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Cervical facet joint platelet-rich plasma in people with chronic whiplash-associated disorders: A prospective case series of short-term outcomes

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ABSTRACT

Objective: To explore the safety and feasibility of a single autologous injection of platelet-rich plasma (PRP) in cervical facet joints of people with chronic WAD and facet-mediated pain, and explore the association between pain relief reported with diagnostic medial branch blocks (MBBs) and 3-months post-PRP.
Design: A prospective case series of people with chronic whiplash-associated disorders and cervical facet joint mediated pain in a community setting.
Interventions: A single autologous PRP injection was provided to cervical facet joints under ultrasound and fluoroscopic guidance.
Measures: Adverse events were recorded one-week, and measures of pain (numerical pain rating scale - NPRS) and disability (Neck Disability Index - NDI) were collected prior to and 3-months following cervical facet joint PRP. People not reached for follow-up were considered failures for worst-case analysis. The correlation between percentage response to diagnostic cervical medial branch blocks (MBBs) and percentage pain relief reported at 3-months was also investigated.
Results: Forty-four people (82% female; mean age (SD): 45.2 (10.8) years) underwent cervical facet joint PRP. There was a significant improvement in pain and disability following PRP. Seventy percent of people exceeded MCID for pain. For NDI scores, 80% of people exceeded MCID. Forty-one percent of people reported greater than 50% relief of pain 3-months post-cervical facet joint PRP.
There was no significant correlation between percentage relief of pain with cervical MBBs and percentage relief of pain 3-months post-PRP ($r = 0.06$, $p = 0.73$).
There were no adverse events reported.
Conclusion: In people with chronic WAD and facet-mediated pain, preliminary data suggests that PRP is safe and it is feasible to move forwards with randomized studies to further investigate efficacy and effectiveness.

1. Introduction

Whiplash-associated disorders is a heterogeneous condition resulting from a cervical acceleration/deceleration injury [1]. This may result in a variety of tissue lesions, including facet joint contusions, fractures or capsular strains; uncovertebral injuries; endplate tears; muscular and neurological tissue haematomas or avulsions; cervical discoligamentous tears and ruptures [2–7].

The most widely studied model of whiplash injury involves facet capsular strains [8]. Biomechanical findings in cadavers [4,9,10], human volunteers [11] and mathematical modelling [12] studies have been replicated in animal studies [13]. These studies have demonstrated that nociceptive signalling is induced in cervical facet capsular strain that does not involve complete rupture [14]. Furthermore, these studies have

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Abbreviations

whiplash-associated disorders (WAD)
platelet-rich plasma (PRP)
medial branch blocks (MBBs)
numerical pain rating scale (NPRS)
neck disability index (NDI)

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demonstrated associated microstructural damage to the collagen matrix [15]; neuromodulatory [16,17], inflammatory [18] and electrophysiological [19–21] changes, which may result in persistent pain behaviours in the animals studied. The pre-clinical study results have been confirmed in clinical populations of people with chronic neck pain following whiplash injury. Studies using controlled diagnostic cervical facet joint blocks have shown that the prevalence of pain stemming from a facet joint following whiplash injury is between 36 and 67% [22–26].

For people with cervical facet-mediated neck pain in chronic WAD, a validated treatment option is available. Cervical radiofrequency neurotomy (RFN) involves thermal lesioning of the medial branches of the dorsal rami which innervate the putative facet joint [27]. Denervation results in complete relief of pain associated with the joint. Relief of pain from RFN is finite, although repeating the procedure provides further relief [28,29]. As with any interventional procedure, RFN may be associated with risks and complications and is generally not indicated in people with multi-level facet joint involvement [30], which may occur in WAD [26] and could possibly result in dropped head syndrome [31] or ataxia [32]. Radiofrequency neurotomy is also not indicated in pregnant women and caution is required for those with implanted medical devices such as pacemakers or spinal cord stimulators. As ongoing pain relief requires repeat procedures being performed, this may result in a burden in jurisdictions with limited health resources. Thus, there is a need for other effective treatment options for chronic facet-mediated neck pain in instances where RFN is not clearly indicated.

