out of the total number of articles assessing the corresponding outcome. Results shown the comparison with the alternative treatment, except for the study by Anjayani et al. [44] which showed the results of the comparison with baseline values, as no statistical comparison between treatments was performed. Created with BioRender.com. * PRP had a positive effect on pain intensity in 8 of the studies. Pain was reduced in 7 articles, while in the study by Anjayani et al. [44] pain perception was improved in patients with sensory loss because of leprosy peripheral neuropathy. ** The concept of quality of life brings together different outcomes that were described in the panel instead of scales. BCTQ: Boston Carpal Tunnel Syndrome Questionnaire; CMAP: compound muscle action potential; CSA: cross sectional area; CTS: carpal tunnel syndrome; DML: distal motor latency; DPN: peripheral neuropathy; HZN: herpes zoster neuralgia; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; LDH: lumbar disc herniation; LPN: leprosy peripheral neuropathy; MN: median nerve; mTCNS: modified Toronto clinical neuropathy score; NRS: numerical rating scale; ODI: Oswestry disability index; OL: onset latency; PHN: postherpetic neuralgia; PL: peak latency; PPP: platelet-poor plasma; PPTs: pressure pain thresholds; PRP: platelet-rich plasma; PS: piriformis syndrome; SNAP: sensory nerve action potential; SNCV: sensory nerve conduction velocity; SWAS: Southampton wound assessment scale; TPDT: two-point discrimination test; VAS: visual analogue scale; WBFS: Wong-Baker faces scale.

due to lumbar disc herniation [43] and CTS [32]. The first two studies used the Oswestry Disability Index (ODI) for their evaluation, while the third used the Quick-DASH (Q-DASH) score. The greatest effect was described by Malahias et al. [32] in CTS, where intergroup statistically significant differences were found in the Q-DASH score after 12 weeks. In PS [42] PRP improved functional status in the early period after treatment, that is 1 week. In both studies, PRP injection was compared to placebo (saline injection). However, no intergroup significant differences were found in patients suffering from radicular pain during the 1-year follow-up period [43].

3.7. Effect of PRP on nerve repair

Seven RCTs [33–35,37,39,41,43] globally involving 454 patients assessed the effect of PRP on nerve repair in different NP conditions. None of the studies by Raeissadat et al. [36] and Wu et al. [38] showed

