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The Course and Prognostic Factors of Symptomatic Cervical Disc Herniation with Radiculopathy: A Systematic Review of the Literature

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Abstract

Background Context. Cervical spine disc herniation is a disabling source of cervical radiculopathy. However, little is known about its course and prognosis. Understanding the course and prognosis of symptomatic cervical disc herniation is necessary to guide patients' expectations and to assist clinicians in managing patients.

Purpose. To describe the natural history, clinical course and prognostic factors of symptomatic cervical disc herniations with radiculopathy.

Study Design. Systematic review of the literature and best evidence synthesis.

Methods. A systematic search of MEDLINE, EMBASE, CINAHL, SportsDiscus and the Cochrane Central Register of Controlled Trials from inception to 2013 was conducted to retrieve eligible articles. Eligible articles were critically appraised using the Scottish Intercollegiate Guidelines Network criteria. The results from articles with low risk of bias were analyzed using best evidence synthesis principles.

Results. We identified 1221 articles. Of those, eight articles were eligible and three were accepted as having a low risk of bias. Two studies pertained to course and one study pertained to prognosis. Most patients with symptomatic cervical disc herniations with radiculopathy initially present with intense pain and moderate levels of disability. However, substantial improvements tend to occur within the first four to six months post-onset. Time to complete recovery ranged

from 24-36 months in approximately 83% of patients. Patients with a workers' compensation claim appeared to have a poorer prognosis.

Conclusions. Our best evidence synthesis describes the best available evidence on the course and prognosis of cervical disc herniations with radiculopathy. Most patients with symptomatic cervical spine disc herniation with radiculopathy recover. Possible recurrences and time to complete recovery need to be further studied. More studies are also needed to understand the prognostic factors for this condition.

Key words: cervical disc herniation, systematic review, epidemiology, prognosis.

Introduction

Cervical spine disc herniation is a common source of cervical radiculopathy [1]. In Rochester, Minnesota, the annual incidence of cervical disc herniations is 18.6 per 100,000 residents and the incidence peaks in the sixth decade of life [2]. The etiology of cervical spine disc herniations is multifactorial [3,4,5]. The proposed risk factors include male gender, current cigarette-smoking, heavy lifting, frequent diving from a board and occupation [3,4,5]. Preliminary evidence suggests the incidence of cervical disc herniations is higher in army aviators, professional drivers and those who operate vibrating equipment [4,5]. However, one study reported only 14.8% of cases had a history of physical exertion or trauma preceding the onset of symptoms [2].

Most patients with symptomatic cervical disc herniations and radiculopathy report severe neck and arm pain [6]. The arm pain typically follows a myotomal pattern, while the sensory symptoms (e.g. burning, tingling) follow a dermatomal distribution [6]. These radicular symptoms may also be associated with reflex changes and motor weakness of the upper extremity [6]. Conservative care is recommended as the first line of treatment for symptomatic disc herniations with radiculopathy [6]. It is estimated that 26% of patients with cervical radiculopathy require surgery [2]. Surgery should be considered when pain persists after conservative therapy for 6 to 12 weeks or when there is evidence of progression of a functionally important motor deficit [6].

Despite the persistence of pain and potentially debilitating symptoms, little is known about the natural history and clinical course of cervical disc herniation. This makes it difficult to manage the condition clinically and to understand treatment effectiveness and prognosis. Information about prognostic factors can aid clinicians in the identification of patients at risk of developing chronic pain and disability. Identifying modifiable prognostic factors is particularly important because modification of these factors may assist clinicians and/or patients in removing barriers to recovery. The purpose of our systematic review was to describe the natural history, clinical course and prognostic factors of symptomatic cervical disc herniations with radiculopathy.

Methods

Registration of Review

The protocol for our systematic review was registered on PROSPERO (CRDXXXXXXXXXXXX) and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRDXXXXXXXXXXX.

Search Strategy

A search strategy was developed with the assistance of a library scientist. Five electronic databases were searched [MEDLINE, EMBASE, CINAHL, SportsDiscus and the Cochrane Central Register of Controlled Trials (The Cochrane Library)] from inception until June 15, 2013. The reference lists in relevant Cochrane systematic reviews [7,8] were hand-searched for additional articles. The search strategy combined terms relevant to cervical disc herniations and course/prognosis, including subject headings specific to each database and free text words (Appendix 1).

