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Cervical facet joint platelet-rich plasma in people with chronic whiplash-associated disorders: A prospective case series of longer term 6- and 12- month outcomes

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ABSTRACT

Objective: To explore the 6- and 12-month effectiveness of a single autologous injection of platelet-rich plasma (PRP) in cervical facet joints of people with chronic WAD and facet-mediated pain.
Design: A prospective case series of people with chronic whiplash-associated disorders and cervical facet joint mediated pain in a community setting.
Interventions: We investigated 44 consecutive people who underwent cervical facet joint PRP (± adjunct physiotherapy) between 2019 and 2021, selected for PRP based on 80% relief following single diagnostic medial branch blocks or 50% relief and a significant improvement in performing a previously limited activity of daily living.
Measures: Measures of pain (numerical pain rating scale - NPRS) and disability (Neck Disability Index - NDI) were collected prior to and 3-, 6- and 12- months following cervical facet joint PRP in an electronic registry database. Success was defined as those exceeding the minimal clinically important difference (MCID) for pain (>15%) and disability (>10%). We also calculated the proportion of people with greater than 50% relief of pain. People not reached for follow-up were considered failures for worst-case analysis.
Results: Forty-four people (82% female, mean age = 45.2 (range: 25–71) years) underwent cervical facet joint PRP. Nine people received repeat PRP interventions. Thirty-five people provided 12-month data. There was a significant improvement in pain and disability following PRP (and possibly adjunct physiotherapy) received during this time period. At 12-months, 53% of people exceeded MCID for pain, reporting a mean improvement of 66% (95%CI: 55–77%) on the NPRS. For NDI scores, 69% of people exceeded MCID, reporting a mean improvement of 48% (95%CI: 38–58%). Thirty-seven percent of people reported greater than 50% relief of pain 12-months post-cervical facet joint PRP.
Conclusion: In people with chronic WAD and facet-mediated pain, our long-term data suggests that PRP (and possibly adjunct physiotherapy) is effective. A controlled study is warranted to evaluate the efficacy of PRP.

1. Introduction

The cervical facet joint is a common source of nociception in people with neck pain following whiplash injury with prevalence estimates ranging from 29 to 60% [1–4]. Cervical facet-mediated pain is associated with high levels of pain and disability and both physical and psychological manifestations of chronic whiplash-associated disorders (WAD) [5].

The standard treatment for cervical facet-mediated pain is radiofrequency coagulation (RFC) [6,7]. It is also the only treatment that has demonstrated effectiveness for treating chronic WAD [8]. This is a minimally invasive, neuroablative treatment that involves denaturation of the medial branches of the putative facet joints [9]. When applying

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Abbreviations

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

rigid selection criteria (double-blind, placebo-controlled diagnostic blocks, requiring complete pain relief following local anesthetic block to be considered positive) and treatment including multiple lesions of the target nerves, it has been demonstrated that the median duration of time until 50% of pain returns is 219 days for all those receiving RFC and 422 days in those reporting greater than 90 days of pain relief [10]. A subsequent study utilizing equally as rigorous selection criteria and operative procedures showed that patients could experience 17–20 months of pain relief [11]. Although the effects of RFC are finite, the procedure can be repeated when the pain returns with similar results [10,11]. These individual study results were supported by a recent systematic review [12]. Based on a qualitative and quantitative analysis with single-arm meta-analysis and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system of appraisal, it was determined that there was level II evidence for managing neck pain (inclusive of people with idiopathic or WAD aetiology) with cervical RFC [12].

Despite success, there are situations where RFC may not be indicated, or participants do not wish to pursue such. As an example, even when a diagnosis has been obtained with stringent selection criteria applied, patients may not report significant pain relief after RFC [10,13,14]. Similarly, the rigorous selection criteria applied above (100% relief of index pain with dual medial branch blocks) assist with improving RFC treatment outcomes [15], but also result in people not being eligible for RFC (e.g. patients experiencing 75% pain relief). Additionally, RFC may be ill advised for people that are young, have multiple symptomatic cervical facet joints requiring treatment, have a pacemaker or neurostimulator, or are pregnant. As a result, further treatment options need to be considered. One of these involves application of platelet-rich plasma (PRP) in and around the putative facet joints.