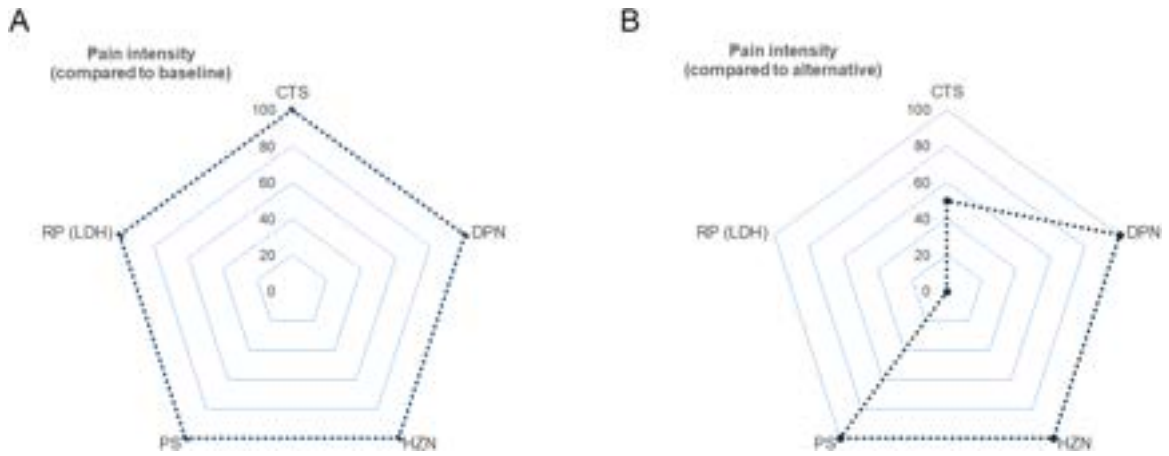

Fig. 4. Radar graphs to illustrate pain intensity reduction. A) Significant reduction in pain scores compared to baseline values. The study by Malahias et al. [35] was not included as they did not make the comparison with baseline values. B) Significant reduction in pain scores compared to alternative treatments. The study by Anjayani et al. [44] was not included in either of the two graphs as their aim was not to reduce but to stimulate pain sensation in patients with sensory loss because of leprosy peripheral neuropathy. CTS: carpal tunnel syndrome; DPN: peripheral neuropathy; HZN: herpes zoster neuralgia; PS: piriformis syndrome; RP (LDH): radicular pain due to lumbar disc herniation.

significant differences with control (splint) in patients suffering from mild-to-to moderate CTS in the electrophysiological study. On the contrary, Senna et al. [37] and Chen et al. [40] did report significant differences between groups in mild-to-moderate and moderate-to-severe CTS, respectively. The former evaluated the effect of PRP injection in comparison with corticosteroid injection. The authors found that the motor conduction velocity of the median nerve along the elbow-wrist segment and the amplitude of the sensory nerve action potential (SNAP) were significantly higher in the PRP group compared to control at 3 months follow-up. At this long-term follow up, the sensory latency (SL) of the median nerve in the PRP group was also significantly lower than in the control. Other electrophysiological parameters, such as distal motor latency (DML), distal compound muscle action potential (CMAP) amplitude, or median nerve sensory conduction did not differ significantly between the two groups at any of the study times. In the study by Chen et al. [40] patients with bilateral CTS were included, allocating either PRP or saline to each wrist. Significant differences were observed in the electrophysiological measurements sensory nerve conduction velocity (SNCV) and DML at all time points and at 12th month, respectively. When it comes to radicular pain due to lumbar disc herniation [46], PRP injection was compared with steroid injection. No significant intergroup differences were found in the rate and latency of F-wave during the 1-year follow-up period. On the contrary, the nerve conduction studies carried out by Hassanien et al. [42] in patients suffering from DPN showed significant improvement after PRP injection at 6th month post-treatment. The PRP intervention group underwent injection in addition to the medical treatment. The control group only received the medical treatment that included selective serotonin reuptake inhibitors and pregabalin, among others. Compared to control, the PRP group exhibited a significantly higher acceleration of mean nerve conduction velocities in both the upper and lower limbs. However, no significant intergroup difference was found in DML. Finally, the study by Anjayani et al. [44] showed that the perineural injection of PRP was able to stimulate nerve regeneration in patients suffering from LPN, according to the significant improvement (reduction) of the two-point discrimination test (TPDT). However, these results, which do not occur in the control (PPP injection), were with respect to baseline values, since the authors did not make an intergroup comparison.

3.8. Effect of PRP on wound healing

Two randomized studies evaluated the effect of PRP injection on the wound healing grade in two different NP conditions: CTS [36] and HZN [40]. In the first case, authors used the Southampton Wound Assessment Scale (SWAS) scores, and they reported no statistically significant differences compared to platelet-poor plasma (PPP) group for the surgical-wound healing grade. However, Zhou et al. [40] did indeed report significative shorter times of herpes dry-up, scab crusting and shedding of patients in the PRP group compared to the control group. PRP injection was performed on the basis of the control group drugs.

