



## DIFFERENTIAL TRENDS OF HIGH SENSITIVE C-REACTIVE PROTEIN AND FUNCTIONAL OUTCOME AFTER ADMINISTRATION OF EPIDURAL STEROIDS IN ACUTE AND CHRONIC CASES OF CERVICAL RADICULOPATHY

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### ABSTRACT

**Background and objectives :** Cervical Epidural steroid injections (CESI) have now been used for a number of years and have shown intense growth in the treatment of radicular pain after failed conservative treatment with oral medication, physical therapy and lifestyle modifications. In their 2010 Guideline for The Treatment of Cervical Radicular Pain, the World Institute of Pain issued a positive recommendation for interlaminar cervical epidural steroid injections for the treatment of cervical radicular pain.(1)

Traditionally radicular pain has been thought to be caused due to the mechanical compression of nerve roots by the herniated nucleus pulposus (HNP). However it has now increasingly become evident that radicular pain also involves an underlying inflammatory component. Prostaglandin E2, tumor necrosis factor - (TNF- ), interleukin-6 (IL-6), nitric oxide (NO), and matrix metalloproteinases are released by the herniated cervical intervertebral discs.(2-4) So it is not only the mechanical compression of nerve roots, but also the inflammation around the nerve roots which is responsible for the pain perceived by the patient. In this study we have used high sensitive C- reactive protein (hsCRP) assay for prediction of inflammation around nerve roots. This ultrasensitive assay is normally capable of measuring serum hsCRP at a concentration of 0.0095 mg/L using ultrasensitive latex enhanced immunoassay on the BN II nephelometer(5) or by using ELISA (Enzyme linked Immunosorbent Assay). We have used the visual analogue scale (VAS) as a measure of pain and functional outcome after CESI.

**Methods:** This study was a prospective study design. A single cervical epidural steroid injection was given to all cases in our study after documentation of the baseline hsCRP levels and VAS scores. All CESIs were administered by a single anesthetist through the interlaminar approach. Blood hsCRP levels and VAS scores were reassessed at the first month, second month and third month of follow up.

**Results :** The blood hsCRP values at presentation or the baseline hsCRP level was significantly elevated in cases of cervical radiculopathy as compared to apparently normal controls without cervical radiculopathy. There was an increase in baseline hsCRP values at presentation in both acute as well as chronic cases of cervical radiculopathy. However the increase in chronic cases was considerably more significant than the increase in acute cases.

**KEYWORDS :** Cervical radiculopathy, high sensitive C-reactive protein, epidural steroid Injections, visual analogue scale.

### INTRODUCTION

Cervical Epidural steroid injections (CESI) have now been used for a number of years and have shown intense growth in the treatment of radicular pain after failed conservative treatment with oral medication, physical therapy and lifestyle modifications. In their 2010 Guideline for The Treatment of Cervical Radicular Pain, the World Institute of Pain issued a positive recommendation for interlaminar cervical epidural steroid injections for the treatment of cervical radicular pain.(1) C-reactive protein (CRP) is an acute phase reactant, the levels of which increase during infection or other inflammatory processes occurring in the body. This increase in CRP is due to increase in the plasma concentration of IL-6, which is produced primarily by macrophages around the disc tissue(6). This underlying inflammation around the herniated intervertebral disc causes increase in CRP level in very minute amounts(7). C-reactive protein is usually measured in clinical laboratories by either immunoturbidimetric or immunonephelometric assays. The current methods are fully automated, reproducible and are capable of measuring CRP with a detection limit of 3–5 mg/L(5). Although this detection limit is adequate for the traditional clinical utility of CRP in monitoring of infection, it renders most of the current assays useless in measuring and assessing the amount of inflammation around herniated discs or atherosclerosis in otherwise apparently healthy populations.