Recently, platelet-rich plasma (PRP) has been used to treat cervical [33,34] and lumbar [35,36] facet-mediated pain. Platelet-rich plasma is a concentrate of centrifuged whole blood to obtain plasma rich in platelets and hence growth factors. The increased concentrate of growth factors promote healing through increased fibroblast and/or osteoblast metabolic activity while reducing cell apoptosis; increasing blood flow to the new tissues via angiogenesis, and increasing tensile strength of the new tissue [37,38]. Leukocyte-rich PRP (LR-PRP) has an increased concentration of white blood cells in addition to a high concentration of platelets. Thus, PRP aims to stimulate and supplement the body's healing mechanisms. The clinical utility of PRP involves the possibility of a sustained recovery and a favourable side-effect risk profile. Although initial study findings involving cervical and lumbar spine facet joint PRP injections are promising, they have not specifically addressed people with chronic WAD and facet-mediated pain, as diagnosed with medial branch blocks (MBBs).

The aims of this prospective case series were to explore the safety and feasibility of a single autologous injection of PRP in cervical facet joints of people with chronic WAD without neurological symptoms or previous fracture (i.e. Grade II) [1] and facet-mediated pain, and explore the association between pain relief reported with MBBs and 3-months post-PRP.

2. Methods

2.1. Participants

Registry data from people attending a multidisciplinary health care clinic in Calgary, Canada were used to collect outcome measures for this prospective case series, prior to, one-week, 3-, 6- and 12-months post-

PRP. This prospective case series is reporting the 3-month outcomes. Each patient undergoing PRP provided signed consent for their de-identified data to be collected in the patient registry. The registry data protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary (Ethics ID#: REB20-0355). The study was conducted according to the Declaration of Helsinki.

Inclusion criteria for this study involved the following: WAD Grade II [1] of greater than 3-months duration; failure to respond to a minimum of six weeks of conservative (physiotherapy, chiropractic or massage) therapy, and a positive response to a single diagnostic cervical medial branch block: defined as greater than 80% relief of index pain or greater than 50% relief of pain AND significant improvement in performing a previously limited activity of daily living. A minimum time-period of 3-months post-intervention was required to evaluate short-term outcomes. Participants were excluded from participating if they had known or suspected serious spinal pathology (e.g. metastatic disease of the spine); WAD Grade III (nerve root compromise); WAD Grade IV (confirmed fracture or dislocation at time of injury); post-concussion syndrome; previous cervical spinal surgery; or history of any mental health conditions such as bipolar disorder, psychosis or schizophrenia (to prevent these pre-existing conditions from confounding disability data). Participants were also excluded if they were unable to stop taking anti-inflammatory medications for 3-days prior to, or 10-days following PRP, had corticosteroid injections within the prior 3-months or were unable to understand or complete validated questionnaire items in English.

2.2. Interventional procedures

2.2.1. Diagnostic medial branch blocks (MBBs)

A single MBB was performed at each spinal level suspected of being a source of underlying nociception. These were performed from a lateral approach [27]. With the person in a side lying position, the articular pillars on each side were superimposed and a 25 or 27 gauge needle was advanced to the centroid of the articular pillar for C3-6, the midpoint of the lateral joint line for C2/3 and at the superior articular process portion of the lateral mass for C7. On the AP view, the needle tip was adjusted to lie in the concavity of the lateral mass waist for C3-6, at the joint line midpoint followed by sites just above and just below the mid lateral joint line for C2/3, and at the junction of superior articular process-transverse process junction for C7. 0.3 mL of 2% lidocaine was injected per medial branch nerve when blocking the C3–C7. 0.3 mL of 2% lidocaine was used at each of the three sites when blocking the 3rd occipital nerve.

2.2.2. Platelet-rich plasma (PRP) formulation

The PRP was formulated using a modified syringe technique [36]. For example, to produce 4 mL of PRP, 13 mL of blood was drawn into a 20 mL sterile syringe that had been primed with and contained 2 mL of 4% sodium citrate using aseptic technique and routine phlebotomy protocol. The syringe was capped and modified (phalanges and plunger trimmed) [39] and placed into a 50 mL conical tube with the capped end facing upward. The syringe containing conical tube was placed into a balance centrifuge (ELMI CM-75) and spun at 1500 G for 7 min. This separated the blood into upper plasma, mid buffy coat, and lower red cell layers. The upper portion of the plasma was drawn off and discarded, leaving the bottom 3.5 mL of plasma. It and the buffy coat layer, including 0.5 mL of the top red cell layer, were drawn into a separate sterile syringe ready for injection. In-house quality assurance testing of the PRP formulated using this technique has confirmed that the PRP has the following cellular characteristics: (mean X concentration of whole blood): platelets 4.2X; neutrophils 1.0X; lymphocytes/monocytes 1.8X; red blood cells 0.1X).