3.9. Effect of PRP on symptom severity and functional status in patients with CTS

Five RCTs [33–37] composed of a total of 260 patients with CTS evaluated the effect of PRP on symptom severity and functional status. They all used the BCTQ that is the most frequently used patient-reported tool, and it is developed specifically for CTS. It consists of two different scales: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). Raeissadat et al. [33] and Trull-Ahuir et al. [36] did not reveal a significant effect of PRP on this outcome compared to controls, splint and PPP injection, respectively. Patients in the PRP group from the Raeissadat et al. study also wore wrist splints. These two studies represented two types of disease severity: mild-to-moderate and mild-to-extreme, respectively. On the contrary, Wu et al. [35] also compared PRP injection with splint on a mild-to-moderate CTS; however, they did find differences between both groups at all follow-up time points (1, 3 and 6 months) in the BCTQ scores except for the 1st month BCTQ-SSS score. In this line, Senna et al. [34] and Chen et al. [37] reported significant improvements in the BCTQ scores in the PRP group compared to the control or placebo groups (corticosteroid and normal saline, respectively). Moreover, Senna et al. [34] reported that both symptom and function scores were significantly improved at 3 months following PRP injection in patients with mild-to-moderate CTS. The findings of the Chen et al. study [37] suggested a long-term significant positive effect of PRP injection in moderate to severe CTS patients (significant differences for SSS at 1, 3, 6 and 12 months and for FSS at 6- and 12-month follow-up).

3.10. Effect of PRP on screening and diagnosis of neuropathy

Four RCTs [32,34,35,37] composed of a total of 219 patients suffering from CTS assessed this effect. Cross-sectional area (CSA) of median nerve was used for screening and diagnosis of neuropathy. Three of the studies showed significant improved CSA of the median nerve after PRP treatment, although at different follow-up time points: 12

weeks [32], 1, 3 and 6 months [35] and 6 and 12 months [37]. Normal saline [32,37] and splint [35] were used as control for these studies. However, Senna et al. [34] reported no significative differences between PRP and corticosteroid injections in none of the study times (1 and 3 months).

3.11. Others

Zhou et al. [40] conducted a randomized study to evaluate the effects of PRP combined with drugs in the treatment of HZN. In addition to the outcomes already described in the previous sections, they also analyzed the effect on gabapentin dose and disease incidence. They concluded that PRP treatment significantly reduced the required dose of gabapentin for all follow-up time points (1 week and 1, 3 and 6 months) when compared to taking oral drugs exclusively. The incidence rate of PHN was also significantly lower in the PRP group (5 %) than in the control (37.5 %), assessed in the last follow-up period (6 months).

On the other hand, Hassanien et al. [39] used the modified Toronto Clinical Neuropathy Score (mTCNS) for the diagnoses and assessment of DPN progress. PRP injection in addition to medical treatment was compared to control group only receiving medical treatment. They concluded that mTCNS values significantly improved (decreased) in patients receiving PRP injection for all follow-up period (1, 3 and 6 months) in comparison with control group.

3.12. Adverse effects

No side-effects were observed in 5 studies [32,35,36,42,43] and when they did occur, they were mild and reversible [33,34,39,40]. Three of the studies did not mention safety condition issues [37,38,41] (table x).

4. Discussion

From a therapeutic point of view, neuropathic pain (NP) is challenging to manage. It usually results from nociceptive neuron hyperexcitability because of infections, metabolic abnormalities, nerve compression or irritation, amputation, surgery or trauma that leads to neuroinflammation and subsequent spontaneous ectopic activity [23,48]. Many of the conventional administered drugs cause serious and multiple side effects providing only temporary pain relief, without fully promoting the wound healing process of dysfunctional nerves. Thus, there is currently no evidence-based "effective" treatment for patients suffering from neuropathic pain [23,48].

This systematic review assessed the overall PRP effect on patients with NP from different aetiology. Twelve randomized studies with 754 patients were included. Our findings from the qualitative analysis, and summarized in Table 4, have shown a positive effect of PRP injection on improving pain intensity (8 studies reported positive effects [34, 35, 37–42] and 4 studies showed no significant differences with the comparison counter-group [32,33,36,43]). Moreover, considering all other outcomes, 9 out of the 12 studies [35, 37, 38, 40–45] reported an overall PRP beneficial effect in patients with NP. Nevertheless, the number of randomized studies included in this systematic review was relatively low and heterogeneous. Despite this heterogeneity of patient phenotypes which may underlie heterogeneous pathophysiological mechanisms and thus, different treatment response, the results reported in this systematic review have been encouraging. The present review also suggested that PRP might not only be an effective therapeutic approach but also a safe intervention for patients with NP, as evidenced by the reported adverse effects.