Selection Criteria

Inclusion criteria were: 1) English language; 2) human studies; 3) adults (eighteen years of age or older) and/or children with symptomatic cervical disc herniation with radiculopathy as confirmed on imaging; 4) use of clinically relevant outcomes; and 5) randomized and quasi-randomized controlled trials (with waiting list or usual care group) or cohort study. Studies that examined cervical radiculopathy from other causes (e.g. degenerative changes, malignancy, infection, fractures, dislocations, congenital anomalies) were excluded. Cervical radiculopathy caused by multiple etiologies (e.g. combined cervical disc herniation and foraminal stenosis) were excluded unless a stratified analysis for cervical disc herniations was performed. Studies with surgical samples (i.e. cervical disc herniations that had undergone surgical management) or invasive interventions (e.g. injections) were excluded. Biomechanical studies,

cadaveric studies, systematic reviews, and studies that focused on spinal cord injury (e.g. paraplegia, tetraplegia) or myelopathy were excluded. Studies with less than 20 human subjects with cervical disc herniations were also excluded.

Study Population

Studies consisting of patients with a cervical disc herniation and radiculopathy confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) were included. Relevant findings on advanced imaging included cervical discs that were herniated or prolapsed. We aimed to identify studies where the cervical radiculopathy was clearly caused by cervical disc herniation (defined as protrusion/herniation of the nucleus pulposis from the disc in the cervical spine) [6]. We did not consider studies that examined cervical radiculopathy caused by degenerative changes, including osteoarthritis of uncovertebral and facet joints, thickening of ligaments, decreased intervertebral height, and degenerative spondylolisthesis of cervical vertebrae [6]. We also excluded studies that examined cervical radiculopathy caused by other pathology, including malignancy, infection, fractures, dislocations, and congenital anomalies.

Outcomes

Outcomes of interest included self-rated recovery, functional recovery (e.g. return to activities, work or school, limitations of activities of daily living) and clinical outcomes (e.g. pain, disability).

Screening of Titles and Abstracts

Two reviewers independently screened all titles and abstracts using the selection criteria to identify the citations that were potentially eligible for this systematic review. Any disagreements were resolved by discussion between the two reviewers to reach consensus.

Assessment of Methodological Quality

All relevant studies were critically appraised by two reviewers. Rotating pairs of reviewers independently performed a critical appraisal of each article to identify strengths, weaknesses and potential sources of bias in study methodology with *a priori* criteria using the Scottish Intercollegiate Guidelines Network (SIGN) criteria [9]. The SIGN criteria were used to qualitatively evaluate the presence and impact of selection bias, information bias, and confounding on the results of a study. We used the SIGN criteria to assist reviewers in making an informed overall judgment on the internal validity of studies. This methodology has been previously described [10,11].

Specifically, we critically appraised the following methodological aspects of a study: 1) clarity of the research question; 2) randomization method; 3) concealment of treatment allocation; 4) blinding of treatment and outcomes; 5) similarity of baseline characteristics between/among treatment arms; 6) co-intervention contamination; 7) validity and reliability of outcome measures; 8) follow-up rates; 9) analysis according to intention to treat principles; and 10) comparability of results across study sites (where applicable). Reviewers reached consensus through discussion. An independent third reviewer was used to resolve disagreements if consensus could not be reached. Studies with adequate internal validity and methodological rigour were considered scientifically admissible and were included in the analysis.

Data Extraction

One pair of reviewers performed data extraction. Each reviewer independently extracted data from the scientifically admissible studies using *a priori* criteria and computerized review forms to form evidence tables. The final versions of the evidence tables were based on validated data reached by consensus between the pair of reviewers.

Analysis

Scientifically admissible studies were classified into phase I, II or III studies, in accordance with the methodology of Côté et al [10], to guide a best evidence synthesis. This model has been used to interpret evidence obtained in prognostic studies of neck pain, breast cancer, whiplash-associated disorders, and mild traumatic brain injuries [10-14]. Phase I studies explore associations between potential prognostic factors and health outcomes in a descriptive way, so that only crude (descriptive) associations are reported. Phase II studies involve more extensive analyses (but still exploratory), using well formulated comparison groups, stratified and/or multivariable analyses to focus on sets of prognostic factors. Phase III studies are confirmatory, by testing a specific hypothesis to confirm or refute the independence of any apparent relationship between a particular prognostic factor and the outcome of interest and controlling for confounding.