The most well known reason for cervical radiculopathy is foraminal infringement of the spinal nerves in 70 to 75 percent of cases which in turn can be due to a blend of factors, including diminished intervertebral disc height and degenerative changes as in cervical spondylosis involving the uncovertebral joints anteriorly and the zygapophyseal joints posteriorly(8) Herniation of the nucleus pulposus is the cause in just 20 to 25 percent of the cases of cervical radiculopathy(9) as opposed to disorders of lumbar spine, where disc herniation is very common. Other causes include cervical spinal stenosis, vertebral body pathology, meningeal pathology, facet joint pathology and pathology involving the blood vessels, nerve sheaths, and nerves. We in our study have focussed on cervical radiculopathy due to disc herniation.

The exact pathogenesis of radicular pain still remains unclear, it is thought that compression alone may not always be enough to cause pain, and that an inflammatory chemical component is often required. It has been found that various chemical mediators involved in the inflammatory process are released from sensory neurons and intervertebral disc tissues, contributing to the occurrence of pain.(10) In addition, the increased permeability of the membrane of dorsal root ganglion with respect to its surrounding nerve root membrane is also hypothesized to be a potential source for radicular pain(11)

Initial treatment is conservative and involves lifestyle modifications, non steroidal anti inflammatory drugs (NSAID) and physiotherapy. Opioid analgesics and other adjuvants are often used when there is persistent pain. A cervical orthosis has also been utilized for some patients in acute conditions. The common treatment modalities for chronic persistent pain due to cervical disc herniation after the failure of conservative management are related to surgery or cervical epidural injections. Along with the escalating growth of surgical interventions, cervical epidural injections have also shown intense growth, though it is less as compared to the growth shown by lumbar epidural injections.

If there is no improvement after three to four weeks of conservative management, CESIs may be administered. Surgery, most commonly, Anterior Cervical Decompression and Fusion (ACDF) being the last resort should be reserved for patients who continue to have persistent and disabling pain even after six to twelve weeks of conservative management, progression of neurological deficits if any or signs of moderate to severe myelopathy. It is estimated that 26% of patients with cervical radiculopathy may require surgery(12). Our study design mainly focused on cervical epidural steroids. The rationale for use of epidural corticosteroids in cervical radiculopathy is the anti inflammatory effect and herniated disc is the most commonly proposed mechanism of increased inflammation and pain. Cervical herniated intervertebral disc specimens have shown increased levels of IL-6, NO, PG-E2 and matrix metalloproteinase activity(7,13)

The benefits of cervical ESIs remain difficult to quantify because of the paucity of randomized trials of sufficient sample size. Small prospective and retrospective observational studies have suggested that either transforaminal or interlaminar ESIs can provide benefits for up to six months or longer in 40% to 84% of patients(14,15,16), evidence been derived from controlled randomized trials. A study by Manchikanti *et al*(16) showed effectiveness of cervical epidurals in 72% of patients who were administered local anaesthetics whereas it was 68% in patients who were given steroids. A systematic review by Benjamin *et al*(17) in 2009, reported that interlaminar CESIs provide a significant effect in relieving short and long term cervical radicular pain in cervical radiculopathy.

CRP is a ring shaped, annular, pentameric protein found in blood plasma. HsCRP is used as a marker of subclinical systemic inflammation, as it has well established clinical and epidemiological determinants(18) very little to no diurnal variation(19) moderate person to person variability and it can be used for long term prediction of disease(20). Among all the acute phase proteins, CRP is the earliest to appear, six to eight hours after infection. By and large, the normal range of CRP in all age groups is 0-10 mg/L, however the values may be influenced by several factors.

It is however crucial, that factors with potential influence on high sensitive c-reactive protein such as alcohol(21), smoking(22), body mass index (BMI)(22), physical activity(23) and medications(21) are taken into account.

Epidural steroid injections (ESI) are one of the most extensively utilized pain management procedure in the world. Favourable outcomes have been reported in the literature to support the use of epidural corticosteroid injections for the treatment of cervical radiculopathy using either an interlaminar or a transforaminal approach. Short term pain relief has been documented for the treatment of cervical radicular symptoms(24). In another study, as many as 60% of patients reported long term relief of their neck and radicular symptoms(14).