Autologous PRP can be obtained from different protocols that might lead to products with different compositions and functionality [49,50]. Unfortunately, none of the included studies provided an accurate description. Complete information should be detailed, as these parameters might have a clear impact on the clinical outcomes and could be used to correlate certain PRP features with different levels of efficacy. Nevertheless, based on the results provided in this systematic review, the efficacy of this therapeutic approach to treat NP seems to be independent of the type of PRP used. Another critical issue for autologous PRP performance is the dose and frequency of injection. The volume of PRP injected ranged from 1 mL to 4 mL. Qualitative analysis of the data did not show any volume performing better. Thus, no clear conclusions about dosage could be drawn. On the contrary, as far as frequency is concerned, in most of the studies a single injection was administered, enough to report beneficial effects. Three PRP injections were administered (once a month) in the study by Anwar et al. [41] However, final assessment was performed after 1-year follow up, thus making it impossible to elucidate whether a single dose would have achieved the same results. In the specific case of piriformis syndrome [45], significant results were only observed in the short treatment period, so the authors suggested that repeated injections might be necessary for a long-term effect.

Several NP conditions were included in this systematic review (CTS, DPN, HZN, LPN, PS and radicular pain due to LDH). Given the scarcity of studies included in each pathology, no conclusions could be drawn regarding the correlation between the aetiology of neuropathic pain and the effectiveness of PRP. The absence of significant differences between PRP treatment and control were detected in two different conditions: lumbar painful radiculopathy [46] and CTS [36,39]. Regarding the first condition, the lack of clear evidence for the efficacy of neuropathic drugs has already been described suggesting the involvement of a complex combination of neuropathic, skeletal and myofascial mechanisms [13]. In the case of CTS, no significant differences were observed in 2 [36,39] out of the 6 studies included in this systematic review in that regard. In the remaining 4 studies [35,37,38,40], a positive effect on PRP-treated patients was reported. Although PRP treatment had an overall positive effect in the remaining evaluated conditions, the small number of studies for each pathology makes it unfeasible to give a strong recommendation. Heterogeneity was also present in the alternative treatment groups. Due to the paucity of studies no correlation or trend in the efficacy of PRP versus a specific treatment could be determined. In fact, 3 different controls (splint [36], PPP [39] and steroid injection [46]) were used in the RCTs where no significant differences were detected.

The exact mechanisms underlying neuropathic pain are not yet fully understood. Nevertheless, a widely accepted hypothesis refers to an aberrant inflammation resolution following nerve injury that prevents axon regeneration, thus avoiding the restoration of normal nociceptive neuron membranes and perpetuating neuropathic pain [23,51,52]. Following nerve injury, several cell types, including Schwann cells and macrophages produce soluble inflammatory cytokines, chemokines and damage-associated molecular patterns (DAMPS) that activate surrounding cells and recruit circulating leukocytes into the site of injury [52–56]. Numerous pro-inflammatory cytokines and chemokines are then released and thus altering the processing of nociceptive information by sensory (dorsal root ganglion (DRG)) neurons, leading to central sensitization and the activation of microglia and astrocytes [9,15,57]. Several studies involving different nervous cell types (microglia, peripheral nerves, neurons, Shawnn cells) have demonstrated a therapeutic potential of PRP products as neuroprotective, neurogenic and neuroinflammatory modulators [27, 58–65]. The therapeutic effects of PRP largely depends on the level of secretory proteins released upon platelet activation, including platelet-derived growth factor (PDGF), transforming growth factor beta 1 (TGFβ1), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), nerve growth factor (NGF), hepatocyte growth factor (HGF) and brain-derived neurotrophic factor (BDNF) that govern inflammation, angiogenesis and macrophage polarization, among others [65–67]. Macrophages have significant functions in regulating neuroinflammation and modulation their polarization is likely to have a major effect on the pathogenesis of neuropathic pain [53, 68–70]. As active

