Interventional Pain Medicine 3 (2024) 100525

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Comparing the efficacy of intra-articular injection of Platelet Rich Plasma (PRP) with corticosteroids (CS) in patients with chronic zygapophyseal joint low back pain confirmed by double intra-articular diagnostic blocks: A triple-blinded randomized multicentric controlled trial with a 6-month follow-up

Anne-Marie Cauchon [a,*], Christopher Mares [b], Xin Yi Fan [c], Marie-Claude Bois [b], Nicola Hagemeister [d], Nicolas Noiseux [e], André Roy [f]

[a] Department of Physical Medicine and Rehabilitation, Université Laval, Québec, Québec, Qc, Canada
[b] Physiatry Department, Université de Montréal, Montréal, Québec, Qc, Canada
[c] School of Medicine, Université de Montréal, Montréal, Québec, Qc, Canada
[d] Laboratoire D'Innovation ouverte en Technologies de la santé, École de Technologie supérieure, Montréal, Québec, Qc, Canada
[e] Centre de Recherche Du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, Qc, Canada
[f] CPMSR and CRCHUM, Montréal, Québec, Qc, Canada

ARTICLE INFO

Keywords:
Platelet-rich plasma
Low back pain
Zygapophyseal osteoarthritis
Intra-articular zygapophyseal injections

ABSTRACT

Objective: To compare the safety and effectiveness in improving function and reducing pain of autologous PRP to corticosteroid (CS) zygapophyseal (Z-joint) intra-articular (IA) injections at six months for patients with chronic osteoarthritis Z-joint mediated low back pain (LBP).
Design: Prospective triple-blinded multicentric randomized controlled trial.
Methods: Fifty participants with radiological signs of Z-joint OA and chronic Z-joint mediated LBP confirmed by a ≥80 % pain improvement after two IA local anesthetic injections were randomized into PRP and CS groups, using a 1:1 ratio. Participants completed questionnaires at baseline, and at 1-, 3- and 6-month post-treatment, with adverse effect data collected at 1 month. Function (Oswestry disability index (ODI)), pain (Numeric Rating Scale (NRS)), treatment satisfaction (modified MacNab criteria), and quality of life (Short Form survey 36 (SF-36)) were assessed at each follow-up. The primary outcome was the percentage of participants improving their function (ODI score) above the minimal clinically important difference (MCID) of 17 points. The secondary outcomes were the percentage of participants with a >50 % NRS improvement, satisfaction to treatment and mean score improvement. Proportions were compared between groups using a chi-square test. Mean scores were compared using a two-way ANOVA or the nonparametric Brunner & Langer test.
Results: Both groups were similar at baseline, no major adverse effects occurred, and no participants were lost at follow-up. The proportion of participants improving their ODI scores above the MCID, the proportion of participants with a >50 % NRS improvement, and mean ODI scores were significantly different between groups in favor of PRP at 6 months. Modified MacNab satisfaction scale, NRS and SF36 mean scores were not statistically different between groups, but all followed the same pattern: the CS groups had a greater improvement a one month, both groups were equivalent at three months and the PRP group had a greater improvement at six months.
Conclusion: This first triple-blinded multicentric RCT demonstrates the safety of PRP IA Z-joint injections and its superiority in improving pain and function at six months post-treatment compared to CS for patients with chronic OA Z-joint mediated LBP. To perform a blinded control study, two intra-articular treatments were compared.

* Corresponding author. 2325 Rue de l'Université, Québec, QC, G1V 0A6, Canada.
E-mail addresses: Anne-marie.cauchon.2@ulaval.ca (A.-M. Cauchon), christopher.mares@umontreal.ca (C. Mares), xin.yi.fan@umontreal.ca (X.Y. Fan), marie-claude.bois.chum@ssss.gouv.qc.ca (M.-C. Bois), nicola.hagemeister@etsmtl.ca (N. Hagemeister), Noiseuxn@videotron.ca (N. Noiseux), sportroy@videotron.ca (A. Roy).

https://doi.org/10.1016/j.inpm.2024.100525
Received 29 October 2024; Received in revised form 19 November 2024; Accepted 20 November 2024
Available online 3 December 2024

However, knowing that radiofrequency neurotomy (RFN) of the medial branch diagnosed by branch blocks has been standard of care for pain originating from Z-joints, further studies comparing PRP to RFN are still needed. *Clinicaltrials gov registry number:* NCT05188820.

1. Introduction

1.1. Background

Low back pain (LBP) is the leading cause of years lived with disabilities and a worldwide socio-economical epidemic. Zygapophyseal joints (Z-joints) are accountable for up to 45 % of LBP. This proportion increases with age and the prevalence of Z-Joint osteoarthritis [1–6].

Two non-conservative treatment options are available for Z-joint LBP: corticosteroid (CS) injections and radiofrequency ablation (RFA) [4,7–9]. CS injections are technically shorter. However, they have a shorter duration of action, are not superior to placebo, and are associated with significant systemic adverse effects [8,10–12]. Recent international multispecialty practice guidelines on interventions for lumbar Z-joint pain recommended that Z-joint CS injections should not be performed routinely [13]. Radiofrequency ablation (RFA) of the medial branches is proven superior to sham, but is more painful and can cause local adverse effects like anesthesia, paresthesia and muscle weakness and atrophy [2,4,13,14]. Because nerves regenerate, RFA is not a permanent treatment [4,13]. In this context, there is undoubtedly a need for new treatment options for Z-joint mediated LBP.

Orthobiologic treatments like autologous PRP, that use the patient's own healing ability, have been studied for different musculoskeletal pathologies in the last decades with positive results [15–19]. More than a medication, PRPs are microenvironments including billions of bioactive molecules that act on degenerated tissues through numerous mechanisms of actions, listed in Table 1.

PRP injection is a potential treatment option because it is technically simple, comparable to Z-joint CS injections, and it is a safe autologous blood-derived treatment.