2.2.3. Platelet-rich plasma (PRP) delivery

This was delivered by injection to each target cervical facet joint(s) (that responded to the cervical MBBs) from a lateral approach most often under fluoroscopic guidance. With the patient in a side lying position, the

articular pillars on each side were superimposed and the needle was advanced to the midpoint of the target facet joint line on the lateral view. The needle was advanced 1–2 mm intra-articularly under AP view. 1 mL of PRP was injected intra-articularly or until capsular distension was perceived. Then, on the lateral view, the needle was withdrawn from the joint and 1 mL of PRP was distributed along the periosteal surface at the superior and inferior margins of the joint lines to target the lateral capsule. This was repeated for each facet joint. Injection of contrast was not performed. There were no limits on the number of cervical facet joints injected. In the event that the lower cervical facet joints were sub optimally visualized on fluoroscopy because of high riding shoulders, or if the participant tended to move during the procedure and superimposition of the bilateral articular pillars was difficult, either a fluoroscopically guided posterior approach or an ultrasound guided approach was utilized (in-plane posterior to anterior technique) [40].

2.2.4. Co-treatments

All people were encouraged to attend physiotherapy (within the community) following PRP to assist with residual interventional discomfort and to address physical impairments such as mobility, isometric strength or endurance deficits. Attendance at physiotherapy was not formally monitored.

2.3. Outcome measures

Outcome measures were collected on the day of the PRP procedure, one-week and 3-months post-procedure. One-week data was collected in person at the clinic or via phone call with a patient care co-coordinator to evaluate presence of adverse events. Outcome measurement data were collected via electronic entry into a registry database. A maximum of three electronic or phone reminders were provided to study participants to complete the electronic outcome measures.

2.3.1. Safety

Safety was defined by the occurrence of an adverse event defined, which is 'a response to an intervention which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' and that likely has a causal relationship with the intervention. The presence of adverse events was evaluated and recorded one-week post-PRP either by (1) personal attendance in-clinic with a staff physiotherapist, or (2) a phone call from a patient care co-coordinator (if not attending physiotherapy).

2.3.2. Pain and disability

Pain: An 11-point (0 = no pain to 10 = the most intense pain imaginable) numerical pain rating scale (NPRS) was used to measure a person's average 24-h neck pain intensity. The minimally clinically important difference (MCID) for chronic musculoskeletal pain has been defined as a 15.0% change [41].

Neck Disability Index (NDI): The NDI includes 10 questions, rated using a 6-point (0–5) Likert scoring system to evaluate how neck pain affects a person's daily life and to assess neck pain-related disability [42]. The sum of the 10 questions was converted to a percentage for analysis. The MCID for mechanical neck disorders is 5.0 point (10%) change [43].

2.4. Data analysis

Based on the normal distribution of data, which were determined with graphs and box plots, parametric statistics were used for data analyses. Pain and NDI scores were described using the mean and 95% confidence intervals. The difference between 3-month and baseline scores were calculated for NPRS and NDI, and the percentage of people meeting or exceeding the MCID for each metric were calculated. The proportion of people reporting greater than 50% relief of pain was also calculated. People not reached for follow-up were considered failures for

worst-case analysis. Paired *t*-tests were used to evaluate whether 3-month scores were significantly different from baseline. Effect sizes were calculated using an online within-subjects calculator: https://memory.psych.mun.ca/models/stats/effect_size.shtml and expressed as Cohen's *d*. We considered effects to be small for Cohen's *d* values between 0.2 or 0.3; medium for values above these values and less than 0.8, and large for values greater than 0.8 [44]. Chi-squared analysis was used to calculate if there was a significant difference in people exceeding MCID for each metric. The Pearson correlation co-efficient was used to investigate the relationship between percentage response to diagnostic cervical medial branch block (MBB) and percentage pain relief reported at 3-months. Chi-squared analysis was also used to evaluate the association between MBB response (50–79% or $\geq$ 80% relief) and dichotomous pain relief at 3-months for both MCID response and 50% pain relief criterions. The level of significance was set at $p \leq 0.05$. All analyses were performed using IBM SPSS Statistics (Ver. 25).