participants in innate immunity, platelets also express many immunomodulatory mediators that may control the responses of macrophages. In fact, platelet derivatives have been reported to promote macrophage polarization towards the pro-repair M2 phenotype [71]. Platelets also release high amounts of prostaglandin E2 (PGE), resulting in increased macrophage production of the anti-inflammatory cytokine IL-10 that reduces the TNF-α secretion, leading to an anti-inflammatory phenotype [72,73]. Platelets also secret pro-resolving signals, so called specialized pro-resolving mediators (SPMs) [72]. Major SPMs are synthetized from polyunsaturated fatty acids (PUFAs) n–3 (omega–3) and n–6 (omega–6) and include lipoxins, resolvins, protectins and maresins [74,75]. SPMs have showed anti-inflammatory, pro-resolution and anti-nociceptive functions. They actively contribute to restore homeostasis by reducing immune cell recruitment and pro-inflammatory cytokine production, promoting bacterial clearance and encouraging efferocytosis, thus emerging as promising targets in the search for effective drugs to counteract neuropathic pain [75–78]. PRP could also exert its action through axon regeneration. Blood vessels and axons often run parallel throughout the central nervous system, suggesting a functional interdependency [79]. In fact, angiogenesis is thought to be crucial for the guidance of sprouting axons [80,81]. Several growth factors contained in PRP may be involved in this process, including TGF-β, fibroblast growth factor (FGF), BDNF and specially VEGF a powerful angiogenic factor that additionally promotes axonal outgrowth [23,27,79,82,83]. Furthermore, PRP-derived extracellular vesicles have been recently described as a promising therapeutic strategy for nerve regeneration [84–86].

This systematic review has multiple strengths. First, a restriction to randomized studies was included to avoid biases from observational studies. Second, the assessment of the risk of bias was performed by the revised Cochrane risk of bias tool for randomized trials. Third, most of the studies (8 out of 12) were longitudinal, with half of the studies having a follow-up of at least 6 months. Fourth, studies were conducted in different countries, covering a more ethnically and culturally diverse sample, that may reduce selection bias. However, there are also some limitations that need to be considered. First, a meta-analysis could not be conducted, and therefore neither did the GRADE approach for certainty in evidence, as the studies were too heterogeneous regarding NP condition, control group, outcome measure or follow-up-period. The conclusions were therefore based on narrative synthesis. Second, the number of studies and sample sizes were small with most conditions poorly represented by 1 or at most 2 studies. Third, some studies used combination treatments which decreased the certainty with which PRP itself can be assessed, as synergies may be occurring. Fourth, most of the studies, some inevitably by design, lacked blinding of both subjects and investigators.

5. Conclusion

Based on this systematic review, PRP treatment might be an effective therapeutic approach for patients with different neuropathic pain conditions according to the reported beneficial effects on pain intensity, related outcomes and safety profile. Further studies with more complex designs to achieve double blinded trials and standardization of the optimal PRP injection time and obtaining protocols should be aimed. The efficacy of PRP was not dependant on the aetiology of the underlying disorder; nevertheless, interpretations of the results should be performed cautiously, as for the under-representation of NP conditions.

CRediT authorship contribution statement

María Troya: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mohammad H. Alkhraisat:** Writing – review & editing, Validation, Supervision, Conceptualization. **Eduardo Anitua:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare the following competing financial interests: E.A. is the Scientific Director of and M.T. and M.H.A. are scientists at BTI Biotechnology Institute, a dental implant company that investigates in the fields of oral implantology and PRGF-Endoret technology.

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