Three RCTs compared PRP to other types of IA Z-joint injection in LBP but only one has compared IA Z-joint PRP injections to CS in patients with Z-joint mediated LBP and OA [23–25]. This study showed that PRP was a safe treatment and that it was superior to CS at 3 and 6 months to improve pain, function and patients' satisfaction [25]. However, patients were recruited with a single intra-articular diagnostic block and the injector was not blinded.

Up to now, no triple or double blinded controlled trials have compared intra-articular PRP to CS injections in Z-joint mediated LBP.

1.2. Objectives

The aim of this study was to compare the safety and effectiveness of intra-articular Z-joint autologous PRP to corticosteroid injections in improving function, pain and patient satisfaction for the treatment of chronic Z-joint osteoarthritis mediated low back pain during a six-month follow-up.

2. Material and methods

2.1. Trial design and setting

This prospective multicentric triple blinded randomized controlled study was performed at the physiatry department of the Centre Hospitalier de l'Université de Montréal (CHUM) and the Clinique de Physiatrie et de Médecine du Sport Rockland (CPMSR). Participants were randomized in two groups with a 1:1 ratio. This study received funding from the International Pain and Spine Intervention Society (IPSIS) and the Association Québécoise des Médecins du Sport et de l'Exercice (AQMSE) in 2021. The study was registered at https://clinicaltrials.gov/ (number NCT05188820).

2.2. Ethical committee approval

The study was approved by the CHUM (project no. 21.246) and the École de Technologie Supérieure (project no. H20210609) ethical boards and was conducted according to the declaration of Helsinki.

2.3. Participants and recruitment

Patients referred to both centers for low back pain were contacted by a research assistant to verify their eligibility according to the criteria listed in Table 2.

Patients who fulfilled initial criteria were assessed by dual intra-articular Z-joint injections, and those who had a reduction of their low back pain of at least 80 % 30 min after both blocks were randomized. If intra-articular blocks were not technically possible, patients were excluded.

2.4. Interventional procedures

2.4.1. Intra-articular Z-joint diagnostic blocks

Participants were placed in prone position. The skin was prepped with Baxedin 4 times, and sterile fields were applied. A C-Arm was used for fluoroscopic imaging and guidance. Z-joint spacings were identified with an oblique view. A spinal needle 22G or 25G of 3½ or 5 inches was positioned in the joint. 0.1–0.2 mL of Isovue was injected to confirm correct needle positioning, and 1 ml of Xylocaine 2 % or Marcaine 0.5 % were injected per joint.

2.4.2. PRP preparation

Blood was drawn according to the number of Z-joints to inject, an anticoagulant (ACDA) was added, and it was then centrifuged in the Angel system by Arthrex (see annex 1) programmed to produce leucocyte-poor PRP with a platelet concentration ratio of five. For the PRP group, few mL of whole blood and PRP were kept for platelets, leucocytes and red blood cell counts.

Table 1
PRP mechanisms [20–22].

Anabolic action through growth factors releases, cellular proliferation activation
Anti-catabolic action through degenerative proteinase (MMP, ADAMTS) inhibition and cellular apoptosis reduction
Angiogenesis stimulation through growth factors releases
Anti-inflammatory action through anti-inflammatory cytokines releases and pro-inflammatory cytokine inhibition
Immunological response activation through chemokines releases
Stem cell activation
Pro-inflammatory macrophage (M1) polarization suppression and Anti-inflammatory macrophage (M2) polarization activation
Inhibition of nuclear factor-B pathway
Production of hyaluronic acid

Table 2
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
At least 18 years old	Less than 18 years old
Low back pain present for more than six months, with an axial predominance	Known inflammatory disease
Failed three months of non-interventional treatment	Intra-articular injection of cortisone 3 months or less before recruitment
Pretreatment ODI score of at least 30/100	Active systemic infection
Pretreatment NRS of low back pain of at least 4/10	Infection at injection site
Radiological signs of Z-joint degeneration (on X-rays, CT Scan or MRI)	Vertebral fracture
Absence of neurological deficit	Spine tumor
Sufficient knowledge of French or English to fill in the questionnaires	Surgical intervention at injection site prior to the study or planned
	Oral corticosteroid use in the last two weeks
	Cognitive disorder
	Pregnancy
	Breastfeeding
	Coagulopathy
	Drug affecting platelets that cannot be stopped (except acetylsalicylic acid)
	Intolerance or allergies to local anesthetics, corticosteroids, contrast agents and blood products

NRS: Numeric Rating Scale; Z-joint: Zygapophyseal joint; MRI: Magnetic resonance imaging.

2.4.3. Therapeutic injections

Diagnostic blocks and therapeutic injections were done on separate days, using the same technique described in section 2.4.1. In each joint, one mL of non-activated PRP was injected for the PRP group and 0.5 ml of Triamcinolone Acetonide 40 mg/mL mixed with 0.5 mL of NS was injected for the CS group. All participants received the same recommendations prior and after the therapeutic procedure. They were not allowed to receive other spinal injections during the follow-up but could continue conservative treatments 2 weeks after the injection.

2.5. Outcome measures and data collection

Our primary outcome was the proportion of participants achieving the Oswestry disability index's (ODI) minimal clinically important difference (MCID) of 17 points at 6 months [26,27]. Our secondary outcomes were the percentage of participants with a greater than 50 % reduction of their numeric pain rating scale (NRS), and the differences in function, pain, patient satisfaction and safety at 1, 3- and 6-month post-treatment [25].

Baseline scores, sociodemographic data and past treatment attempts were collected before intervention. Participants were followed remotely at 1, 3- and 6-month post-treatment by a blinded research assistant using the following questionnaires:

- A numeric rating pain scale (NRS) that assessed pain from 0 (none) to 10 (worse possible pain).
- The Oswestry Low Back Disability Index (ODI) that assessed participants' function through 10 questions rated from 0 (no disability) to 5 (maximal disability). Final scores ranged from 0 % to 100 % and were calculated as the percentage of the maximal possible score (50 points if all 10 questions were answered). If an answer was missing or not applicable, the denominator was adjusted accordingly, and the final score remained on the same scale [28].
- The modified MacNabb criteria assessed satisfaction to treatment as excellent, good, fair or poor.
- The 36-Item short-form survey (SF-36) was used to assess pain and physical functioning. Both scores went from 0 (worse clinical outcome) to 100 [29].
- Other questions assessed the use of medication and conservative treatments (ex: physiotherapy).
- The occurrence of adverse events was assessed at one-month post-treatment.