3. Results

Forty four people fulfilled the study criteria (82% female; mean age (SD): 45.2 (10.8) years). One person was lost to follow-up and two people did not complete the NDI questionnaires. Their data was retained for worst-case analysis. The median duration of neck pain was 24 [Interquartile Range: 17 to 34] months. There were no adverse events reported.

The most common level receiving PRP was C5/6 and the least common was C7/T1 (Table 1). Six people had one level injected, 14 two levels, 13 three levels and 11 had four levels injected. Twenty four people received bilateral injections in the cervical spine. Fifty percent (n = 22) of people receiving PRP also received PRP in the thoracic or lumbosacral spine regions during the same or a separate appointment.

3.1. Pain and disability levels

There was a significant improvement in pain and disability levels following PRP (p < 0.001; Table 2; Figs. 1 and 2). Seventy percent of people exceeded MCID for pain ($\chi^2 = 6.7$; $p = 0.01$), whilst 80% of people exceeded MCID for NDI scores ($\chi^2 = 15.2$; $p < 0.001$). Forty one percent of people reported greater than 50% relief of pain ($\chi^2 = 1.1$; $p = 0.29$) 3-months post-cervical facet joint PRP.

3.2. Response to cervical medial branch block and 3-month pain outcomes

Forty two of the 44 people reported raw pain scores pre- and post-MBBs. The other two people receiving cervical PRP indicated that they had a 'successful' response to MBB when followed up, but did not record raw pain scores pre- and post-MBB. Twenty people reported greater than 80% relief of pain, whilst 22 reported 50–79% relief post-MBB.

There was no significant correlation between percentage relief of pain recorded post-MBB and percentage relief of pain 3-months post-PRP ($r = 0.06$, $p = 0.73$). There was also no significant difference in those exceeding MCID or 50% pain relief and the amount of pain relief (50–80% or > 80%) reported with diagnostic cervical MBBs (MCID: $\chi^2 = 0.77$; $p = 0.38$; >50% pain relief: $\chi^2 = 0.13$; $p = 0.72$).

4. Discussion

This is the first study investigating PRP in chronic WAD with cervical facet-mediated pain following successful diagnostic MBBs which confirmed the putative joints. The study suggests that a single autologous

Table 1
Number of people receiving platelet-rich plasma at each cervical facet joint level.

Facet Joint Level	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1
Number	24	26	26	28	12	1

Table 2

Pain and disability levels prior to and following a single cervical facet joint injection of autologous platelet-rich plasma. Relative Change reflects group level measurements, whilst Responder Changes reflect responses for those exceeding MCID for NPRS and NDI. NPRS = numerical pain rating scale; NDI = neck disability index; CI = confidence interval.

