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Observational Study

Cervical Radiofrequency Neurotomy Reduces Psychological Features in Individuals with Chronic Whiplash Symptoms

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Background: Individuals with chronic whiplash associated disorder (WAD) demonstrate various psychological features. It has previously been demonstrated that cervical radiofrequency neurotomy (cRFN) resolves psychological distress and anxiety. It is unknown if cRFN also improves or reduces a broader spectrum of psychological substrates now commonly identified in chronic whiplash, such as post-traumatic stress disorder (PTSD) and pain catastrophizing.

Objectives: To determine if reducing pain in the cervical spine (following cRFN) significantly reduces psychological features (distress, pain catastrophizing and post-traumatic stress symptoms) in individuals with chronic WAD.

Setting: Tertiary spinal intervention centre in Calgary, Alberta, Canada.

Study Design: Prospective observational study of consecutive patients.

Methods: Patients: Fifty-three individuals with chronic whiplash associated disorder symptoms (Grade 2). Intervention: Cervical RFN following successful response to cervical facet joint blockade. Measures were made at 4 time points: 2 prior to RFN, and 1-month and 3-months post-RFN. Psychological measures included the General Health Questionnaire (GHQ-28); Pain Catastrophizing Scale (PCS) and the Post Traumatic Stress Diagnostic Scale (PDS). Self-reported pain (VAS) and disability (NDI) measures were also collected.

Results: Pain, disability, psychological distress and pain catastrophization significantly decreased at both 1-month and 3 months following cervical RFN. There was no significant change in post-traumatic stress symptom severity (P = 0.39). Reducing pain via cRFN was associated with significant improvement in psychological distress and pain catastrophizing, but not posttraumatic stress symptoms.

Limitations: Individual administering questionnaires was not blinded to aim(s) of the study. Other psychological features possibly present in WAD were not measured.

Conclusion: Effective pain relief would seem a crucial element in the management of psychological features associated with chronic WAD.

IRB Approval: University of Calgary Conjoint Health Research Ethics Board ID#: E-22082.

Key words: Whiplash, radiofrequency neurotomy, cervical facet joints, psychology, psychological distress, pain catastrophizing, post traumatic stress disorder

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Chronic whiplash associated disorders (WAD) following a motor vehicle crash are a significant public health problem that incur substantial personal and economic costs (1-3). Psychological distress is common in many chronic pain conditions (4-6), including chronic WAD. Psychological features which may be evident include anxiety, distress, depression, and posttraumatic stress disorder (PTSD) (7-11).

Relationships have been demonstrated between pain and psychological distress in individuals with WAD. Initial distress in those who recover abates in parallel with resolving pain and disability (6,12,13). In contrast, psychological distress remains elevated in those with poor recovery and ongoing pain and disability (14,15). It has been demonstrated in patients with chronic WAD that pain relief following successful cervical radiofrequency neurotomy (RFN) resolves psychological distress and anxiety (16). Relationships have not been examined between pain and a broader spectrum of psychological substrates now commonly identified in chronic WAD, such as PTSD and pain catastrophizing.

Chronic pain and PTSD often co-exist (17-20), with increasing recognition of potentially shared aetiological pathways of WAD and PTSD (21). A recent study explored directional relationships between PTSD and chronic pain in 323 survivors of accidents (not whiplash) (22). A mutual relationship was found between pain intensity and posttraumatic stress symptoms at 5 days post-injury; but by 6 months post-injury (chronic stage), PTSD symptoms impacted significantly on pain but not vice versa (22). Further, a recent preliminary randomized controlled trial demonstrated that decreasing PTSD symptoms with a trauma-focused cognitive behavioral intervention resulted in decreased levels of pain related disability; with no changes in pain intensity or sensory pain thresholds demonstrated (23), thus providing partial support for the possibility that PTSD symptoms impact pain related factors. One way to further explore these relationships would be to modulate pain and evaluate effects on PTSD symptoms. To our knowledge such an investigation has not yet been undertaken.