2.6. Sample size calculation

Prior to study beginning, a sample size calculation was conducted on R software using a two-sample *t*-test to detect a difference between PRP and CS groups of 17 points on the ODI score at 6 months. The expected standard deviation was 14, based on the study by Wu et al. [30]. The power was set at 0.8 and the level of significance at 0.025. 14.2 participants were required per group. To compensate possible losses at follow-up and to have a sample size that would be more acceptable to influence future clinical practice, a total of twenty-five participants per group was planned to be recruited [25].

2.7. Randomization

Fifty participants were randomized to the PRP group or the CS group with a 1:1 ratio, using a computer-generated random listing. Intervention assignment was done by the nurse on the injection day by adding the participant's name to the list. Only the nurse team had access to the listing until the end of the follow-up.

2.8. Blinding

This is a triple-blinded study: participants, injectors and research assistants remained blinded throughout the follow-up. On injection day, after blood draw, the nurse went to another room to assign study group and never saw the participant again. The nurse prepared the treatment syringe and waited 30 min (corresponding to PRP centrifugation time) before giving it to the injector. The unused blood draw from participants in the CS group was discarded. Syringes were covered by opaque stickers to conceal its content from the physician performing the injection and the participant.

2.9. Statistical analyses

Baseline quantitative sociodemographic variables were compared between groups with a two-sample T-test or the Mann-Whitney-Wilcoxon test depending on data normality. Categorical baseline variables were compared using a chi-square test. Adverse effects, complications and their frequency were reported for both groups. Laboratory analyses conducted on the PRP were presented in a Table.

Categorical data were compared at each follow-up using a chi-square test. The percentage of participants using pain medication was presented for both groups at baseline and at six months. Mean ODI, NRS and SF-36 scores were compared between groups over time with a two-way ANOVA or the Brunner & Langer's nonparametric tests depending on residual normality [31]. The two factors used were time and group. For statistically significant parameters, Tukey's honestly significant difference post-hoc test was conducted.

To see if PRP composition variations impacted on treatment responsiveness, simple regression analyses were conducted using the number of platelets and leucocytes injected per joint and the PRP to blood platelet and leucocyte concentration ratio as independent variables and ODI, NRS and SF-36 scores as dependent variables.

All analyses were conducted using R version 4.4.1 and Statgraphics version 19. The significance level was set at $\alpha = 0.05$ for all statistical tests. More details on statistical analyses are presented in the Annex 2.

3. Results

3.1. Recruitment and baseline groups

342 patients were assessed for study eligibility from May 2022 to December 2023, and fifty participants were randomized into two groups. More details regarding recruitment process are presented in the recruitment flow chart (Fig. 1).

No participants were lost to follow-up and no serious adverse effects (including infection) were reported. Groups' baseline sociodemographic characteristics are presented in Table 3. Demographic data and scores (ODI, NRS and SF-36) were not statistically different between groups ($p > 0.05$) at baseline. All injections were intra-articular, except for two participants in PRP group and one in the CS group that had one extra-articular injection out of four z-joint injections.

3.2. PRP content analysis

PRP's content was analyzed for 23 of the 25 participants in PRP group, because one blood sample coagulated, making ratio calculation impossible, and only hemoglobin concentration was assessed in another PRP sample. Although the centrifuge was programmed to produce leucocyte-poor PRP, five participants received autologous conditioned plasma (ACP, ACP to blood platelets ratio <3) instead of PRP. Among the eighteen participants who received PRP, only one received leucocyte-poor PRP (PRP to blood leucocyte ratio <1). Mean PRP composition with standard deviations are presented in Table 4.

3.3. Oswestry Disability Index (ODI), numeric rating pain scale (NRS) and Short Form survey 36 (SF-36) scores analysis

ODI and NRS scores improved for both groups throughout the 6-month follow-up. According to results presented in Tables 5 and 6 as well as in Figs. 2 and 3, groups were statistically similar at the 1- and 3-month follow-ups regarding the percentage of participants with an ODI's improvement greater than 17 points (MCID) and the percentage of participants with an NRS diminution greater than 50 % [26,27]. However, at 6 months, the PRP group had a statistically significant ($p < 0.05$) greater percentage of participants reaching both of these outcomes. Moreover, the percentage of participants responding to treatment in the PRP group kept improving between 3 and 6 months and had not reached a steady state yet. The percentage of participants who improved their NRS according to pre-established cut-offs of 30 %, 50 %, 75 % and 90 % is also shown in Table 7. Twenty-eight percent of participants in the PRP group decreased their score by more than 75 % at 6 months, compared to only 12 % in CS group. These results could not be compared because the chi-square test was not valid with such a small number of observations per cell.