A qualitative synthesis of findings from the scientifically admissible studies was performed to develop evidence statements according to principles of best evidence synthesis as used by the Neck Pain Task Force [11]. Specifically, the research team reviewed the evidence tables and summary statements regarding course and prognosis to describe the body of evidence. More emphasis was placed on scientifically admissible studies judged to have the highest methodological rigour, quality and clinical adequacy based on discussions with the research team. Relevant studies and their results were categorized into 1) natural history or clinical course and 2) prognostic factors for cervical disc

herniations. Prognostic factors were further subcategorized into non-modifiable and modifiable prognostic factors.

Results

Literature Search

Our literature search yielded 1221 articles (Figure 1). We excluded 352 duplicates and therefore screened 869 titles and abstracts for eligibility. Of those, 861 articles did not meet the eligibility criteria. We critically appraised eight articles [16-23] and three were deemed scientifically admissible. All scientifically admissible studies (two cohort studies and one cohort within a randomized trial) described the course and/or the prognostic factors for symptomatic cervical spine disc herniation with radiculopathy [21-23].

Methodological Quality

The results of our critical appraisal are presented in Tables 1 and 2. Several methodological weaknesses were common to most reviewed papers. For example, most studies: 1) did not describe the representativeness of their sample (7/8); 2) failed to control for confounding (7/8); and 3) most did not have adequate follow-up intervals (7/8). The scientifically admissible studies had limitations that should be considered when interpreting their results.

Study Characteristics related to Cervical Disc Herniations

The selection criteria for cervical disc herniations across admissible studies varied slightly (Table 3). All admissible studies aimed to investigate cervical radiculopathy due to disc herniation only. Bahadir et al included participants with focal acute cervical disk protrusion and root compression confirmed on MRI with myotomal weakness compatible with cervical radiculopathy [21]. Cesaroni et al included participants with imaging evidence of a single contained symptomatic focal disc protrusion between C3 and T1 which did not compromise more than one third of the anterior-posterior diameter of the spinal canal, minimal corroborative myotomal deficit, and a positive diagnostic nerve root block [22]. Scuderi et al included participants with an MRI confirmed single or two level cervical herniated discs (herniated nucleus pulposus) as interpreted by a spine surgeon or radiologist [23]. The admissible studies also excluded other potential causes for cervical radiculopathy (spondylotic changes, fractures, dislocations) (Table 3).

Course for Cervical Disc Herniations

Two studies (one phase I studies and one cohort within a randomized trial) described course of symptomatic cervical disc herniations [21,22] (Tables 4 and 5). Overall, the results suggested that the course of symptomatic cervical disc herniation with radiculopathy was favourable and that few patients experienced long-term disability. Most patients initially presented with intense neck/arm pain

and moderate-to-severe levels of disability. Substantial improvements in pain and disability occurred within the first four to six months post-onset [21,22]. Improvements were generally maintained over two to three years [21]. One phase I study reported that 5/23 (22%) subjects with acute cervical disc herniations had recurrences in pain of moderate intensity over 24-36 months, though not as severe as the initial onset of pain [21]. None of the patients with persistent cervical disc herniation and radiculopathy developed progressive neurological deficits or myelopathy at follow-up [21].

Prognostic Factors for Cervical Disc Herniations

One phase I cohort study described prognostic factors for symptomatic cervical disc herniations [23] (Table 4). Preliminary evidence suggested that subjects on workers' compensation were associated with a poorer prognosis in traumatic cervical disc herniations [23]. In a phase I study, subjects with approved workers' compensation claims required more invasive treatment (i.e. cervical epidural injections and/or surgery) and days off work than those without workers' compensation claims.

Discussion

The results of our systematic review suggest that the course of cervical disc herniations with radiculopathy is favourable. Substantial improvements appear to occur in four to six months post-onset for acute and chronic cases, with time to

complete recovery spanning 24-36 months in most subjects. In the long-term, a small proportion of patients appear to have residual impairments, such as pain and activity limitations. None of the patients in the reviewed articles had progressive neurological deficits or developed myelopathy, though it could not be determined if patients had recurrent episodes. In regards to prognosis, workers' compensation claims were associated with poorer outcome in one phase I study. However, the effect of this prognostic factor is unknown, as the degree of strength or association was not assessed.