Catastrophization refers to an exaggerated negative orientation toward noxious stimuli (24). Catastrophizing is associated with enhanced pain reports, disability (25,26), poor prognosis (27), and lower pain threshold/tolerance levels (28) in individuals with WAD. Treatment addressing catastrophization in individuals with WAD has demonstrated reductions in catastrophic thinking, with only modest improvements in pain and disability measured (29,30). In contrast, reduced catastrophic thinking was demonstrated following successful knee joint arthroplasty, suggesting that catastrophizing is modulated by pain intensity (31). We are not aware of studies in chronic WAD investigating the influence of modulating pain and its effect on pain catastrophizing.

Cervical RFN is a neuroablative technique that denatures the sensory nerves of the cervical facet joints, resulting in reduction of nociception and related pain (32,33). We have reported on a cohort of individuals with chronic WAD for whom RFN led to significant and clinically relevant reductions in pain, disability, and sensory hypersensitivity, and improved neck movement (34).

The aim of this study was to determine if psychological distress, pain catastrophizing, and PTSD symptoms were modulated with the reduction of pain following RFN. We hypothesized that following pain reduction with RFN there would be concomitant reductions in psychological distress, pain catastrophizing, and posttraumatic stress symptoms.

Methods

Design

A prospective cohort study design was employed at a tertiary spinal intervention center in Calgary, Alberta, Canada. Patients were assessed and completed questionnaires at the following time points: (t1) at a time period when their familiar baseline neck pain was present (when symptoms returned following successful cervical facet joint blockade) (34); (t2) immediately prior to receiving RFN; t(3) one month following RFN; and t(4) 3 months following RFN.

Procedure

Diagnostic facet joint and RFN procedures used in this study have been previously documented (34,35). In summary, symptomatic facet joints were initially chosen based on clinical assessment (36). Patients demonstrating reproducible symptom relief of at least 50% with serial diagnostic blocks (intra-articular facet joint injections and medial branch blocks) were considered appropriate candidates for RFN. RFN was performed using local anesthetic and fluoroscopic guidance, typically using a 21-gauge RF cannula with a 5 mm active tip, placing the tip parallel to the expected course of the nerves supplying the target joints (i.e. the medial branch above and below the joint). Thermal lesions were then made at each site, heating the tip of the can-

nula to 80 degrees Celsius for 75 seconds. In addition, the third occipital nerve was targeted when treating the C2-3 facet joint.

Patients

Inclusion Criteria

Consecutive patients were recruited from individuals aged 18 – 65 years; with WAD Grade II (3) of a duration greater than 6 months post motor vehicle collision (MVC); who had had a successful response (greater than 50% of neck pain relief) to cervical facet joint blockade (intra-articular block followed by confirmatory medial branch block) (34); and who subsequently underwent RFN (34).

Exclusion Criteria

Individuals were excluded from the study if they were classifiable as WAD Grade III (neurological deficit) or IV(fracture or dislocation) (3); sustained a concussion or loss of consciousness as a result of the trauma; if they were not fluent in spoken or written English; had a major psychiatric history (e.g., psychosis, schizophrenia, bipolar disorder, etc.) or were previously treated for depression/anxiety.

All the patients were unpaid volunteers. Ethical clearance for this study was granted from the institutional medical research ethics committees. All patients provided informed consent.

Outcome Measures

Questionnaires

As previously reported (35), a general intake questionnaire was provided to capture the details of collision related factors, symptoms, and demographics of the patients. Measures of pain (visual analogue scale – VAS) and disability (Neck Disability Index – NDI, [35)] were also collected and have previously been reported (34).

All patients completed the General Health Questionnaire-28 (GHQ-28) (37) as a measure of general psychological distress. The GHQ-28 consists of 4 subscales, measuring 28 items of emotional distress in medical settings: somatic symptoms (items 1 to 7), anxiety/insomnia (items 8 to 14), social dysfunction (items 15 to 21), and severe depression (items 22 to 28). Each item has a 4-point rating scale ranging from 0 to 3. The total score provides a measure of psychological distress, with greater distress indicated by a higher score. The GHQ-28 has been used in previous research of WAD (6,12).

