Original article

Transforaminal epidural Etanercept for the treatment of prolapsed lumbar intervertebral disc induced sciatica

Ashish Dagar*, Ramesh Kumar, Abhishek Kashyap, Vinay Prabhat, Hitesh Lal, Lalit Kumar

Central Institute of Orthopaedics, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

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ABSTRACT

Study design: Hospital based prospective study.

Objective: To study clinical response of transforaminal epidural Etanercept for lumbar prolapsed intervertebral disc induced sciatica.

Method: Patients presenting to O.P.D and Emergency services of our hospital were screened for inclusion and exclusion criteria & suitable candidates were enrolled in study. Patients received 2 transforaminal epidural injections of Etanercept 2 mg, 2 weeks apart, and were assessed for efficacy at 2 week, 1 month and 3 months after the second injection. Primary outcome was based on Visual Analog Scale for leg (VASL) and back pain (VASB) and secondary outcome was based on Modified Oswestry back related disability index (ODI).

Results: 31 of 33 enrolled patients completed study. Patients showed clinically and statistically significant ($p < 0.001$) reduction in VASL, VASB and ODI. There was no incidence of adverse events.

Conclusion: Epidural Etanercept is promising and effective non-operative treatment for patients with sciatica. But these results need to be confirmed by a randomized controlled trial.

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1. Introduction

Sciatica is defined as radicular pain that radiates from the lower back into the leg following a radicular Dermatomite.¹⁷ Pain is sharp shooting in character, burning in quality.¹⁸ Lumbar disc herniation is one of the most common causes of low back pain and/or sciatica¹ with point prevalence of 12–35%.²

Pathophysiology of sciatica has long been considered as mechanical nerve root compression,¹⁷ but clinical observations in several cases cannot be adequately explained by mechanical compression. Some patients with large herniation have no radicular symptoms, whereas some patients with no evidence of disc herniation on imaging have severe radiculopathy.^{20–22} Recent studies have emphasized the importance of local inflammation in addition to mechanical compression in development of clinical symptoms.¹⁹ Nucleus pulposus have no blood supply and is unexposed to immune system after embryonic development and hence is immunogenic.^{23–26} Herniated disc material hence may release substances capable of inducing autoimmune response and

chronic inflammation.^{27–29} Various inflammatory mediators as interleukin 1, interleukin 6, cyclo-oxygenase-2 and TNF-alpha have been strongly implicated in causing this chronic inflammation.^{30,31} Although all these inflammatory markers have a role in causing inflammation, the role of TNF-alpha is pivotal.^{10,32} TNF-alpha causes nerve root inflammation, central sensitization and neuropathic pain that underlie sciatica.^{33–35} In animal models application of TNF-alpha on nerve roots and dorsal root ganglion has resulted in neuropathic changes similar to those induced by nucleus pulposus.⁹ Selective inhibition of TNF-alpha prevents such damage in porcine model.¹⁰ TNF-alpha blockers prevent neuro-pathologic activity such as edema formation, demyelination, and decreased conduction.^{10,15,43,44}

Conventional modes of management of sciatica have been conservative therapies, epidural steroid injections and surgery. Conservative therapies for its management such as drug and physical therapies have proven not much effective.³ Efficacy of epidural steroid injections is doubtful⁷ and offers short term relief if any.⁸ There is evidence that transforaminal epidural steroid injections are more effective than the conventional interlaminar injections.^{36–38} However, there are reports that transforaminal epidural steroids can cause catastrophic results as spinal cord infarcts due to particulate nature of depot steroids and hence there is need for safer alternatives.^{39–41} Surgery is an option but it is irreversible undertaking with failure rates ranging from 3–14%⁴ to

* Corresponding author at: 146, V.P.O Dhansa, New Delhi, India.

E-mail addresses: dagarash@gmail.com (A. Dagar), drkumarramesh@gmail.com (R. Kumar), kashyap.dr@gmail.com (A. Kashyap), vinay.prabhat@rediffmail.com (V. Prabhat), drhiteshlall@gmail.com (H. Lal), lalitkumarkain@gmail.com (L. Kumar).