The course of symptomatic cervical disc herniations with radiculopathy appears comparable to neck pain in the general population. The course of neck pain in the general population is recurrent, and at times, persistent and/or progressive in nature. Côté et al [24] described the course of neck pain in individuals with prevalent neck pain that were followed for one year. The study showed that the annual incidence of complete resolution was 36.6%; 37.3% reported persistent problems and 9.9% experienced worsening of their condition [24]. Finally, the annual incidence of developing a recurrent episode of neck pain was 22.8%. Overall, the preliminary evidence identified in our review suggests a similar course for cervical disc herniations but the initial pain intensity may be higher and more disabling than those with general neck pain. Recovery from cervical disc herniations may also be slower, though the rate of recurrence is not known.

The evidence suggests that the early clinical course of cervical disc herniations is similar to that of lumbar disc herniations. In a randomized trial comparing surgical versus non-surgical interventions for lumbar disc herniations, Atlas et al reported that substantial improvements in pain and disability from lumbar disc herniations occurred in the first 6 to12 months in both groups [25], and low levels of pain and disability were maintained over a 10-year follow-up period without recurrences in symptoms [26].

Our review highlights that little is known about prognostic factors for cervical disc herniations with radiculopathy. Our findings suggest that there is preliminary evidence (one phase I study) suggesting that patients with workers' compensation claims have a poorer prognosis. However, these findings need to be tested in phase II and phase III studies where confounders are adequately controlled. Overall, there were few relevant and admissible studies examining the course or prognostic factors of symptomatic cervical disc herniations with cervical radiculopathy. This is likely because our review examined cervical radiculopathy from isolated cervical disc herniations, which is less common than those related to multiple etiologies. A large epidemiological survey of cervical radiculopathy in Rochester, Minnesota reported an annual incidence of cervical disc herniations of 18.6 per 100,000 residents [2]. This is in contrast to the higher annual incidence of 58.5 per 100,000 residents for cervical radiculopathy related to combined spondylosis and disc involvement (e.g. osteophytes, narrow disc space or foramen) [2].

It is often challenging to identify the exact patho-anatomical cause of cervical radiculopathy. Common lesions include cervical disc herniations, degenerative foraminal stenosis, or a combination of the two. Since the clinical course of radiculopathy may depend on its etiology, it is important to describe its clinical course according to the implicated patho-anatomical cause. All studies in our review attributed the cervical disc herniation as the cause of radiculopathy in their subjects. Moreover, all admissible studies in our review excluded patients with degenerative changes (i.e. serious spondylotic changes, degenerative disc disease, or hyperostosis) associated with foraminal stenosis at the symptomatic level [21,22,23].

State of Literature and Study Limitations

Based on our selection criteria, the literature on course and prognostic factors of cervical disc herniations with radiculopathy is very limited. Out of 1221 potential studies in this area, only eight studies (0.7% of potential studies) were eligible, of which three (0.2%) studies were deemed scientifically admissible for this systematic review. All reported settings in the accepted studies of this systematic review involved small samples selected from the secondary or tertiary care level. Therefore, the course of symptomatic cervical spine disc herniation with radiculopathy in the general population remains uncertain. It is also uncertain if a marked proportion of subjects with cervical disc herniations

experienced recurrences in pain. Further research would help fill this important gap in our current knowledge of cervical disc herniations with radiculopathy.

Our systematic review has limitations. First, the validity of our conclusions is limited by the poor methodological quality of the reviewed studies. Second, our search strategy was restricted to the English language, which may be a source of bias. However, previous literature found that the exclusion of non-English clinical trials from a meta-analysis did not lead to biased results [27]. Third, we aimed to include studies where the cervical radiculopathy was clearly defined as having been caused by a cervical disc herniation/protrusion. We restricted our review to studies that used imaging (MRI, CT) to diagnose the herniated cervical disc and exclude degenerative causes (e.g. osteoarthritis of uncoverterbal and facet joints, thickening of ligaments, decreased intervertebral height, degenerative spondylolithesis) or other causes of radiculopathy (e.g. malignancy, infection, fractures, dislocations, congenital anomalies). However, we cannot rule out that participants included in the studies did not have minor degenerative changes that may have contributed to the cervical radiculopathy. Although some participants may have been misclassified, we are confident that it did not bias our results. Specifically, two admissible studies required imaging evidence of focal disc protrusions with corroborative myotomal weakness [21,22] and one required symptomatic MRI-confirmed single or two level cervical herniated pulposus as interpreted by a spine surgeon or radiologist [23]. The admissible studies excluded other pathology that can cause cervical radiculopathy (spondylotic

changes, fractures, dislocations) [21, 22, 23]. Finally, the generalizability of our review is restricted to patients who have cervical disc herniations and radiculopathy (rather than myelopathy) and who are managed conservatively. Studies that investigated surgical interventions may include subgroups of patients with more severe cervical disc herniations and radiculopathy, which are more likely to progress to myelopathy.