The Posttraumatic Diagnostic Scale (PDS) (38) was used to assess the presence of post-traumatic stress symptoms according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision; DSM– IV–TR [39]) diagnostic criteria for PTSD. Patients completed the questionnaire in relation to the MVC which resulted in their WAD injury. Using a Likert 4-point scale, patients rated 17 items representing the cardinal symptoms of PTSD experienced in the past month. Finally, patients rated the level of impairment caused by their symptoms across 9 areas of life functioning. A probable diagnosis of PTSD is made only when a specified number of DSM IV criteria are met across symptom clusters. The PDS also includes a symptoms severity score which ranges from 0 to 51, obtained by adding up the individual's responses of the 17 symptom items. The cut-offs for symptom severity rating are 0 no rating, 1 – 10 mild, 11 – 20 moderate, 21 – 35 moderate to severe and > 36 severe. The PDS has demonstrated high internal consistency and good stability and is a valid instrument for the assessment of PTSD in survivors of various traumatic events including MVC (40,41).

Pain catastrophizing was evaluated using the Pain Catastrophizing Scale (PCS) (24). This 13-item questionnaire describes various thoughts and feelings that individuals experience when in pain, and indicates the degree to which each of the items applies to them, when reflecting on their past pain experiences. Each item has a 5-point rating scale ranging from 0 not at all to 4 all the time, with addition of these scores providing a total for the PCS. The PCS measures 3 distinct components: rumination, magnification, and helplessness (24). Research indicates that the PCS is associated with heightened pain severity and has high internal consistency (42).

Statistical Analysis

Stata 9.0 statistical software was used to analyze data. To detect meaningful differences over time, power analyses were conducted to determine the number of patients required. Given the lack of previous research on these specific co-morbidities with utilization of these outcome measures, effect sizes were estimated from relevant previous research on catastrophization (30) and psychological distress (16). Moderate-to-large effect sizes were estimated. On the basis of the previous research and in accordance with guidelines set out by Cohen (43), power was set at 0.80 and the significance level at 0.05. Following collation

of these results, it was determined that a minimum of 17 patients would be required to allow enough power to detect meaningful differences over time.

Assumptions of normality, residual normality, and sphericity were tested through examination of histograms, box plot graphs, and plots of predicted to residual values respectively. Normality was not demonstrated in the following questionnaire measures – GHQ-28, PCS, and PDS.

For GHQ-28, PCS, and PDS results (and their respective sub-components), non-parametric Friedman repeated measure tests were utilized to analyze differences over time. Significance level was set at 0.05. Where there was a significant group difference demonstrated (over time), Mann-Whitney U tests were performed between each and every time point (6 comparisons) to evaluate where the differences occurred. Bonferroni adjustment was used, such that the significance level was set at 0.008.

Chi-squared analysis was utilized to determine if there was a difference in proportions of individuals over time with "above threshold" scores for GHQ-28 (> 23) (37), PCS (>24) (29), and probable diagnosis of PTSD as determined by the PDS questionnaire (38).

The data were assessed for effect size using Cohen's d for normally distributed data and Cliff's Delta for non-parametric analyzed data (44). The established convention rates were used. A Cohen's d effect size of 0 < 0.50 is small, a size of 0.50 to < 0.80 is moderate, and > 0.80 is large (45). The corresponding effect sizes for Cliff's Delta are < 0.147 is small; between 0.148 and 0.33 is moderate, and > 0.33 is large (46). Effect size was calculated utilizing t(4), being the primary end point of this study, and t(2), the time period immediately prior to receiving RFN.

Results

Patients

Fig. 1 demonstrates the flow of patients through the study. This study investigated 53 individuals (36 women, 17 men, mean age = 44.7 +/- 10.9 [SD] years) who underwent cervical RFN. Three individuals failed to complete the study (one pregnancy; 2 lost to follow-up). The median (range) duration of symptoms post whiplash was 43 [9 – 195] months. All patients received initial treatment following the MVC (35). As previously reported, pain scores (VAS 0 – 100: mean +/- SD) were stable between t(1) (58 +/- 19) and t(2) (55 +/- 19) prior to the RFN but reduced significantly as measured at the 2 time points post RFN t(3) (25 +/- 20) and t(4) (25 +/- 21) (34). Similarly, disability scores (NDI%: mean +/- SD) remained stable between t(1) (42 +/- 15) and t(2) (43 +/- 16), with significant improvement measured following RFN at t(3) (29 +/- 16) and t(4) (27 +/- 16).