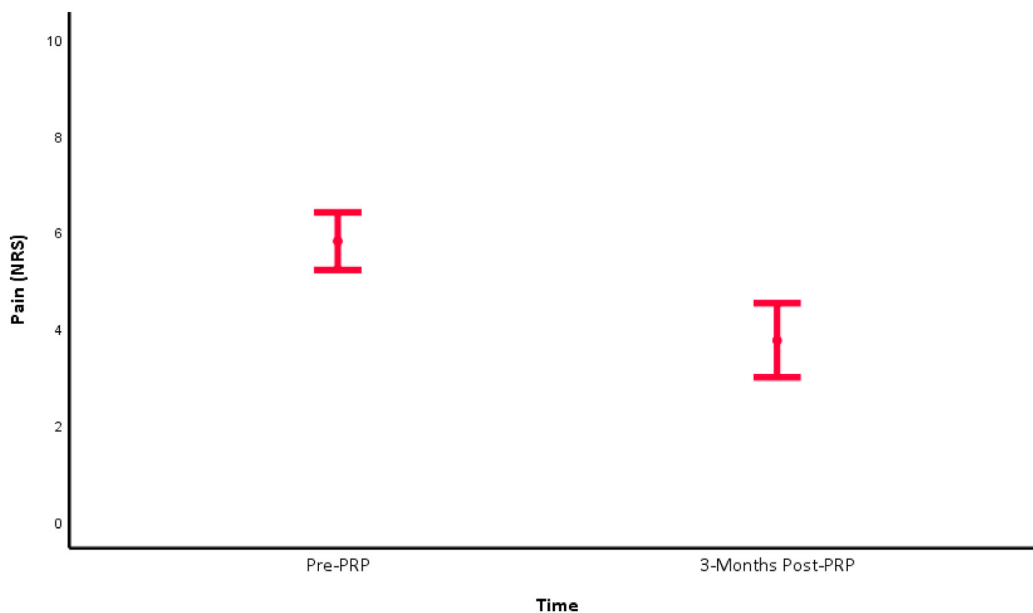|	Pre-PRP (95%CI)	3-months Post-PRP (95%CI)	Raw Change (Post - Pre) (95%CI)	Effect Size (Cohen's d)	Relative Change % ((Post - Pre)/Pre) (95%CI)	Exceeded MCID (>15% NPRS) (>10% NDI) (95%CI)	Responder % Change
NPRS (/10)	5.8 (5.2, 6.4)	3.7 (3.0, 4.4)	2.2 (1.4, 2.9)	0.897	35% (23%, 48%)	70% (55%, 84%)	56% (44%, 67%)
NDI (%)	45.2% (40.9%, 49.5%)	30.7% (26.2%, 35.2%)	14.5% (10.7%, 18.4%)	1.184	30.4% (21.0%, 39.9%)	80% (68%, 93%)	45% (36%, 54%)

Fig. 1. 95% confidence intervals for pain scores (0−10) pre- and post-cervical facet joint platelet-rich plasma injections.
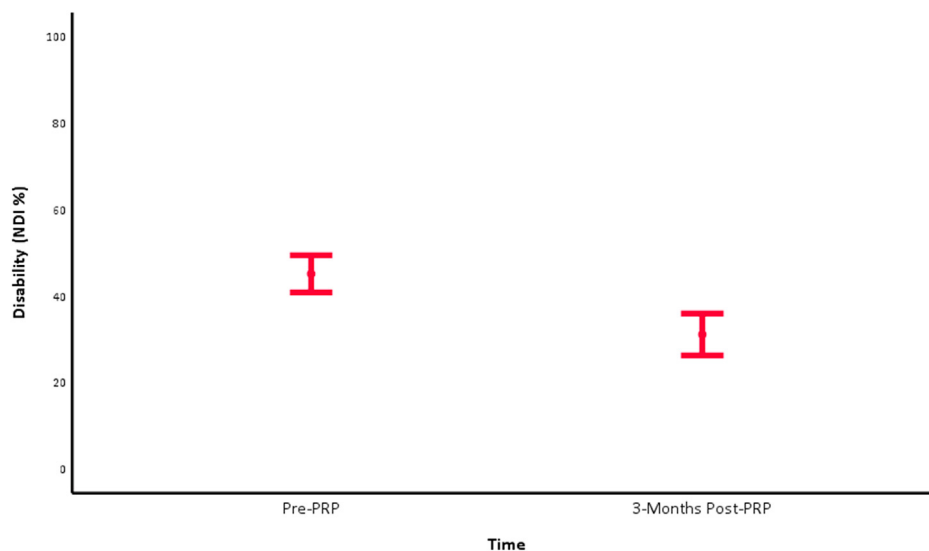

Fig. 2. 95% confidence intervals for neck disability index (NDI) percentage scores pre- and post-cervical facet joint platelet-rich plasma injections.

PRP intervention, possibly in combination with physiotherapy, for people with chronic WAD and facet-mediated pain is a feasible intervention and warrants further investigation through a RCT study design to further evaluate efficacy and effectiveness. Preliminary data showed a significant and clinically relevant reduction in pain and disability levels 3-

months post-intervention. No adverse events were reported. There was no association between pain relief reported for the diagnostic MBBs performed and that reported 3-months post-PRP.