Research Priorities

The course and prognostic factors of symptomatic cervical disc herniations with radiculopathy need to be explored in future research. High-quality prognostic studies (phase II and phase III) with frequent intervals and longer follow-up are needed to determine the rate of recurrence and the long-term course. These studies should differentiate between neck or arm pain alone and neck pain associated with referred arm pain. Future studies should also use valid and reliable outcome measures for assessing pain, disability and quality of life. Future studies are needed to determine the effect of workers' compensation claims on the prognosis of cervical disc herniations and to understand the strength of the association. Studies are also needed to assess the role of other potential prognostic factors of cervical disc herniations with radiculopathy, such as poor health, prior pain episodes and psychological factors. Emphasis placed on modifiable prognostic factors may also help inform public health strategies.

Key Points:

- The quality of the current literature on the course and prognostic factors of symptomatic cervical disc herniations with radiculopathy is poor.
- Most patients with cervical disc herniations with radiculopathy experience substantial improvements within four to six months post-onset. Time to complete recovery ranged from 24-36 months in most patients.
- Patients did not have progressive neurological deficits or develop myelopathy in the long term. However, it is unknown if patients with cervical disc herniations suffer from a recurrent course.
- Preliminary findings suggest that subjects with workers' compensation claims have a poorer prognosis. However, conclusions regarding this prognostic factor cannot be made based on the current literature.
- Further research with high quality prognostic studies is needed to better understand the clinical course and prognostic factors of cervical disc herniations with radiculopathy.

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Figure Captions

Figure 1: Systematic Review Flow Diagram

1 Table 1: Results of SIGN Criteria for Potentially Relevant Cohort Studies

SIGN Criteria	Bahadir et al., 2008 [21]	Scuderi et al., 2005 [23]	Heckmann et al., 1999 [18]	Nardi et al., 2005 [19]	Olah et al., 2008 [16]	Gong et al., 2011 [20]
1. Addresses appropriate and clearly focused question	AA	WC	PA	PA	AA	AA
2. Case definition is clear	AA	WC	WC	PA	AA	AA
3. Groups being studied are comparable in all respects	PA	AA	AA	NR	NA	AA
4. Reports participate rates of each group being studied	NA	WC	NR	NR	NA	NR
5. Likelihood subjects had outcome at time of enrolment	AA	AA	NA	AA	NA	AA
6. Reports drop-out/withdrawal rates	Yes	Yes	No	Yes	No	No
7. Compares full participants with those lost to follow-up	NA	AA	NR	NR	NA	NR
8. Outcomes are clearly defined	AA	AA	PA	PA	AA	PA
9. Assessment of outcome is made blind to exposure	AA	NA	AA	NR	NR	NA
10. Recognizes that knowledge of exposure could have influenced assessment of outcome	N/A	PA	PA	NA	NR	NA
11. Measure of assessment of exposure is reliable	N/A	NA	N/A	N/A	N/A	N/A

12. Measure of assessment of exposure is valid	N/A	NA	N/A	N/A	N/A	N/A
13. Evidence that outcome assessment method is reliable	NA	NA	NA	NA	NA	PA
14. Evidence that outcome assessment method is valid	NA	PA	NA	NA	NA	PA
15. Exposure/prognostic factor assessed more than once	N/A	NA	N/A	N/A	N/A	N/A
16. Addresses main potential confounders	N/A	PA	N/A	N/A	N/A	N/A
17. Overall assessment of study based on risks of bias, clinical considerations and evaluation of methodology	Scientifically admissible - Phase 1 Study	Scientifically admissible - Phase 1 Study	Scientifically inadmissible	Scientifically inadmissible	Scientifically inadmissible	Scientifically inadmissible

1 WC - well covered; AA - adequately addressed; PA - poorly addressed; NA - not addressed; NR - not reported; N/A - not applicable

2

3

1 Table 2. Results of SIGN Criteria for Potentially Relevant Randomized Trials

SIGN Criteria	Cesaroni and Nardi, 2010 [22]	Persson et al., 2000 [17]
1. Addresses appropriate and clearly focused question	WC	AA
2. Case definition is clear	WC	AA
3. Assignment of subjects to treatment groups is randomized	WC	AA
4. Adequate concealment method is used	AA	AA
5. Subjects and investigators are kept blind to treatment allocation	NA	N/A
6. Treatment and control groups are similar at start of trial	AA	PA
7. The only difference between groups is the treatment under investigation	AA	PA
8. All relevant outcomes are measured in a reliable way	WC	PA
9. All relevant outcomes are measured in a valid way	WC	PA
10. Reports drop-out/withdrawal rates	Yes	No
11. All subjects are analyzed in groups to which they are randomly assigned	WC	AA