We have previously reported on the 3-month outcomes of 44 people who underwent cervical facet joint PRP following whiplash injury and who had not responded to prior conservative therapy [16]. The purpose of this study was to determine the longer 6- and 12-month outcomes of these same people to further examine the effectiveness of cervical PRP for longer term management of neck pain following whiplash injury in suitably selected people. Further, a description of repeat PRP procedures performed was made to enable insight on possible dose responsiveness. The combination of this data also informs further research to overcome methodological considerations associated with case series designs.

2. Methods

This prospective observational study was performed at a private community multidisciplinary chronic pain centre in Calgary, Canada. People attended a multidisciplinary evaluation for persistent symptoms resulting from whiplash injury that had not responded to prior conservative therapy. Methodology associated with the study design, participant recruitment, diagnostic procedures performed, PRP formulation and delivery, and outcomes measured have been reported elsewhere [16]. Ethics approval was obtained through the Calgary Research Ethics Board (Ethics ID#: REB20-0355) and the study was conducted according to the Declaration of Helsinki.

A brief summary of the study's methodology is reported for clarity's sake. All participants entered measures of pain (numerical rating scale: 0–10) and disability (Neck Disability Index) into an electronic registry database on the day of receiving PRP and 3-, 6- and 12-months later. Safety data was also collected within the first week. No adverse events were reported [16]. Participants were eligible to participate if they presented with WAD grade II classification (axial neck pain without radiculopathy, fracture or dislocation) [17]. A clinical examination was performed at the initial evaluation. After clinical examination determined that the person's neck pain may be arising from the cervical facet joints [18], the person was referred for diagnostic facet joint procedures in the form of medial branch blocks. Upon achieving a positive response following a single MBB (>80% relief of index pain, or >50% relief of pain with significant improvement in an activity of daily living in the 6-h post-procedure), the person was informed that they were eligible to receive PRP for management of their facet-mediated neck pain. Various treatment options together with their respective risks, precautions and available levels of evidence for each therapy available were thoroughly explained to each person prior to the person consenting to receive PRP as their preferred treatment option. Platelet-rich plasma was formulated and delivered as previously described, with in-house quality assurance testing confirming 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). Procedurally, 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 [16]. Following PRP, participants were encouraged to attend physiotherapy to address any physical impairments identified in the physical examination. Attendance was not formally monitored. Participants were emailed 3-, 6- and 12-months post-PRP to enter their outcomes into the patient registry. Three reminders were sent at each time period, with an additional phone call at 12-months to remind participants of the emails sent. People lost-to-follow up had available data analysed and were considered 'non-responders' for worst-case scenario/intention-to-treat (ITT) analyses.

2.1. Data analysis

Data was investigated for normality through data inspection, graphical representation and Shapiro-Wilk statistics. Descriptive statistics were used to analyze demographic variables, measures of pain and disability and responder rates (means and 95% confidence intervals). Differences between 3-, 6- and 12-month and baseline data were calculated for numerical pain rating score (NPRS) and neck disability index (NDI), and the percentage of people meeting or exceeding the minimal clinically important difference (MCID) for each metric (NPRS = 15% [19]; NDI = 10% [20]) were calculated. The proportion of people reporting greater than 50% relief of pain was also calculated. Linear mixed models with random intercepts were developed to investigate a) the relationship between pain intensity AND disability and b) responder rates (dependent variables) OVER time (independent variable: pre-PRP, 3-, 6- and 12-months post-PRP). Age and sex were entered as co-variates and kept in the model if significant. If significance was detected, pairwise comparisons were performed to determine at which time periods differences existed. Effect sizes were calculated using baseline and 12-month data via an online within-subjects calculator [21] and expressed as Cohen's *d*. Categorically, values were considered 'small' between 0.2 or 0.3; 'medium' for values exceeding 0.3, but less than 0.8 and 'large' for values greater than 0.8 [22]. Level of significance was set at 0.05. All analyses were performed using IBM SPSS Statistics (Ver. 26.0).