General Health Questionnaire (GHQ-28)

The median scores, interquartile ranges, and proportion of patients exceeding the threshold score (≥ 23) for GHQ-28 are presented in Table 1. The threshold score is indicative of presence of generalized psychological distress (37).

There was a significant effect of time, both in terms of proportion of individuals over the threshold score of 23/24 ($\chi 2$ = 14.8, 3 d.f., P = 0.002), and their respective total scores ($\chi 2$ = 13.5,3 d.f., P = 0.0012). Post-hoc analysis revealed a significant decrease in GHQ-28 total scores between t(1) and t(3) (P = 0.0025), t(1) and t(4) (P = 0.0002), t(2) and t(3) (P < 0.0001), and t(2) and t(4) (P = 0.0001), with no significant differences measured prior to undergoing RFN (P = 0.64) or following RFN (P = 0.92). A large effect size was demonstrated (Cliff's Delta: 0.68).

Immediately prior to undergoing RFN (t(2)), approximately two-thirds (64%) of the individuals had a total threshold score > 23/24 (presence of generalized psychological distress), while 3 months following RFN (t(4)), only one-third (34%) of individuals recorded a score above this threshold; with the median group score reducing from 25 to 19 (below threshold) over the intervening period.

The median scores for the sub-component categories of the GHQ-28 are presented in Table 2 (somatic symptoms, anxiety/sleeplessness, social dysfunction, and severe depression). In respect to the sub-component scores of the GHQ-28, there was a significant effect of time demonstrated in 3 of the 4 sub-components. Somatic symptoms ($\chi 2$ = 11.7,3 d.f., P = 0.0029), anxiety/sleeplessness ($\chi 2$ = 7.99,3 d.f., P = 0.018), and social dysfunction ($\chi 2$ = 14.5,3 d.f., P = 0.0007) all demonstrated significant improvement following RFN. There was no significant effect of time for the depression subscale ($\chi 2$ = 4.0,3 d.f., P = 0.14).

Pain Catastrophization (PCS)

The median scores, interquartile ranges, and proportion of patients exceeding the threshold score (> 24) for PCS (29) are presented in Table 1.

There was a significant effect of time for PCS scores ($\chi 2$ = 20.9,3 d.f., P < 0.0001). Post-hoc analysis revealed