3.4. Modified MacNab scale

Patients' satisfaction reported by the MacNab Scale is presented in

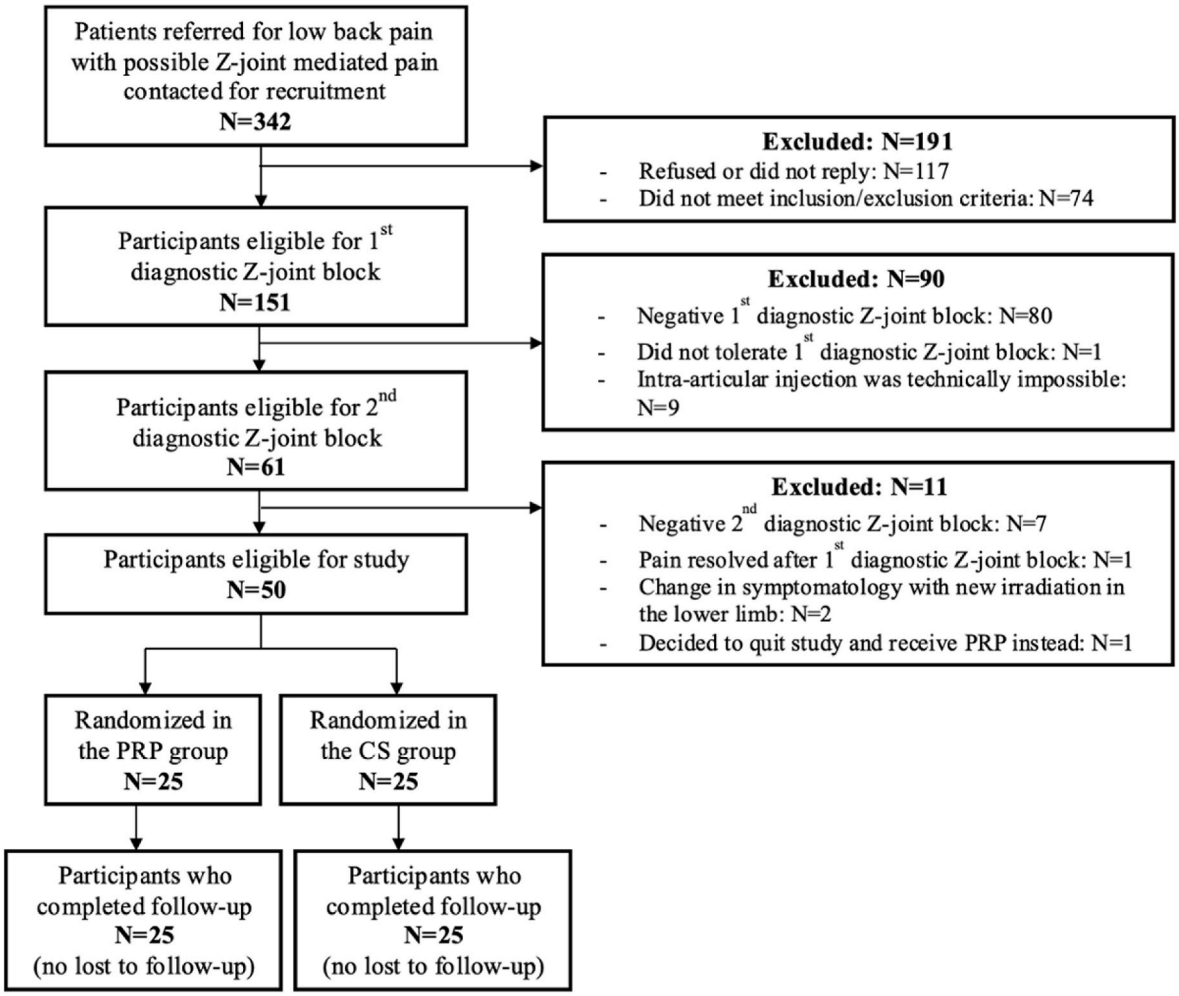

Fig. 1. Recruitment flow chart.
Z-joint: Zygapophyseal joint; CS: Corticosteroid; PRP: Platelet-Rich Plasma.

Table 3
Groups' sociodemographic characteristics at baseline.

Characteristic	PRP group	CS group
Participants, number	25	25
Women, number (%)	12 (48)	10 (40)
Age, years ± SD	60 ± 9	61 ± 8
BMI, kg/m2 ± SD	27.8 ± 4.7	28.3 ± 4.7
Duration of symptoms, mean in years ± SD	11.3 ± 12.6	9.8 ± 8.8
Relief after first diagnostic bloc, mean % ± SD	95.9 ± 7.7	97.8 ± 4.6
Relief after second diagnostic bloc, mean % ± SD	96.2 ± 6.3	97.8 ± 6.0
Number of levels injected, mean ± SD	2.1 ± 0.4	2.1 ± 0.5
Side of injection, number (%)		
Bilateral injection	18 (72)	16 (64)
Right side	6 (24)	3 (12)
Left side	1 (4)	6 (24)
Level(s) of injection, number (%):		
L3-L4	4 (16)	5 (20)
L4-L5	24 (96)	22 (88)
L5-S1	25 (100)	25 (100)
S1-S2	0 (0)	1 (4)
Have tried physiotherapy, number (%)	20 (80)	23 (92)
Takes pain medication, number (%)	23 (92)	23 (92)
Takes opioid medication, number (%)	7 (28)	7 (28)
Have consulted other health care professionals than physiotherapist (e.g.: chiropractitionner, osteopath, etc.), number (%)	22 (88)	19 (76)

SD: Standard Deviation.

Table 4
PRP characterization.

Characteristic	PRP composition
Number of platelets injected per joint, mean (*10^9) ± SD	1.18 ± 0.72
PRP/Blood platelets ratio, mean ± SD	4.9 ± 2.5
Number of leucocytes injected per joint, mean (*10^9) ± SD	0.0152 ± 0.011
PRP/Blood leucocytes ratio, mean ± SD	2.4 ± 1.6

SD: Standard deviation; PRP: Platelet-Rich Plasma.

Table 5
Percentage of participants who significantly improved their ODI scores by more than the MCID of 17 points at each follow-up.

Follow-up	PRP group	CS group	p-value[a]
1 month, number (%)	6 (24)	10 (40)	0.225
3 months, number (%)	5 (20)	5 (20)	1
6 months, number (%)	11 (44)	4 (16)	**0.031**

Significant p-value in bold and underlined.
MCID: minimal clinically important difference (corresponding to 17 points for the ODI); ODI: Oswestry Disability Index; PRP: Platelet Rich Plasma; CS: Corticosteroid.
[a] Chi-square test.

Table 6
Percentage of participants with an NRS decrease greater than 50 %.