30%.⁵ Its long term outcomes have also not been better than conservative therapies.⁶ So, although surgery does not increase risk of poor outcome, it could be unnecessary as it does not alter ultimate outcome.

Newer proposed alternative in injection line of management is use of TNF-alpha inhibiting agents. TNF-alpha inhibition can be achieved with a monoclonal antibody against it such as Infliximab, Adalimumab or with a circulating receptor fusion protein such as Etanercept. All these agents have shown promising results in various trials.^{11–13} Systemic use of Etanercept, Infliximab & Adalimumab has certain limitations as increased risk of systemic side effects, low drug concentration at actual pathological site. Moreover as vertebral disc is poorly vascularized, systemic administration of these drugs require high doses to achieve efficacy and hence localized administration can be more beneficial with fewer adverse events.⁴² Safety of Infliximab & Adalimumab for epidural use has not been proven yet but randomized controlled trial has proved safety of epidural Etanercept for use in humans.¹²

Etanercept is a recombinant fusion protein of the p75 subunit of the TNF receptor with the Fc component of the human immunoglobulin G1.⁴² Etanercept can bind to two TNF molecules, thereby effectively removing them from pathological site. Traditional route of administration for Etanercept have been subcutaneous but controlled study found no significant difference between control and treatment group.¹⁴ Explanation given for these paradoxical results is that systemic administration is less effective than local administration in blocking deleterious cascade of TNF-alpha induced cellular events. This point is supported by various animal¹⁵ and human¹⁶ studies. Moreover risk of side-effects is much more in systemic drug administration. Transforaminal epidural Etanercept may overcome this short coming with additional advantage of decreased chances of side effects.

The purpose of this study was to evaluate clinical response of transforaminal epidural Etanercept for lumbar prolapsed intervertebral disc induced sciatica.

2. Materials and methods

Study design: Hospital based prospective study was conducted for period of one and a half year.

Inclusion criteria:

- 1) Cases of unilateral radiculopathy due to lumbar PIVD with duration of symptoms for at least 2 months but less than 1 year.
- 2) Failure to respond to conservative therapy.
- 3) MRI evidence of herniated disc concordant with the patient's symptoms.
- 4) Normal leukocyte count.

Exclusion criteria:

- 1) Pregnancy.
- 2) Age <18 years and >70 years.
- 3) History of previous back surgery.
- 4) Unstable medical or psychiatric condition.
- 5) Severe spinal stenosis.
- 6) Any condition known to be amenable to TNF-alpha inhibitors e.g. Crohn's diseases, spondylarthropathy.
- 7) Immunodeficiency of any type.
- 8) Lymph proliferative disease or malignancy.
- 9) Systemic infections.
- 10) Contrast allergy.
- 11) Tuberculosis.
- 12) Diabetes Mellitus.
- 13) Low leukocyte count.

Fig. 1. Etanercept injection.

Injection technique: Patients were positioned prone on O.T table. Parts were scrubbed, painted and draped. Landmarks and desired lumbar level was confirmed by image intensifier. Under an image intensifier guidance, a 22-gauge, 5-inch spinal needle was placed in epidural space by transforaminal route. Correct needle position was then confirmed in antero-posterior and lateral image intensifier views using a radio-opaque dye, Omnipaque; spreading into epidural space and lining exiting and Cauda-Equina nerve roots.

2 mg of Etanercept was then injected into epidural space (Fig. 1).

Post injection period: Patients were instructed to limit strenuous activities for 6 hours post-injection and to then resume normal activities as tolerated.

2 weeks after first injection, second injection was repeated. Before follow up visits, no patient was given any additional therapeutic interventions.

Follow up assessment: Clinical assessment was done by using clinical examination, Visual Analog Scale score for leg and back pain, Oswestry back related disability index score at 2 weeks, 1 month and 3 months after second injection.