12. Where study is carried out at more than one site, results are comparable for all sites	N/A	NA
13. Overall assessment of study based on risks of bias, clinical considerations and evaluation of methodology	Scientifically admissible – Cohort within randomized trial	Scientifically inadmissible

1 WC - well covered; AA - adequately addressed; PA - poorly addressed; NA - not addressed; NR - not reported; N/A - not applicable

2

Table 3: Selection Criteria for Cervical Disc Herniations of the Scientifically Admissible Studies

Author, Year	Inclusion Criteria	Exclusion Criteria
Bahadir et al., 2008 [21]	- Focal acute cervical disk protrusion and root compression confirmed with magnetic resonance imaging - Myotomal muscle weakness compatible with cervical radiculopathy	- Multilevel cervical disc herniations - Myelopathy - Weakness in more than one myotome - Previous cervical surgery, cervical or brachial plexus trauma - Serious spondylotic changes
Cesaroni et al., 2010 [22]	- Neck/arm pain visual analogue score of 50 on a scale of 0–100 - Imaging evidence of a single contained symptomatic focal disc protrusion between C3 and T1 which did not compromise more than one-third of the AP diameter of the spinal canal - Minimal corroborative myotomal deficit - A positive diagnostic nerve root block - Failed to respond to or refused epidural steroid injection	- Evidence of an extruded or sequestered disc herniation - History of anterior fusion in the cervical level to be treated - Spinal fracture, tumor, or infection, a central cord lesion in the cervical spine - Progressive neurological deficit, focal protrusion exceeding one-third of the spinal canal - Hyperostosis causing concurrent foraminal stenosis at the symptomatic level - Myotomal deficit with motor strength less than 4/5 - Disc height reduction of 50% - Carotid stenosis or significant plaque-like carotid disease
Scuderi et al., 2005 [23]	- Magnetic resonance imaging confirmed diagnosis of a cervical herniated disc (herniated nucleus pulposis) - Single or two-level disc herniation as interpreted by a spine surgeon or radiologist - Persistent symptoms past 6 weeks after motor vehicle collision	- History or evidence of a bony or significant ligament injury i.e. fracture or subluxation - Cervical degenerative disc disease - Cervical disc herniations at three or more levels

1 Table 4: Evidence Table of Cohort Studies

Author(s), Year [reference]	Setting and Subjects, Number Enrolled (n)	Case Definition	Follow-up, Number (n) at Follow-up	Prognostic Factors/Outcome	Study Design and Key Findings
Bahadir et al., 2008 [21]	NR; ages 27-55 years, consecutive patients who refused surgical intervention and received medication, physical therapy and rehabilitation programs defined by treating physician. (n=23)	Focal acute cervical disk protrusion and root compression confirmed with MRI and myotomal weakness compatible with cervical radiculopathy; excluded subjects with serious spondylotic changes	4,8,12, 24, 36 months (n=23 at 24 months, n=19 at 36 months)	Prognostic factors: none. Outcome: Needle EMG, mean VAS at rest, mean VAS with Spurling's test, muscle strength and sensory changes, surgery; categorized into excellent (no signs or symptoms of radiculopathy, no abnormal EMG), good (VAS ≤3 and no muscle weakness), poor (VAS ≥4 or muscle weakness)	Phase I: Significant decrease in mean VAS at rest and with Spurling's until 12 months (no significant difference between 12 and 36 months), muscle strength returned to normal for most subjects by 36 months; at 24 months, 11/23 (48%) subjects had excellent outcome, 8/23 (35%) had good, 4/23 (17%) had poor; at 36 months, 9/19 (47%) had excellent, 6/19 (32%) had good, 4/19 (21%) had poor; 0 subjects required surgery
Scuderi et al., 2005 [23]	Tertiary care; ages 25-62, patients referred to spine specialist (1 day to 4 weeks after injury) with diagnosis of neck pain	Single or two-level cervical disc herniation noted on MRI with no evidence of	Weekly for 2 weeks, monthly for 2 months, every 3 months until return to	Prognostic factors: Presence of WC Outcome: days off work, number of patient visits for non-operative therapy, number of subjects receiving cervical epidurals, number of subjects undergoing surgery	Phase I: WC group had a greater percentage of subjects undergo the following when compared to non-WC group: surgery (26/54 or 48% vs. 26/216 or 12%), epidural injections (14/54 or 26% vs. 11/216 or 5%), lost work days at 3