Time	PRP group	CS group	p-value[a]
1 month, number (%)	6 (24)	10 (40)	0.225
3 months, number (%)	6 (24)	7 (29)[b]	0.682
6 months, number (%)	9 (36)	3 (12)	**0.047**

Significant p-value in bold and underlined.
PRP: Platelet Rich Plasma; CS: Corticosteroid.
[a] Chi-square test.
[b] One missing data in CS group at 3 months.

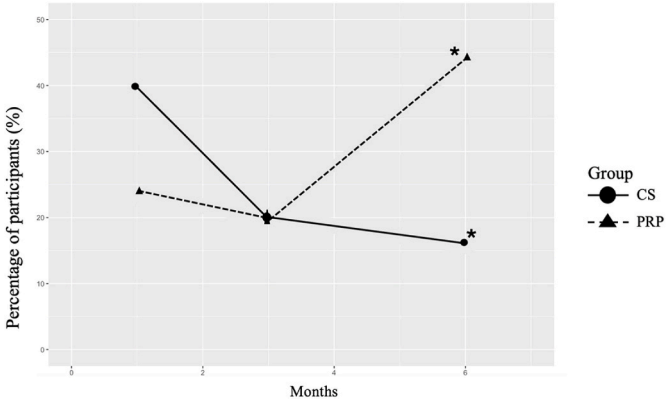

Fig. 2. Percentage of participants who significantly improved their ODI scores by more than the MCID of 17 points at each follow-up
*Significant difference between groups (p = 0.031).

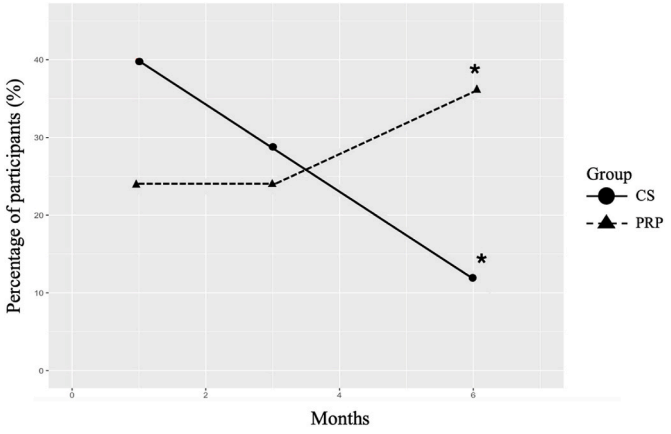

Fig. 3. Percentage of participants with an NRS decrease greater than 50 %
*Significant difference between groups (p = 0.047).

Table 7
Participant's improved NRS distribution according to study groups at follow-ups.

Timeline and group	Percentage of NRS reduction			
	30 to 50	51 to 75	76 to 90	≥91
1 month, number (%)				
PRP	2 (8)	3 (12)	3 (12)	0 (0)
CS	3 (12)	4 (12)	3 (12)	3 (12)
3 months, number (%)				
PRP	3 (12)	3 (12)	1 (4)	2 (8)
CS*	3 (13)	3 (13)	4 (17)	0 (0)
6 months, number (%)				
PRP	5 (20)	2 (8)	4 (16)	3 (12)
CS	5 (20)	1 (4)	2 (8)	1 (4)

*One missing data in CS group at 3 months.
NRS: pain Numeric Rating Scale; PRP: Platelet Rich.
Plasma; CS: Corticosteroid.

Table 8. At 6 months, participants in the PRP group tended to report greater satisfaction compared to the CS group (44 vs 28 %). However, between-group differences were not statistically significant. Participants who answered "excellent" and "good" were considered as satisfied and those who answered "fair" and "poor" as unsatisfied for the chi-square test to be valid and to be consistent with Wu et al.'s study [25].

Table 8
MacNab satisfaction score distribution.

Timeline and group	Excellent	Good	Fair	Poor
1 month[a]				
PRP, number (%)	2 (8.3)	6 (25)	5 (20.8)	11 (45.8)
CS, number (%)	3 (12)	11 (44)	3 (12)	8 (32)
3 months[a]				
PRP, number (%)	1 (4.1)	4 (16.7)	10 (41.7)	9 (37.5)
CS, number (%)	1 (4)	6 (24)	6 (24)	12 (48)
6 months				
PRP, number (%)	2 (8)	9 (36)	6 (24)	8 (32)
CS, number (%)	2 (8)	5 (20)	8 (32)	10 (40)

PRP: Platelet-Rich-Plasma; CS: Corticosteroid.
[a] One missing data in the PRP group at these timelines.

3.5. Pain medication

Ninety-two percent of participants took pain medication and 28 % took opioids for pain management in both groups at baseline and at the 6-month follow-up.

3.6. Mean scores comparison

ANOVA showed that ODI scores were significantly different between groups according to time ($p = 0.041$), in favor of the PRP group at 6 months. NRS and SF-36 pain and physical functioning mean scores were compared using Brunner & Langer nonparametric test [31]. Interaction between time and group was not significant for NRS and SF-36 pain scores, with a borderline P-Value of 0.051. However, participants from both groups significantly improved their NRS and SF-36 scores at each follow-up compared to baseline.

Figs. 4–7 represent ODI, NRS and SF-36 mean scores' evolution according to treatment group. Even though the interaction between group and time was significant only for ODI scores at 6 months, plots all followed the same pattern: the CS group tended to have a better improvement (corresponding to a reduction of ODI and NRS scores and an increase in SF-36 scores) at 1 month, followed by a slow deterioration at 3 and 6 months. Meanwhile, the PRP group showed a steady improvement overtime. Therefore, both groups tended to have similar mean scores at 3 months and PRP tended to have greater mean scores improvement at 6 months.

3.7. PRP subgroup analysis

Simple regression analyses were not statistically significant: The number of platelets and leucocytes injected per joint as well as the PRP to blood platelet and leucocyte ratios were not predictive of ODI, NRS and SF-36 scores evolution.