3. Results

Forty-four consecutive participants (82% female, mean age = 45.2 (range: 25–71) years) with a median duration of 24 [Interquartile Range: 17 to 34} months of symptoms were eligible to participate in this study.

The 3-month results have been reported elsewhere [16]. Thirteen participants failed to enter registry data at 6-months (n = 31), and 9 people (n = 35) failed to enter registry data 12-months post-PRP. Their data is included in the intention-to-treat (ITT) analyses.

3.1. Pain and disability levels

After controlling for age and sex, there was a significant pain*time interaction ($F_{3,109.802} = 17.5$, $p < 0.001$; Fig. 1) and disability*time interaction ($F_{3,104.866} = 25.5$, $p < 0.001$; Fig. 2). Post hoc testing demonstrated that there was a significant reduction in pain and disability at 3- (each $p < 0.001$), 6- (each $p < 0.001$) or 12-months (each $p < 0.001$) when compared to baseline. There were no significant differences in pain or disability levels between 3- (p's > 0.39), 6- (p's > 0.33), and 12-months (p's > 0.33).

3.2. Categorical data

In the best-case scenario, which includes responses from those people completing registry data at each respective time point, there was no significant change in the proportion of people meeting 'responder' status (exceeding MCID) for both pain ($F_{2, 69.231} = 2.53$, $p = 0.09$) and disability ($F_{2, 65.537} = 1.09$, $p = 0.34$) over time (Table 1). Also, the magnitude of pain ($F_{2, 66.048} = 0.352$, $p = 0.71$) or disability ($F_{2, 65.634} = 1.63$, $p = 0.20$) relief did not significantly change over time (Table 1). Similar findings were demonstrated for 50% pain relief status ($F_{2, 67.365} = 1.16$, $p = 0.32$; Table 2). The ITT analysis ('worst-case scenario') demonstrated a significant reduction in responder status between 3- and either 6- or 12-months for both pain ($F_{2, 86} = 5.70$, $p = 0.005$) and disability ($F_{2, 85.466} = 6.18$, $p = 0.003$; Table 1). Significantly less people reported 50% pain relief at 6- when compared to 3-months ($F_{2, 86} = 3.51$, $p = 0.03$; Table 2) in the ITT analysis. At 12-months, responders to cervical PRP demonstrated moderate-to-large effect sizes for pain and disability relief respectively (Table 1).

3.3. Repeat procedures

Five of the initial 44 (11%) participants requested repeat procedures be performed within the 12-month period following their initial PRP intervention. This request was made when initial pain relief dissipated over time. One person received three interventions. Two of the five reported significant reductions in pain and disability at 12-months and were considered 'responders', with one reporting greater than 50% pain relief. As previously reported, no adverse events were recorded for initial or repeat procedures.

4. Discussion

This study provides longer-term outcomes for PRP in chronic WAD with cervical facet-mediated pain. At the group level, significant and large reductions in pain and disability were reported at 3-months and maintained at the 6- and 12-month periods. There was a gradual, but not significant reduction in those meeting 'responder' status for both pain and disability over time, such that approximately half of the participants reported a significant improvement in pain and approximately 70% a significant improvement in disability at 12-months; down from 70% to 80% respectively 3-months post procedure. Interestingly, for those who responded, the magnitude of pain reduction increased slightly from 56% to 66%, whereas the magnitude of disability relief remained stable between 55 and 60%.