For chronic WAD, various treatment options may be considered for symptom relief [45]. For those with concurrent facet-mediated pain,

recent consensus guidelines on interventions for cervical spine (facet) joint pain from a multispecialty international working group provides an extensive overview of therapeutic rationales and options when considering optimal outcomes for patients [46]. The reference standard and strongest evidence for long term pain relief is RFN. This is largely based on the seminal study by Lord et al. [26] At 3–6 months post-intervention, 60% of participants continued to demonstrate 50% pain relief, with 33% reporting 50% improvement at 12-months [26]. Radiofrequency neurotomy requires repeating, approximately 7–14 months post-intervention [29]. Our data compares favorably with these outcomes with 41% of people reporting 50% pain relief within 3-months. It remains to be seen if these improvements are maintained over time or if repeat procedures are required to sustain improvement. The benefits of RFN also need to be weighed against the risk of possible adverse consequences. Although rare, intra-operative vascular or neural injury and post-operative disequilibrium or weakness can occur. More common post-procedural risks and complications include cutaneous numbness and dysesthesias (17–88%) [28,47]. Also, for people requiring multilevel cervical facet RFN, there is risk of developing neck extensor weakness (i.e. dropped head syndrome) [31] and ataxia (particularly with bilateral simultaneous C2/3 facet joint RFN) [32]. These potential RFN adverse effects are of particular concern in young people with multiple potential sources of underlying nociception or multiple bodily regions of pain who may require years of repeat multilevel RFN procedures. Such a scenario is possible in the whiplash population [26]. If confirmed to be safe, effective and enduring, PRP would be an attractive alternative.

Other treatment options for people with chronic WAD also need to be considered [45]. Unfortunately, recent conservative therapy trials have only demonstrated modest pain reduction [48–52]. Systematic reviews investigating conservative therapy for WAD also report that the current evidence base is weak; with only short-term effects on neck pain reported [45,53–55]. Thus, people may seek interventional treatment for longer term pain relief. Although intra-articular corticosteroid injections have been shown in an unblinded RCT to supplement rehabilitation improvements for people with myofascial pain [56], this has not been replicated in chronic WAD, where there was no significant difference until return of 50% pain levels, demonstrated between a group of people receiving local anaesthetic alone (3.5 days) or those receiving betamethasone (3 days) [57].

Insofar as prior PRP interventions are concerned, only two prior small, observational studies have investigated PRP injections into the cervical facet joints. These have utilized a 'functional unit' approach, which involved injecting any or all of the spinal structures (e.g. disc, vertebral body, facet joint, ligaments, epidural space and/or nerve roots) with a variety of substances (i.e. PRP, prolotherapy, platelet lysate or leukocyte-free PRP - PRGF) [33,34]. No diagnostic blocks were performed in these studies to determine if the structures injected were responsible for the person's pain. Thus, non-specific interventions with a variety of injectates were performed. In Williams' study, a mean 2-point reduction of pain (MCID) was evident within 3-months, with 45% of people achieving pain relief exceeding MCID within 3-months [34]. In comparison, our data demonstrated that 70% of people exceeded MCID (15% reduction in NPRS) when MBBs were employed to implicate and specifically treat putative cervical facet joints. Of note is that further improvements were demonstrated over time for Williams et al., with 79% of people exceeding MCID at 24 months [34]. In Kirchner and colleagues study using PRGF, there was an approximate 4-point improvement in median pain scales in their retrospective study [33]. However, participants' outcomes were measured at variable times post-procedure with a minimum of one-month period required, making comparisons between studies challenging. Previous studies (one trial and one observational study) in the lumbar spine specifically investigated facet joint nociception following diagnostic injections [35,36]. In the trial, approximately 80% of people reported 50% pain relief six months post-PRP [36]. It remains to be seen if further improvements occur over time in our study cohort or if participants require further PRP for effective dose responsiveness.