4. Discussion

To our knowledge, this is the first multicentric triple or double-blinded study comparing intra-articular autologous PRP and CS zygapophyseal (Z-joint) injections for patients with chronic osteoarthritis Z-joint mediated low back pain.

Our primary outcome was the proportion of participants who improved their function as measured by the Oswestry disability index (ODI) score beyond the MCID of 17 points [26,27]. This outcome was statistically significant at 6 months in favor of the PRP group. Similarly, the percentage of participants with an NRS pain score reduction greater than 50 % was statistically significant at 6 months in favor of the PRP group. Satisfaction, assessed by the modified Macnab criteria, was not statistically different between groups, but followed a pattern where participants in the CS group tended to be more satisfied at 1 month and participants in the PRP group, at 6 months.

When comparing mean scores, ODI was the only score that was statistically different between the two groups, in favor of PRP at 6 months. Even though there was no statistically significant difference for other mean scores, p-values were borderline for NRS, and SF-36 pain scores ($p = 0.051$ in both cases). ODI, NRS, SF-36 pain, and SF-36 physical functioning scores' evolution graphics (see Figs. 4–7) followed the same pattern as the MacNab satisfaction distribution: the CS group had a greater improvement at one month, both groups were similar at 3 months and the PRP group had a greater improvement at 6 months. Considering the evolution pattern and the borderline p-values, it is possible that differences could become statistically significant between groups with a longer follow-up.

The evolution patterns are similar to the results presented in the only other RCT comparing PRP to CS injections for Z-joint mediated pain in patients with Z-joint OA [25]. However, PRP became superior to CS at the 2-month follow-up in their study, while this occurred later (at 6 months) in our study. This could be explained by differences in methodology. Even though our study was triple-blinded and had a more rigorous methodology, results supported Wu's study and PRP still had a greater long-term effect compared to CS. At 6 months, participants in the PRP group had not reached a plateau yet. This suggests that studies on PRP efficacy should have longer follow-up and should not plan cross over before 6 months.

To our knowledge, this is the first RCT comparing PRP to any other treatment for low back pain (LBP) that performed laboratory analyses on PRP. Despite an identical configuration of the centrifuge for all participants, only one of them received the planned treatment: Leucocyte-Poor PRP. This emphasizes that heterogeneity in PRP formulations does not only exist between centrifugation systems but also between the PRP formulation produced by the same system. It also suggests that all clinics and institutions should have a cell count system to ensure that the PRP injected respects their expected characteristics in terms of platelets and leucocytes concentrations and ensure a certain 'quality control' of the injectate. It also highlights the need for systematic laboratory analysis and a more rigorous description of PRP in further studies to confirm the given treatment.

To our knowledge, this is the first study on LBP that created regression models based on PRP characteristics. Regression analyses showed that the total number of platelets and leucocytes injected per joint, and that PRP's platelets and leucocyte concentration ratio did not correlate with clinical outcomes. Since our sample size was small ($n = 23$), we cannot conclude with certainty that these components do not influence treatment responsiveness. Our results do not support the actual PRP literature stating that the clinical response is 'dose-related' and correlates to the total number of platelets [32–34]. Even though the total number of platelets injected in a Z-joint is small, due to the joint's volume capacity, PRP injection has produced a statistically and

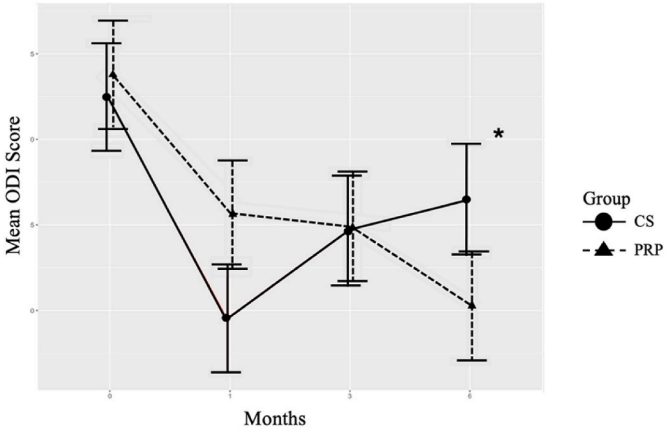

Fig. 4. ODI score evolution in PRP and CS groups.
*Significant difference between groups ($p < 0.05$).

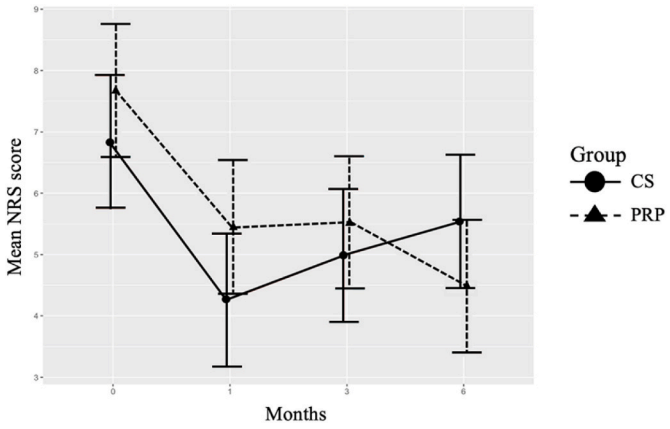

Fig. 5. NRS pain score evolution in PRP and CS groups.

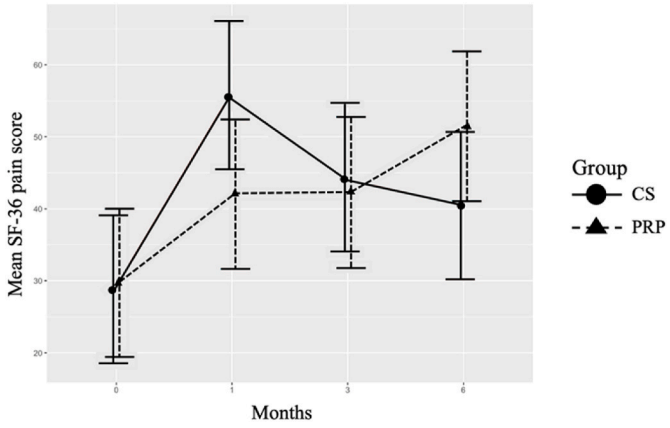

Fig. 6. SF-36 pain score evolution in PRP and CS groups.