Upon first examination, these findings support the utility of cervical facet joint PRP for people with chronic WAD and facet-mediated pain. Initial promising results demonstrated at 3-months were maintained at 6- and 12-months. However, any report of treatment success in chronic WAD for those with facet-mediated pain requires comparison to other validated treatment options. To that end, data from studies using cervical RFC can act as a comparator to determine treatment effectiveness in the real world. Lord's randomized controlled trial provides data for comparison [13]. At 12-months, 33% of trial participants reported 50% pain relief [13]. The data from our study is comparable, with 37% of those completing registry data reporting 50% pain relief. Even if we consider the worst-case scenario, whereby absent registry data resulted in determination of 'non-responder' status at each respective time point, 34% of participants still reported treatment success at 12-months, with an average magnitude of pain relief of 66% when compared to their NPRS on the day of the procedure. Thus, although the overall numbers of participants exceeding 50% pain relief reduced by 12-months, the majority of participants continued to report a significant reduction in pain and disability levels at 12-months that exceeded MCID. Many of these reported pain relief greater than 50%, given that the overall magnitude of relief for responders was 66%. This is encouraging, barring the limitations of this study design, which have previously been reported [16].

When comparing our results to comparable studies investigating PRP for facet-mediated pain utilizing diagnostic blockade to ascertain the source of underlying nociception, our results are similar to those demonstrated in people with facet-mediated pain in the lumbar spine, whereby 80% of people reported symptom improvement 6-months post-PRP [23]. The underlying mechanisms responsible for these changes are

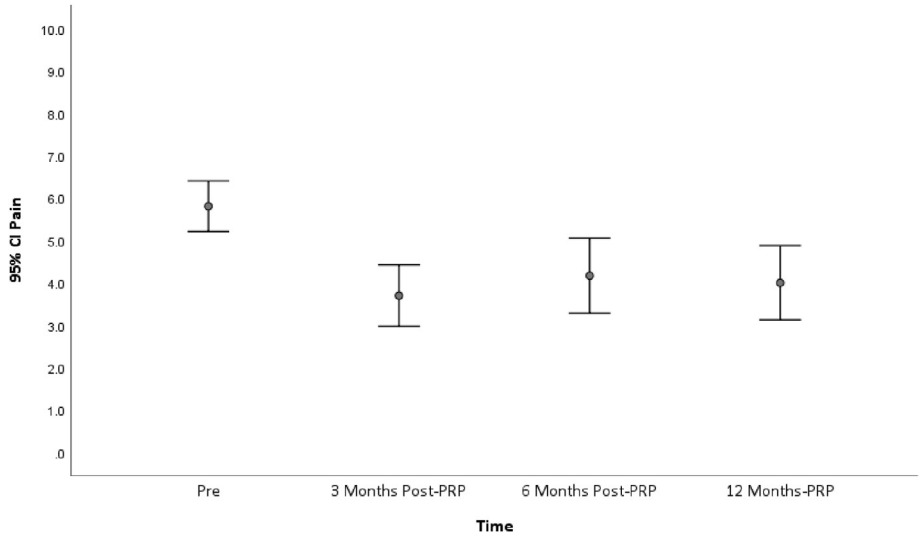

Fig. 1. Mean numerical pain ratings and 95% confidence intervals over time for study participants.