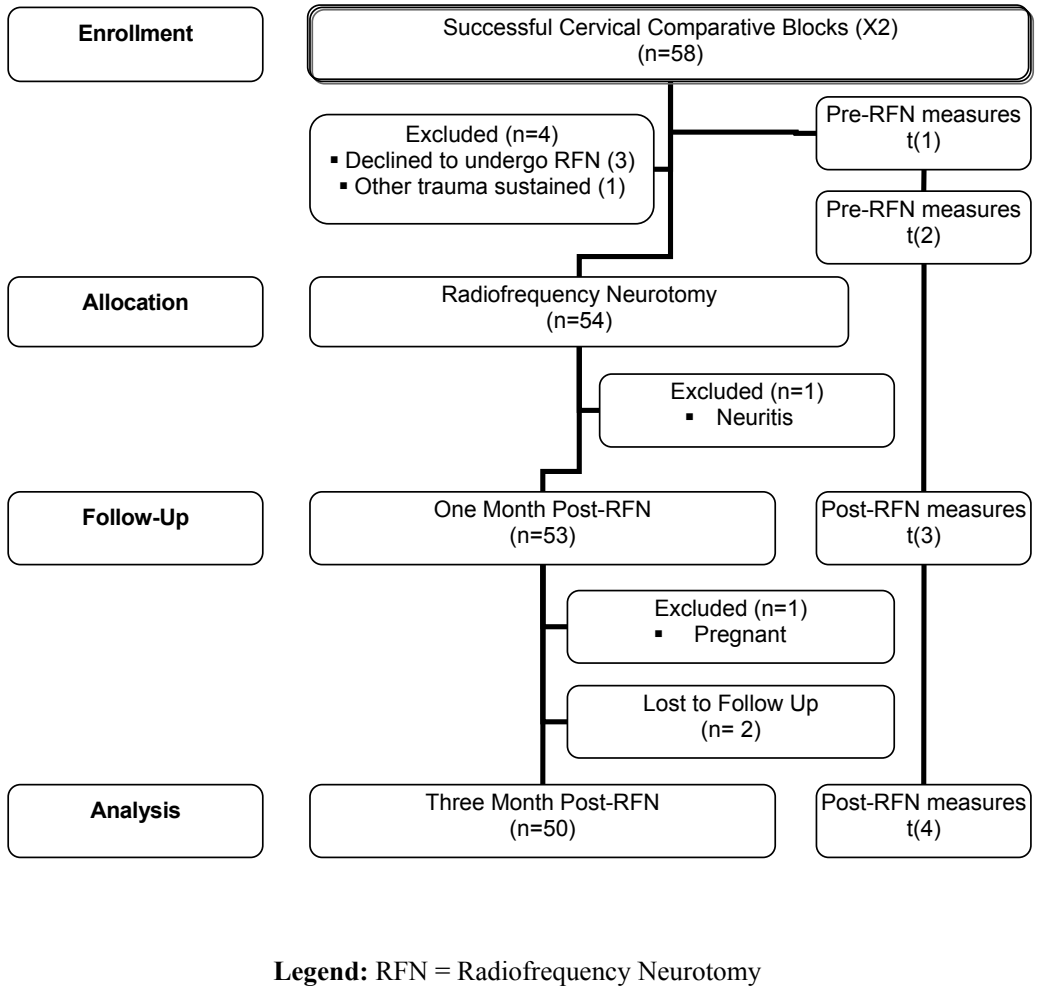

Fig. 1. *Flow of participants through the study.*

Table 1. *Median [Interquartile Range] scores for psychological measures over time.*

Time Period	GHQ-28		PCS		PDS	
	% ≥23	Score [IQR]	% ≥24	Score [IQR]	% met criteria probable PTSD	Severity Score [IQR]
t(1)	64%	24 [19.32]	19%	15 [9.22]	30%	7 [2,13]
t(2)	62%	25 [17.37]	23%	17 [7.23]	34%	8 [2,14]
t(3)	40%	17 [12.31]	13%	10 [4.17]	26%	5 [0,14]
t(4)	34%	19 [12.26]	10%	8 [1.15]	16%	6 [2,11]

Legend: GHQ = General Health Questionnaire; PCS = Pain Catastrophization Scale; PDS = Post Traumatic Stress Diagnostic Scale; t(1) = time-point 1 (admission to study following cervical facet joint injection double blockade); t(2) = time-point 2 (immediately prior to receiving radiofrequency neurotomy); t(3) = time-point 3 (one month following radiofrequency neurotomy); t(4) = time-point 4 (three months following radiofrequency neurotomy)

Table 2. *Median [Interquartile Range] scores for each sub-component of the GHQ-28.*

GHQ-28 Subscale	Somatic	Anxiety/Sleeplessness	Social Dysfunction	Severe Depression
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
t(1)	8 [5.10]	6 [4.10]	8 [7.10]	1 [0.3]
t(2)	9 [7.11]	7 [4.10]	8 [7.12]	1 [0.3]
t(3)	5 [3.9]	6 [2.8]	7 [6.11]	0 [0.2]
t(4)	6 [4.9]	5 [3.7]	7 [5.9]	0 [0.1]

Legend: GHQ = General Health Questionnaire; t(1) = time-point 1 (admission to study following cervical facet joint injection double blockade); t(2) = time-point 2 (immediately prior to receiving radiofrequency neurotomy); t(3) = time-point 3 (one month following radiofrequency neurotomy); t(4) = time-point 4 (three months following radiofrequency neurotomy)

a significant decrease in PCS scores between t(1) and t(3) ($P = 0.0001$), t(1) and t(4) ($P < 0.0001$), t(2) and t(3) ($P < 0.0005$), and t(2) and t(4) ($P = 0.0001$), with no significant differences measured prior to receiving RFN ($P = 0.78$) or following RFN ($P = 0.012$). The demonstrated effect size was large (Cliff's Delta: 0.72).

There was no significant difference in proportion of individuals over the threshold score of 24 ($\chi 2 = 3.65$,3 d.f., $P = 0.30$). Immediately prior to RFN (t(2)), 23% of individuals had a total threshold score > 24, while 3 months following RFN (t(4)), 10% of individuals scored above this schedule; with the median group score reducing from 17 to 8 during this time period.