Visual Analogue Scale (VAS) is often used in clinical research

and epidemiological studies to measure the intensity or frequency of various symptoms(25). Accordingly the VAS can be used as a measure of pain and the range may vary from feeling no pain to feeling extreme pain. The most simple VAS is a straight horizontal line of fixed length, usually 10 cm. The ends are defined as the extreme limits of the parameter to be measured, example pain(26), orientated from the left (worst) to the right (best), or vice versa. The patient is asked to mark his pain level on the line between the two endpoints of the horizontal line.

## MATERIALS & METHODS

The study was approved by the ethics committee at our institution. Informed and written consent was obtained from all the participants before enrolment in the study. Our population of interest consisted of patients with cervical radiculopathy due to disc herniation attending the orthopaedics out patient department at PGIMER, Chandigarh, India.

90 patients with cervical radiculopathy due to disc herniation as per criteria laid down by North American Spine Society (NASS) in the age group between twenty to sixty years and who were on conservative treatment for at least four weeks were enrolled as cases. Patients with duration of symptoms of more than 3 months were considered as chronic cases, whereas patients with duration of symptoms of 3 months or less were considered as acute cases. The control group consisted of 80 apparently healthy subjects without any symptoms of cervical radiculopathy, matched with the cases for age, sex, and body mass index.

## INCLUSION CRITERIA

1. Age between 20 to 60 yrs.
2. Patients fulfilling the criteria for cervical radiculopathy as laid down by NASS (2010).
3. Clinical evidence of herniation in the form of disc related radicular pain of more than four weeks duration interfering with daily activities.
4. Failure to respond to conservative treatment modalities including physical therapy, a structured exercise program and drug therapy.
5. Radiological evidence of disc herniation on MRI cervical spine.

## EXCLUSION CRITERIA

1. Patients who have chronic inflammatory disease or malignancy.
2. Patients having any local or systemic source of infection.
3. Patients with ischemic heart disease and history of stroke.
4. Patients suffering from diabetes.
5. Patients with history of smoking.
6. Patients with history of chronic alcoholism.
7. Patients with high body mass index (BMI > 25).
8. Patients on statins, corticosteroids, ACE inhibitors, antiplatelets and beta blockers.
9. Patients with history of cervical spine surgery and radiculitis secondary to spinal stenosis.
10. Patients with history of any major surgical procedure in the past one year.
11. Patients suffering from Psychiatric disorders.
12. Patients showing signs and symptoms of any acute inflammatory disease during the study were withdrawn from the study.

All cases were subjected to a detailed evaluation with help of VAS. Patients were asked to mark the horizontal line which was divided from left to right as No pain, Minimal pain, Mild pain, Moderate pain and Extreme pain. Pre procedural 2 ml blood sample was collected from the cubital vein of the patients under all aseptic precautions in a plain vial for estimation of baseline hsCRP levels at presentation. A single

cervical epidural steroid injection was given to all cases in our study after documentation of the baseline hsCRP levels and baseline VAS scores. All CESIs were administered by a single anesthetist through the interlaminar approach.

Blood sample was recollected at the first, second and third month of follow up for assessment of blood hsCRP levels. Similarly all patients were re-evaluated at one month, two months and three months for functional outcome as measured by the VAS score.

**RESULTS**

A total of 90 patients were enrolled in the study. The control group consisted of 82 apparently normal subjects matched with the cases for age, sex, and body mass index. Cases were further subdivided into acute and chronic cases depending upon duration of symptoms. Patients with duration of symptoms of more than three months were considered as chronic cases, whereas patients with duration of symptoms of three months or less were considered as acute cases. There were 63 acute and 27 chronic cases.