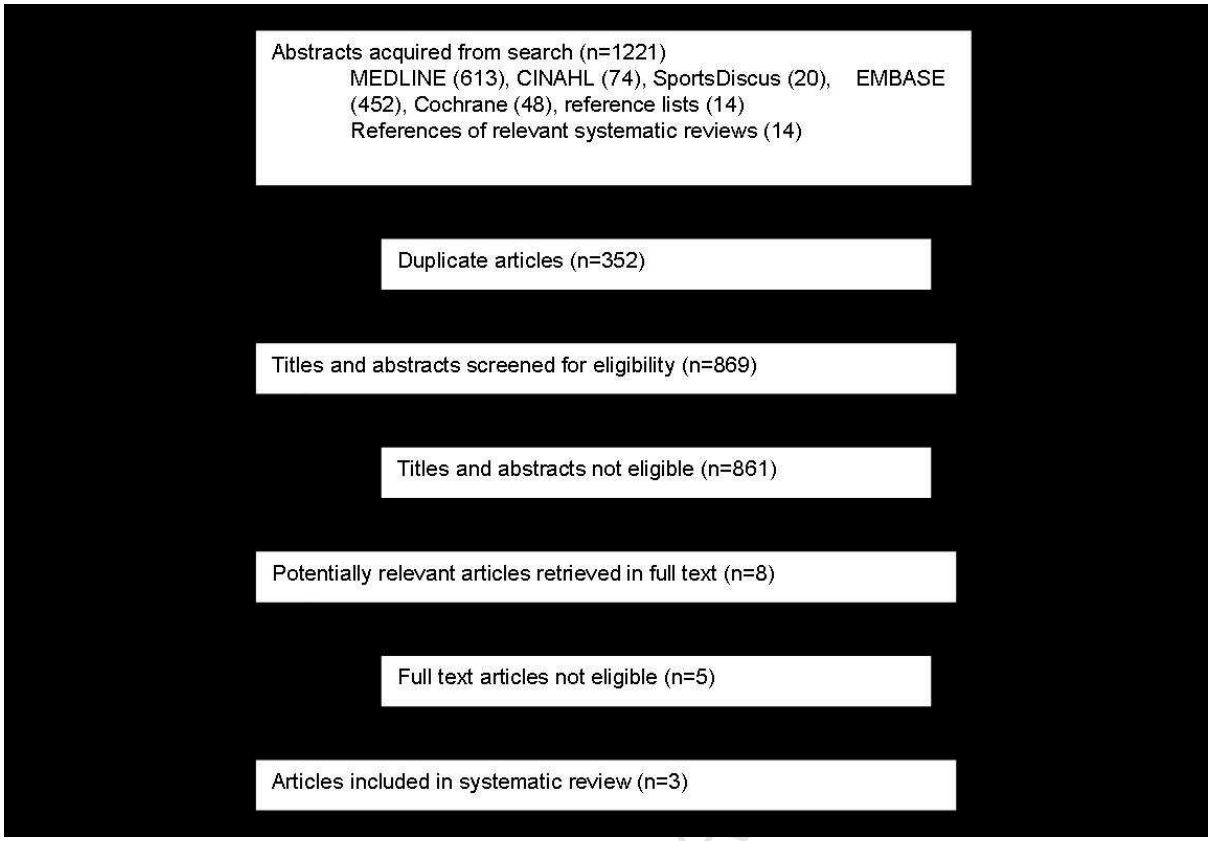
	after motor vehicle accident and failed to respond favourably to non-operative treatment measures. (n=296)	significant bony or ligamentous injury; excluded subjects with fractures, dislocations, or cervical degenerative disc disease	work/maximum medical improvement or lost to follow-up after 2 years (n=270, 19 from WC group, 7 from personal injury group)		months (average 37.1 days per subject vs. 5.1 days per subject), lost work days at 2 years or MMI (average 131.6 days per subject vs. 28.7 days per subject). WC group had fewer physiotherapy visits (average 22.7 visits per subject) than non-WC group (average 26.8 visits per subject)

1 NR - not reported; MRI - magnetic resonance imaging; EMG - electromyography; VAS - visual analogue scale; WC - workers' compensation