Post-Traumatic Stress (PDS)

The median scores, interquartile ranges, and proportion of patients meeting the criteria for a probable diagnosis of PTSD (38) are presented in Table 1.

There was no significant difference demonstrated over time, in regard to proportion of individuals with a probable diagnosis of PTSD as measured on the PDS ($\chi 2 = 4.68$,3 d.f., $P = 0.20$). There was also no difference in severity of posttraumatic stress symptoms for the group over time ($\chi 2 = 1.90$,3 d.f., $P = 0.39$). There was no difference over time in regard to the number of posttraumatic stress symptoms demonstrated by individuals ($\chi 2 = 2.24$,3 d.f., $P = 0.33$).

At entry into the study (t(1)), 30% of individuals met criteria for a probable diagnosis of PTSD based on the scoring criteria of the PDS, which was essentially unchanged (26%) one month after receiving RFN. At 3 months following RFN, 16% of individuals fulfilled the PDS criteria for probable diagnosis of PTSD. In so far as the severity of symptoms were concerned, the group median score of 7 (at entry to the study) and 6 (3 months post-RFN) equate to a mild level of stress symptoms being present (38).

Discussion

Patients presented with initial moderate to severe levels of pain and disability and clinical levels of psychological distress, similar to previous studies of individuals with WAD (47,48), and individuals undergoing cervical RFN (33,49-52). We have previously shown that cervical RFN led to significant, and clinically relevant, early and sustained reductions in their pain and disability, together with improved sensory and motor function (34). In parallel, this study demonstrated reductions in psychological distress and pain catastrophizing post-RFN. No significant changes in posttraumatic stress symptoms were found post-RFN although there were trends towards reduced severity and number of symptoms, as well as a reduced proportion of individuals meeting criteria for a probable PTSD diagnosis.

Our results are consistent with prior studies where reductions in psychological distress (16,50), anxiety (16), depression (50), and somatic symptoms (50) were demonstrated following RFN for patients with chronic WAD. In contrast, prospective data from non-interventional studies indicate that levels of psychological distress remain relatively consistent over time, with little evidence of fluctuation or resolution (8,12-15). This differs from those with a resolving acute condition, who exhibit decreasing levels of distress that parallel decreases in pain and disability (6,12,13). Results of the current study support the hypothesis that ongoing distress is associated with higher levels of pain. Levels of depression did not change significantly in the current study and this

may reflect the instrument used, given that other studies have documented that depressive symptomatology after whiplash injuries is common (53) and predictive of poor prognosis (54). The depression sub-scale of the GHQ-28 measures severe depression which was not a characteristic of our group. Our participants scored very low on this sub-scale at baseline, leaving little room for improvement and possibly resulting in a floor effect. Further research is needed using a more sensitive measure to evaluate the effects of pain relief with RFN on depression.

Prior to RFN, 30 – 34% of our patients had a probable diagnosis of PTSD, based on the criteria of the PDS (55). This is consistent with previous research indicating the prevalence of PTSD in chronic WAD to be similar to more major traumatic injuries requiring hospital admission (56). The proportion of patients with a probable PTSD diagnosis decreased from 34% to 16% following RFN, although this was not statistically significant. Similarly, a small and non-significant decrease in PTSD symptom levels was found. This may also be due to a floor effect, given that patients reported only mild PTSD symptoms at baseline and post-RFN, but also may be a reflection of the sample size of the study or indicate that PTSD symptoms are not as dependent upon pain levels as the other psychological substrates measured. In a prospective, longitudinal study following traumatic injury, Jenewein et al (22) showed that in the chronic stage, PTSD symptoms impacted pain, but not vice versa. Our results support these findings as significant reductions in pain following RFN were not associated with significant reductions in posttraumatic symptoms. In addition, in chronic WAD, decreasing PTSD symptoms with trauma-focused cognitive behavioural therapy resulted in decreased pain related disability but not pain intensity or pain thresholds (23). Thus, our non-significant results for PTSD when pain was targeted and the inconsistent results on pain outcomes in Dunne et al's study (23) when PTSD symptoms were targeted indicate that the nature of the relationship between pain and PTSD remains unresolved. Both our study and that of Dunne et al's are likely hampered by low sample size and future studies with larger samples are required. Taken together, these results may indicate that both pain and PTSD should be targeted in the management of chronic WAD. Treatment of underlying nociception to reduce pain (e.g. RFN) combined with treatment of PTSD (e.g. cognitive behavioural therapy) may be an option in the management of chronic WAD with identified facet joint involvement.