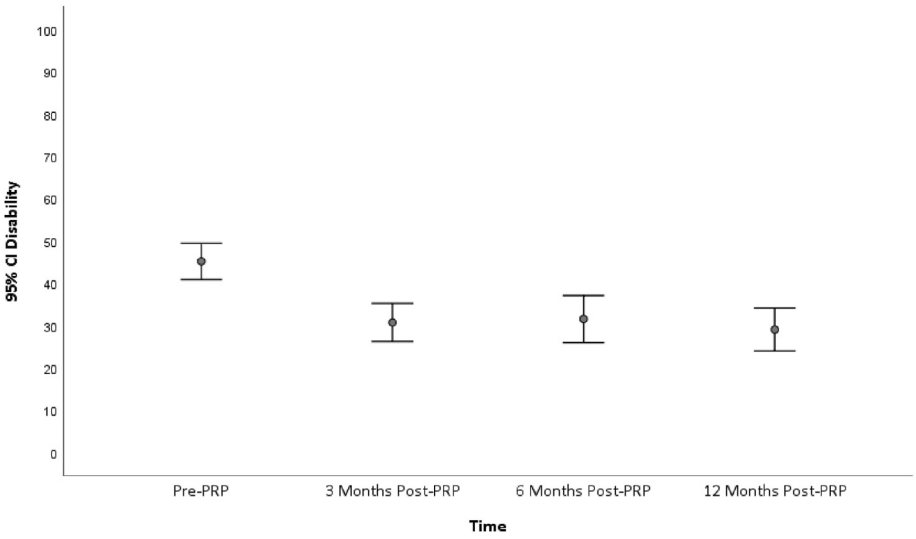

Fig. 2. Mean Neck Disability Index scores and 95% confidence intervals over time for study participants.

Table 1
Responder rates (and 95% confidence intervals) for study sample for best- (data recorded in registry) and intention-to-treat analysis/worst-case (assuming lost-to-follow up is a treatment failure) scenarios for pain and disability (Neck Disability Index) levels 3-, 6-, and 12-month post-PRP. A pain 'responder' was defined as a person whose numerical pain rating score (NPRS) improved by 15%, whilst a 'responder' for disability improved by 10% or greater.

	3-months Responder Rate	Magnitude of Responder Change	6-months Responder Rate	Magnitude of Responder Change	12-months Responder Rate	Magnitude of Responder Change	Effect Size (Cohen's d)
NPRS (Best)	70% (55%, 84%)	56% (44%, 67%)	70% (53%, 87%)	50% (39%, 61%)	53% (36%, 70%)	66% (55%, 77%)	0.71
NPRS (Worst)	68% (54%, 83%)	–	48% (32%, 63%)	–	43% (28%, 58%)	–	–
NDI (Best)	80% (68%, 93%)	45% (36%, 54%)	75% (58%, 92%)	43% (33%, 53%)	69% (54%, 85%)	48% (38%, 58%)	0.98
NDI (Worst)	75% (62%, 88%)	–	48% (32%, 63%)	–	58% (43%, 74%)	–	–

Table 2
Proportion of participants (95% confidence intervals) achieving 50% pain (Numerical Pain Rating Scale) relief for best- (data recorded in registry) and worst-case (assuming lost-to-follow up is a treatment failure) scenarios/intention-to-treat analysis 3-, 6-, and 12-month post-PRP.

	3-months >50% pain relief	6-months>50% pain relief	12-months>50% pain relief
NPRS (Best)	42% (26%, 57%)	30% (13%, 47%)	37% (21%, 52%)
NPRS (Worst)	41% (26%, 56%)	20% (8%, 33%)	34% (20%, 49%)

largely unknown. As previously reported, initially observed benefits may result from the anti-inflammatory effects of PRP [24–27]. However, the longer-term effects demonstrated also suggest that other factors, including tissue regeneration [28] and/or adjunct therapies may influence long-term outcomes.

The contrarian viewpoint suggests that the results are disappointing, as only 50% of participants in a best-case scenario reported significant pain relief at 12-months, and possibly as low as 30% when considering the lower limits of confidence attached to the worst-case scenario. The worst-case scenario suggests that only 50% of all participants demonstrated significant relief at 6-months. When examining the combined responder rate in conjunction with magnitude of relief, it is apparent that those with a milder response at 3-months experience diminishing benefits as time progresses, such that the effects have dissipated by 12-months. Given the sharp drop-off in responder rates between 6- and 12-months for pain relief in the best-case scenario, it might suggest that booster procedures are required to improve the 12-month results. This is underlined by the 11% of people who pursued boosters in this time period. The optimal PRP dosing schedule is yet to be determined. For those that maintained improvement from 3- to 12-months, the magnitude of improvement in pain and disability increased over time, which is encouraging. As previously reported, it is unclear if this is due to the PRP effects or confounding treatments participants may have received [16].