**COMPARISON OF BASELINE HSCRP AT PRESENTATION AMONG CASES AND CONTROLS**

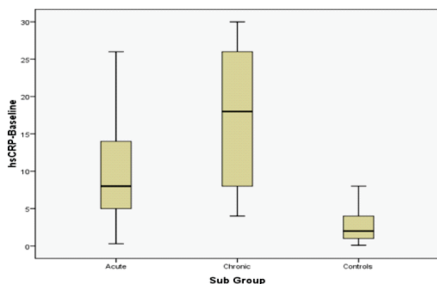
Mean hsCRP at presentation or the baseline hsCRP among cases was 12 +/- 8.281, whereas the mean baseline hsCRP among controls was 2.42 +/-1.881. T-test was applied and it was found that there is a significant statistical difference (p value < 0.0001) among the cases and controls in terms of baseline hsCRP levels. Thus we can conclude that the baseline hsCRP level is significantly elevated in cases of cervical radiculopathy as compared to normal controls.

**COMPARISON OF MEAN HSCRP AT PRESENTATION AMONG ACUTE AND CHRONIC CASES**

Mean of hsCRP at presentation or the baseline hsCRP among acute cases was 10.12 +/- 6.926, whereas the mean of baseline hsCRP among chronic cases was 17.17 +/-9.750. T-test was applied and it was found that there is a significant statistical difference (p value= 0.010) among acute cases and chronic cases in terms of baseline hsCRP levels.

**Table 1: Distribution of baseline hsCRP at presentation among acute and chronic cases.**

	Sub Group	N	Mean	Std. Deviation	Std. Error Mean
hsCRP-1	<b>Acute</b> (3 months or less)	63	10.12	6.926	1.206
	<b>Chronic</b> (> 3 months)	27	17.17	9.750	2.815



**Figure 1 : Box plot depicting baseline hsCRP values at presentation among acute cases, chronic cases and controls.**

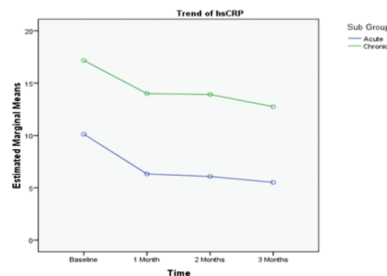
**Following observations were made :**

There is an increase in baseline hsCRP values at presentation in both acute as well as chronic cases of cervical radiculopathy as compared to apparently normal subjects. However the increase in chronic cases was found to be more

significant than the increase in acute cases. Patients with higher baseline hsCRP levels at presentation show a better functional outcome after cervical epidural steroids as indicated by improvement in VAS scores.

**COMPARISON OF TRENDS OF HSCRP IN THE ACUTE AND CHRONIC GROUPS**

Baseline hsCRP level at presentation is more in chronic patients as compared to baseline hsCRP levels in the acute group. The decline in hsCRP is more in acute patients after administration of cervical epidural steroid injection along with an improvement in VAS scores than the decline present in the chronic group. The reduction in hsCRP levels is more in the first month of administration of cervical epidural injection coinciding with improvement in VAS scores than in the subsequent months of follow up.



**Figure 2 : Trend of hsCRP values in the acute and chronic groups.**

**DISCUSSION**

In our study we found that there is significant elevation in baseline hsCRP levels at presentation in patients of cervical radiculopathy in both acute and chronic cases as compared to the control group. Over a three month follow up it was observed that there was a significant decrease in hsCRP levels and pain and a corresponding improvement in functional outcome as measured by the VAS after administration of CESI in acute cases. However hsCRP levels more or less remained constant in chronic cases and the functional improvement was much less as compared to the acute cases. Increase in baseline hsCRP in acute cases is expected due to the inflammatory component involved. Chronic pain in cervical radiculopathy may be multifactorial in origin involving a larger component of non inflammatory pathology and this can be the reason for the above mentioned finding in our study. In our study we found that the baseline hsCRP at presentation in chronic cases is more than the baseline hsCRP in acute cases. This finding is a matter of debate. It can be explained on the basis that chronic pain may be multifactorial in origin and involve persistent, prolonged and recurring inflammation which may lead to a higher baseline hsCRP in these patients.

**CONCLUSION**

Functional outcome after interlaminar cervical epidural steroid injection was better in acute cases of cervical radiculopathy as compared to chronic cases.

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