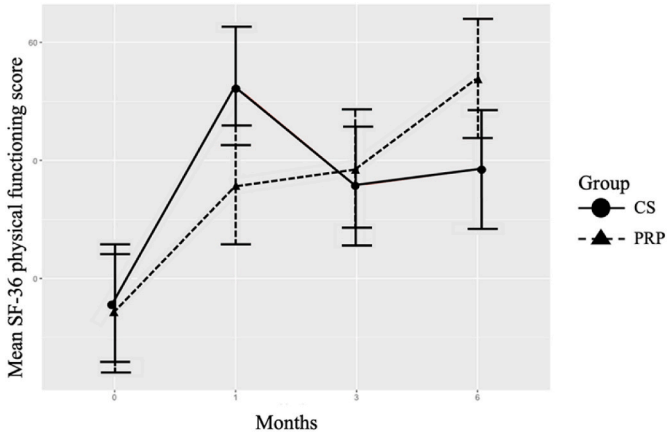

Fig. 7. SF-36 physical functioning score evolution in PRP and CS groups.

clinically superior to CS improvement in pain and function at 6 months.

This study has a few limitations. First, our sample size was large enough to detect statistically significant changes for our primary outcome but was too small for other secondary outcomes at 6 months. A larger sample size could have led to statistical significance, especially in results where p-values were borderline. PRP includes billions of bioactive molecules that were not measured in this study and Z-joint osteoarthritis stage was not assessed. Both could be determining factors in clinical response to PRP and should be explored in further studies. Our follow-up is limited to six months, and participants in the PRP group had not reached a steady state yet. Therefore, this study does not allow us to assess the whole duration of action of PRP. Moreover, considering the pattern of evolution in both groups, a longer follow-up could have led to statistical significance in favor of PRP for NRS and SF-36 mean scores, or shown that PRP's effect fade after 6 months. Radiofrequency neurotomy (RFN) of the medial branch diagnosed by branch blocks has been standard of care for pain originating from Z-joints. Since PRP was not compared to RFN in this study, it is not possible to tell if PRP is as efficient as RFN to relieve patients with LBP, and further research is still needed in that regard. PRP was also not compared to a control group with a sham procedure, a placebo or a standard conservative treatment, which should also be explored in the future.

5. Conclusion

In conclusion, this first triple blinded multicentric RCT has demonstrated the statistical and clinical superiority of PRP injection over CS in improving function and pain for patients with zygapophyseal (Z-joint) osteoarthritis mediated low back pain at 6 months. There was no serious adverse effect in both groups. Other outcomes, such as patient satisfaction and SF36 scores, were not statistically different between groups. However, they all followed the same pattern: the CS group tended to have a greater improvement at one month, both groups were similar at 3 months and the PRP group tended to have a greater improvement at 6 months. Moreover, the PRP group showed a continuous improvement over the 6-month follow-up and did not reach a plateau yet. Further triple-blinded RCT are still needed to confirm these results, and longer follow-ups are needed to determine PRP's duration of action.

Declaration of competing interest

All authors declare that they have no know competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors want to thank Professor Sylvie Gervais, Professor Serge Vincente and the Bureau de Consultation en Statistique (BCS) at the École de technologie supérieure (ÉTS) for their support in data analysis and its presentation, as well as Sacha Hobeila, Martin Kaniki, Cathy Peruch for their participation to the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inpm.2024.100525.

References

[1] DePalma MJ, Ketchum JM, Saullo TR. Multivariable analyses of the relationships between age, gender, and body mass index and the source of chronic low back pain. Pain Med 2012;13(4):498–506. https://doi.org/10.1111/j.1526-4637.2012.01339.x.

[2] MacVicar J, MacVicar AM, Bogduk N. The prevalence of "pure" lumbar zygapophysial joint pain in patients with chronic low back pain. Pain Med 2021;22(1):41–8. https://doi.org/10.1093/pm/pnaa383.

[3] Manchikanti L, Manchikanti KN, Cash KA, Singh V, Giordano J. Age-related prevalence of facet-joint involvement in chronic neck and low back pain. Pain Physician 2008;11(1):67–75.

[4] Perolat R, Kastler A, Nicot B, Pellat J-M, Tahon F, Attye A, et al. Facet joint syndrome: from diagnosis to interventional management. Insights Imaging 2018;9(5):773–89. https://doi.org/10.1007/s13244-018-0638-x.

[5] Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Is the lumbar facet syndrome a clinical entity? Spine 1994;19(10):1132–7. https://doi.org/10.1097/00007632-199405001-00006.

[6] Schwarzer AC, Wang SC, Bogduk N, McNaught PJ, Laurent R. Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Ann Rheum Dis 1995;54(2):100–6.