When considering options for long term symptom relief, participants could also choose to forgo interventional therapy and focus on conservative measures. As all study participants had not previously responded to conservative therapy over a significant time period (i.e., approximately 2 years) and were provided that option prior to receiving informed consent for PRP, this was not a viable option for those studied here. This is supported by more recent clinical trials in chronic WAD for people receiving conservative therapy, which only demonstrate modest pain reduction benefits for pain and disability [29–33]. Given that chronic WAD is a heterogeneous disorder with a variety of physical and psychological manifestations that are associated with chronic neck pain [34], treatment success also depends on reducing these clinical features in conjunction with neck pain. Radiofrequency coagulation has been shown to reduce other manifestations of chronic WAD – that being cervical mobility, physical manifestations associated with central sensitization and psychological distress [35–37]. Our study did not measure these outcomes, and as such the utility of PRP for chronic WAD has not yet been fully explored to determine its effectiveness in reducing a person's overall symptom profile.

More broadly, consideration of a person's pain classification may also be important. People presenting with nociplastic pain states (pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral

nociceptors or evidence for disease or lesion of the somatosensory system causing the pain) [38] present with clinical manifestations consisting of pain hypersensitivity, which can make interventional procedures challenging to endure. One of the indications for PRP would seem to involve those with multiple levels of facetogenic involvement who are not eligible for RFC. Empirically, patients receiving PRP may complain of procedure-related pain. This may be due to the number of locations injected, or possibly the leukocyte rich composition utilized in this study. However, further studies should investigate the success of PRP in people with different mechanistic pain classifications (i.e. predominantly nociceptive vs. nociplastic).

As previously reported, case series and registry data have limitations regarding the overall clinical utility attached to them [16]. The lack of randomization, data quality, blinding and control group should caution readers as to the overall benefits observed. Validation is required in longitudinal randomized trials with larger study numbers and a control group. This would establish the efficacy of PRP and is currently underway [39]. The effects of co-treatments, such as medication and physiotherapy also need to be established. Selection criteria for PRP only involved a positive response to a single MBB, with further research warranted to determine what the most appropriate selection criteria is to assist with treatment success. Consideration of single versus dual versus intra-articular blocks are warranted. Optimal PRP composition and dosing schedule for treatment effectiveness in chronic WAD requires further investigation. This study also had a 20% loss-to-follow up at 12-months, although we accounted for this in a worst-case scenario. As such, our analysis is very conservative, as seven participants recorded responses at 12-months that did not report results at 6-months with three meeting 'responder' status and two of those reporting greater than 50% relief of symptoms. Hence, our worst-case responder rates are likely underestimating the true effect of PRP success. Finally, an economic evaluation is also required to determine the cost utility of PRP. Until the pandemic, cervical facet joint interventions in a Medicare population in the United States demonstrated annual increases of approximately 2%, whilst radiofrequency neurotomy procedures increased by 8.9% [40]. It is anticipated that this will continue [12]. As such, procedures, such as PRP that can possibly provide enduring pain and disability relief with a favourable side effect risk profile, with reduced likelihood of requirement for repeat or additional procedures would assist with health care resource utilization.

5. Conclusion

Our previous study demonstrated that cervical spine PRP, which may or may not have included physiotherapy, was safe and feasible for people with chronic WAD and facet-mediated pain. This study expands on these results, suggesting that the benefits are maintained over 12-months for many people, with results comparable to RFC. However, caution remains, given the case series nature of this study and declining responder rates observed over time, suggesting that further research is warranted prior to the widespread adoption of cervical spine PRP for people with chronic WAD. A randomized, double-blind, controlled trial is the only valid tool for assessing the efficacy of any therapeutic procedure. These study results provide sufficient encouragement to justify a controlled study.

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Declaration of competing interest

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

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