There is debate on whether catastrophization is a stable (enduring) (57) or dynamic trait related to particular constructs such as pain (58). Individuals with chronic WAD presenting with pain catastrophizing demonstrate poor physical outcomes (28), concurrent disability (25,26), and poor prognosis (27). When catastrophic thinking has been addressed (in work-disabled individuals with sub-acute WAD) through multidisciplinary rehabilitation (29), physical therapy, or multifaceted psychosocial risk factor-targeted interventions (30), reductions in catastrophizing have resulted, however with only modest improvements in pain and disability (29,30). Approximately 20% of our patients presented with clinically significant catastrophic thinking. In contrast to the modest improvements in pain in other studies, our study demonstrated concurrent reductions in both pain and catastrophizing scores, with large effect sizes. It is also notable that the scores for catastrophizing following RFN (median score = 8) were substantially less than the post-treatment scores following physiotherapy (score = 14.0) or a 10-week program of physiotherapy combined with a multi-pronged strategy aimed at reducing psycho-social risk factors (score = 20.6) (30). The significant reduction in pain following RFN was associated with substantial improvement in pain catastrophizing, similar to findings of a recent study of individuals undergoing total knee arthroplasty (31). In combination, these findings support the proposal by Buitenhuis et al (25), who argue that catastrophization likely results from high levels of pain and disability.

Thirty-four percent of individuals continued to report ongoing generalized psychological distress (GHQ-28) 3 months after receiving RFN. While levels of pain related disability decreased significantly, the mean NDI score of the group indicated the presence of persistent mild to moderate levels in some individuals. This may be a reason for ongoing levels of distress. Alternatively the ongoing distress may be related to the "other" symptoms reported by over 50% of individuals in this study including headaches, shoulder/arm pain, thoracic spine, pain and lumbar spine pain (35). The reverse relationship may also exist, whereby ongoing psychological distress leads to persistent pain and disability (59). Additional management addressing psychological distress may be required to further decrease pain and disability in this patient group.

There are additional limitations of the current study that warrant discussion. Review of patients was limited to 3 months post-RFN to allow investigation

regarding the role of reduced pain on symptom presentation. Thus, the longer term effects of RFN on psychological manifestations cannot be established with this study. While patients completed the questionnaires independently, they were administered by the researcher who was aware of the aims of the study. Additionally, in order to minimize patient burden, we did not investigate other psychological factors shown to be present in WAD, such as self efficacy (60), fear of movement (61,62), coping styles (63-66), and beliefs and attitudes regarding expected recovery (25,67,68). Investigation of these factors following RFN is warranted.

Limitations

Individuals in this study were also free to pursue treatment following RFN. Fifteen individuals attended treatment following RFN. One individual continued to attend the regional multidisciplinary chronic pain center. Thus, the psychological improvements noted in this study cannot categorically be all attributed to RFN. However, given that these individuals were receiving, and had received, lengthy doses of treatment prior to RFN, without improvement in any measures documented between t(1) and t(2), we are confident that the results demonstrated can be attributed to the effects of cervical RFN.

Conclusion

In summary, our results support the hypothesis that pain reduction following cervical RFN is associated with reductions in psychological distress and pain catastrophizing. Further research on the relationship between pain and posttraumatic stress symptoms is warranted.

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Contributions:

AS: conception and research design; data collection, statistical analysis and interpretation; manuscript preparation and revision

GJ: research design, intellectual contributions; data interpretation; manuscript preparation and revision

GS: conception and research design, intellectual contributions; data interpretation; manuscript preparation and revision

AH: intellectual contributions, manuscript preparation and revision

BF: conception and research design, intellectual contributions; manuscript preparation and revision

MS: conception and research design, intellectual contributions; data analysis and interpretation, manuscript preparation and revision.

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