[7] Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 2006;15(Suppl 2):S192–300. https://doi.org/10.1007/s00586-006-1072-1.
[8] Cohen SP, Raja SN. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain. Anesthesiology 2007;106(3):591–614.
[9] Gouvernement du Québec. Algorithme de prise en charge interdisciplinaire du syndrome de douleur régionale complexe (SDRC). 2015.
[10] Carette S, Marcoux S, Truchon R, Grondin C, Gagnon J, Allard Y, et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. N Engl J Med 1991;325(14):1002–7. https://doi.org/10.1056/NEJM199110033251405.
[11] Kennedy DJ, Fraiser R, Zheng P, Huynh L, Levin J, Smuck M, et al. Intra-articular steroids vs saline for lumbar Z-joint pain: a prospective, randomized, double-blind placebo-controlled trial. Pain Med 2019;20(2):246–51. https://doi.org/10.1093/pm/pny225.
[12] Québec (Province), Ministère de la santé et des services sociaux. Algorithme de prise en charge de la douleur lombaire. 2015.
[13] Cohen SP, Bhaskar A, Bhatia A, Buvanendran A, Deer T, Garg S, et al. Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group. Reg Anesth Pain Med 2020;45(6):424–67. https://doi.org/10.1136/rapm-2019-101243.
[14] Lee C-H, Chung CK, Kim CH. The efficacy of conventional radiofrequency denervation in patients with chronic low back pain originating from the facet joints: a meta-analysis of randomized controlled trials. Spine J 2017;17(11):1770–80. https://doi.org/10.1016/j.spinee.2017.05.006.
[15] Aufiero D, Hunter V, Sampson S, Bodor M. Regenerative injection treatment in the spine: review and case series with platelet rich plasma. J Stem Cell Res Rev Rep 2015;2(1):1019.
[16] Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP injections for the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Cartilage 2021;13(1_suppl):364S–75S. https://doi.org/10.1177/1947603520931170.
[17] Hohmann E, Tetsworth K, Glatt V. Is platelet-rich plasma effective for the treatment of knee osteoarthritis? A systematic review and meta-analysis of level 1 and 2 randomized controlled trials. Eur J Orthop Surg Traumatol 2020;30(6):955–67. https://doi.org/10.1007/s00590-020-02623-4.
[18] Migliorini F, Driessen A, Quack V, Sippel N, Cooper B, Mansy YE, et al. Comparison between intra-articular infiltrations of placebo, steroids, hyaluronic and PRP for knee osteoarthritis: a Bayesian network meta-analysis. Arch Orthop Trauma Surg 2021;141(9):1473–90. https://doi.org/10.1007/s00402-020-03551-y.
[19] Nouri F, Babaee M, Peydayesh P, Esmaily H, Raeissadat SA. Comparison between the effects of ultrasound guided intra-articular injections of platelet-rich plasma (PRP), high molecular weight hyaluronic acid, and their combination in hip osteoarthritis: a randomized clinical trial. BMC Musculoskelet Disord 2022;23(1):856. https://doi.org/10.1186/s12891-022-05787-8.
[20] Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord 2018;4(1):18–24. https://doi.org/10.1159/000477353.
[21] Rodríguez-Merchán EC. Intra-articular platelet-rich plasma injections in knee osteoarthritis: a review of their current molecular mechanisms of action and their degree of efficacy. Int J Mol Sci 2022;23(3):1301. https://doi.org/10.3390/ijms23031301.
[22] Vladulescu D, Scurtu LG, Simionescu AA, Scurtu F, Popescu MI, Simionescu O. Platelet-Rich plasma (PRP) in dermatology: cellular and molecular mechanisms of action. Biomedicines 2023;12(1):7. https://doi.org/10.3390/biomedicines12010007.
[23] Byvaltsev VA, Kalinin AA, Okoneshnikova AK. [Comparative analysis of the effectiveness of PRP therapy and facetoplasty in older patients with isolated lumbar facet syndrome: long-term results of a randomized controlled trial. Adv Gerontol 2019;32(5):804–11.
[24] Kotb SY, Sherif NM, Saleh HA, Ahmed SF, Sakr HM, Taeimah MO. The role of intra-articular injection of autologous platelet-rich plasma versus corticosteroids in the treatment of synovitis in lumbar facet joint disease. Saudi Med J 2022;43(11):1200–8. https://doi.org/10.15537/smj.2022.43.11.20220449.
[25] Wu J, Zhou J, Liu C, Zhang J, Xiong W, Lv Y, et al. A prospective study comparing platelet-rich plasma and local anesthetic (LA)/Corticosteroid in intra-articular injection for the treatment of lumbar facet joint syndrome. Pain Pract 2017;17(7):914–24. https://doi.org/10.1111/papr.12544.
[26] Hung M, Saltzman CL, Kendall R, Bounsanga J, Voss MW, Lawrence B, et al. What are the MCIDs for PROMIS, NDI, and ODI instruments among patients with spinal conditions? Clin Orthop Relat Res 2018;476(10):2027–36. https://doi.org/10.1097/CORR.0000000000000419.
[27] Maughan EF, Lewis JS. Outcome measures in chronic low back pain. Eur Spine J 2010;19(9):1484–94. https://doi.org/10.1007/s00586-010-1353-6.
[28] Fritz JM, Irrgang JJ. A comparison of a modified Oswestry low back pain disability questionnaire and the quebec back pain disability scale. Phys Ther 2001;81(2):776–88. https://doi.org/10.1093/ptj/81.2.776.
[29] 36-Item short form survey (SF-36) scoring instructions. RAND. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html. [Accessed 6 August 2024].
[30] Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, et al. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. Pain Physician 2016;19(8):617–25.
[31] Brunner F, Dumhof S, Langer F. Nonparametric analysis of longitudinal data in factorial experiments. seventeenth ed. Wiley, New York: Wiley Series in Probability and Statistics; 2002.
[32] Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Author Correction: platelet-rich plasma (PRP) in osteoarthritis (OA) knee: correct dose critical for long term clinical efficacy. Sci Rep 2021;11(1):18612. https://doi.org/10.1038/s41598-021-98365-2.
[33] Berrigan WA, Bailowitz Z, Park A, Reddy A, Liu R, Lansdown D. A greater platelet dose may yield better clinical outcomes for platelet-rich plasma in the treatment of knee osteoarthritis: a systematic review. Arthroscopy 2024. https://doi.org/10.1016/j.arthro.2024.03.018. S0749-8063(24)00206-8.
[34] Patel S, Thami T, Gahlaut S, Chouhan D, Dhillon MS. Comparison of conventional dose versus superdose platelet-rich plasma for knee osteoarthritis: response. Orthop J Sports Med 2024;12(6):23259671241255962. https://doi.org/10.1177/23259671241255962.