There is considerable uncertainty in the literature regarding the optimal composition of PRP, dose responsiveness and its treatment effectiveness. Typically, intra-articular structures are treated with Leukocyte Poor-PRP (LP-PRP) whereas extra-articular structures with Leukocyte LR-PRP [58]. We used a single dose of LR-PRP both intra- and extra-articularly, to address both the proposed predominant capsular-strain model of WAD [12] and also intra-articular lesions that have been documented in dissection studies [3]. There is also evidence that, although early post injection pain and inflammation may be temporarily increased, leukocytes play an important role in triggering the "regenerative inflammation" integral to the healing process, with LR-PRP demonstrating clinical effectiveness when used intra-articularly [59,60]. On the other hand, excess neutrophils may stimulate the generation of reactive oxygen species and metalloproteinase proteins which adversely affect healing [59]. The spin protocol we used created monocyte/lymphocyte rich and neutrophil neutral PRP with an acceptable therapeutic platelet concentration, providing confidence of PRP treatment fidelity. The heterogeneity of whiplash injuries and the lack of diagnostic accuracy in diagnostic imaging modalities to differentiate intra-articular compared to extra-articular lesions [3,5,61], makes decision-making around optimal PRP preparation challenging. Comparison in treatment outcomes for single or multiple doses of LR- or LP-PRP requires further investigation and is currently underway.

Whereas a recent systematic review demonstrated that greater responses to multiple diagnostic MBBs resulted in greater relief of pain following RFN [62], the optimal selection criteria for PRP responsiveness has yet to be fully determined. Our data demonstrated that the percentage of MBB pain relief was not associated with the magnitude of pain relief post-PRP. Our selection criteria for PRP suitability involved greater than 50% pain relief to a single MBB, which carries a risk of 27–63% false positive response [22]. Thus, the 30% of people not responding to PRP in our study may have been due to a false positive response to MBBs. Further research is warranted to determine which diagnostic criteria and patient characteristics are associated with improved treatment outcomes for PRP following whiplash injury. Our selection criteria also resulted in a large number of multi-level and multi-regional injections. In comparison to RFN, this is likely not critical for future function, but is also not ideal, given the procedural discomfort and possible risks that can result with multiple interventions.

Caution is required when evaluating these results. This study involved a prospective case series. No control group, randomization or blinding of participants was employed. Thus, regression to the mean was possible, although all people had previously participated in a minimum of six weeks of conservative care (physiotherapy, chiropractic or massage therapy) without reported symptom improvement and thus the self-reported results are presumed to be an accurate reflection of their condition. The composition of the PRP was assumed based on prior quality assurance testing using the same PRP preparation technique. However, PRP for each subject in this study was not confirmed by individual analysis. Patients were also encouraged to attend post-PRP physiotherapy to address any physical impairments and restore functional limitations. Physiotherapy attendance was not monitored. It is possible that the responder rate was influenced by the therapeutic effect of physiotherapy. As one of the inclusion criteria related to an initial lack of improvement with conservative care, any improvement with subsequent physiotherapy would likely be associated with the combined effect of both PRP and physiotherapy, rather than physiotherapy alone. This is currently under investigation. Given the number of participants also receiving PRP for other spinal regions, it is also possible that participants completed their NDI measures in relation to other bodily pain restrictions. Thus, it is possible, that the NDI scores underestimated the overall improvement reported. Other health outcomes such as medication intake or health care resource utilization were initially not collected through our registry database and require further investigation. A positive aspect of registry data is that outcomes are entered independently through computer access, free of assessor bias. However, the fact that

approximately 9% of outcomes were not available for analysis could be seen to be a negative associated with registry databases. To overcome this, worst case analyses were provided to allow a conservative estimate of effects. Platelet-rich plasma is largely an uninsured service in Alberta, Canada, with a number of the study participants funding the treatment themselves. As wealth is associated with better health [63], the results may not be generalizable to the general population.

Notwithstanding the limitations reported, when compared to other treatment options for longer term pain relief in chronic WAD, initial outcomes for PRP are promising with safety and feasibility demonstrated. Although these preliminary findings are promising for chronic WAD and cervical facet-mediated pain, further studies are required to evaluate the efficacy and effectiveness of PRP in other cohorts of WAD and these are underway."

5. Conclusion

In people with chronic WAD and cervical facet-mediated pain who fail to respond to previous conservative therapy, PRP provides a safe and effective option for longer term relief of symptoms.

Funding

Declaration of competing interest

The authors do not have any conflict of interests to declare.

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