1 Table 5: Evidence Table of Randomized Trials

Author(s), Year [reference]	Setting and Subjects, Number Enrolled (n)	Case Definition	Intervention Groups	Follow-up, Outcomes Measured, Number at Follow-up	Study Design and Key Findings
Cesaroni and Nardi, 2010 [21]	Tertiary care; ages 45.03 (SD 10.72) for intervention group, 47.43 (SD 11.49) for conservative treatment group (given in outpatient basis), all subjects had neck/arm pain > 50 on VAS after failing at least 30 days of prior conservative care. (n=62 for intervention group, n=53 for conservative group)	Single contained symptomatic focal cervical disc protrusion from C3-T1 not compromising >1/3 of anteroposterior diameter of cervical canal on MRI, minimal corroborative myotomal deficit, positive nerve root block; excluded subjects with hyperostosis causing concurrent foraminal stenosis at the symptomatic level or disc height reduction of 50%	PDD compared to conservative care (including transcutaneous electrical nerve stimulation, progressive neck mobilization, collar use, postural rehabilitation, analgesics and/or NSAIDs)	6 weeks, 3 months , 6 months, 12 months; mean VAS neck/arm pain, NDI, SF-36 (n=120 at 3 months, n=118 at 6 months and 1 year with 1 subject undergoing surgery from each group)	A cohort within RCT: Conservative care group had improvements over time in VAS (-15.26±1.97 at 6 weeks, -40.26±2.56 at 6 months, -36.45±2.86 at 1 year), NDI (-4.61±0.53 at 6 weeks, -12.86±0.8 at 6 months, -12.40±1.26 at 1 year) and SF-36 scores (physical function 4.35±4.17 at 6 weeks, 10.86±7.65 at 6 months, 9.95±10.9 at 1 year; role emotional 4.69±6.7 at 6 weeks, 13.34±9.33 at 6 months, 9.82±11.78 at 1 year), with slight regression in symptoms at 1 year

1 PDD - plasma disc decompression; NSAIDs – nonsteroidal anti-inflammatory drugs; MRI - magnetic resonance imaging; CT - computed tomography; VAS - visual analogue scale; NDI
2 - neck disability index; SF-36 - short-form-36; RCT - randomized controlled trial; MCID - minimal clinically important difference



Appendix 1: Electronic Supplementary Material – Search Strategy

MEDLINE (613)

1. MH Intervertebral Disc Displacement
2. dis*
3. herniat*
4. or/1-3
5. MH Neck
6. MH Neck Pain
7. MH Neck Injuries
8. cervical
9. or/5-8
10. MH Natural History
11. MH Prognosis
12. prognos*
13. outcome*
14. course*
15. predict*
16. or/10-15
17. 4 and 9 and 16
18. Limit 17 to English language, Human Studies

CINAHL (74)

1. MH Intervertebral Disc Displacement
2. dis*
3. herniat*
4. or/1-3

5. MH Neck
6. MH Neck Pain
7. MH Neck Injuries
8. cervical
9. or/5-8
10. MH Natural History
11. MH Prognosis
12. prognos*
13. outcome*
14. course*
15. predict*
16. or/10-15
17. 4 and 9 and 16
18. Limit 17 to English Language, Human Studies

SportsDiscus (20)

1. dis*
2. herniat*
3. or/1-2
4. neck*
5. cervical
6. or/4-5
7. natural history
8. prognos*
9. outcome*
10. course*
11. predict*

12. or/7-11
13. 3 and 6 and 12
14. Limit 13 to English language, Human Studies

EMBASE (452)

1. MH Intervertebral Disc Hernia
2. dis*
3. herniat*
4. or/1-3
5. MH Cervical Spine
6. MH Neck Pain
7. MH Neck Injury
8. or/5-7
9. MH Prognosis
10. MH Disease Course
11. natural history
12. prognos*
13. outcome*
14. course*
15. predict*
16. or/9-15
17. 4 and 8 and 16
18. Limit 17 to English Language, Human Studies

Cochrane Central Register of Controlled Trials (48)

1. dis*
2. herniat*

3. or/1-2
4. neck*
5. cervical*
6. or/4-5
7. natural history
8. prognos*
9. outcome*
10. course*
11. predict*
12. or/7-11
13. 3 and 6 and 12
14. Limit 13 to English Language, Human Studies

TOTAL citations across all databases (1207)

Additional references from 2 Cochrane reviews (14)