Outcome measurement:

1. **Primary outcome** – primary outcome was based on Visual Analog Scale score for leg and back pain
2. **Secondary outcome** – secondary outcome was based on Oswestry back related disability index score.

3. Result

Total of 33 patients enrolled in study, out of which 2 were lost to follow up and 31 completed study [$n = 31$]. Out of the total 31 patients in this study, eleven (35.5%) were in age group of 31–40 years, eight (25.8%) patients were in age group of 21–30 years, five (16.1%) were in age group 41–50, four (12.9%) were in age group ≤ 20 , whereas only 3 (9.7%) were in age group of >50 years. Patients mean age was 34.10 years ranging from 18 years to 65 years. Majority of the patients 17 (54.8%) were females whereas 14 (45.2%) were males. The distribution of the study group showed a female preponderance with female to male ratio of 1.21 (Table 1).

Visual Analog Score for back pain: At 2 weeks follow up, mean VASB decreased by 68.11% to 1.84 with standard deviation (SD) of ± 1.16 and range from 0 to 5. This improvement in back pain was

Table 1

VASB at different time points from baseline during study.

VASB	Mean $\pm$ SD	Min–Max	p values		
			Pre vs. 2 weeks	Pre vs. 1 month	Pre vs. 2 months
Pre-Injection	5.77 $\pm$ 1.06	4–7	<0.001*	<0.001*	<0.001*
2 weeks	1.84 $\pm$ 1.16	0–5			
1 month	1.55 $\pm$ 1.12	0–5			
3 months	1.39 $\pm$ 1.09	0–5			

Table 2

VASL at different time points from baseline during study.

VAS L	Mean $\pm$ SD	Min–Max	p values		
			Pre vs. 2 weeks	Pre vs. 1 month	Pre vs. 2 months
Pre-Injection	7.48 $\pm$ 0.99	6–10	<0.001*	<0.001*	<0.001*
2 weeks	1.19 $\pm$ 0.98	0–4			
1 month	0.87 $\pm$ 0.99	0–4			
3 months	0.84 $\pm$ 0.93	0–4			

Table 3

VASL at different time points from baseline during study.

ODI	Mean $\pm$ SD	Min–Max	p values		
			Pre vs. 2 weeks	Pre vs. 1 month	Pre vs. 2 months
Pre-Injection	64.07 $\pm$ 4.93%	53–72%	<0.001*	<0.001*	<0.001*
2 weeks	13.43 $\pm$ 5.17%	4.8–23.8%			
1 month	12.65 $\pm$ 5.34%	1.3–23.0%			
3 months	12.55 $\pm$ 5.08%	4.0–23.8%			

clinically and statistically significant with p value <0.001. At 1 month follow up assessment, mean VASB had further decreased by 15.76% from 1.84 at 2 weeks to 1.55 with SD $\pm$ 1.12 and range from 0 to 5. As compared to Pre-Injection, mean VASB had reduced by 73.14%. This improvement is statistically significant (p < 0.001). At 3 months follow up, mean VASB had further decreased by 10.32% from 1.55 at 1 month to 1.39 with SD $\pm$ 1.09 and range from 0 to 5. As compared to Pre-Injection, mean VASB had reduced by 75.91%. This improvement is statistically significant (p < 0.001) (Fig. 2).

Visual Analog Score for leg pain: At 2 weeks follow up, mean VASL decreased by 84.09% to 1.19 with standard SD of $\pm$ 0.98 and range from 0 to 4. This improvement in leg pain was clinically and statistically significant with p value <0.001. At 1 month follow up assessment, mean VASL had further decreased by 26.89% from 1.19 at 2 weeks to 0.87 with SD $\pm$ 0.99 and range from 0 to 4. As compared to Pre-Injection, mean VASL had reduced by 88.37%. This improvement is statistically significant (p < 0.001). At 3 months follow up, mean VASL had further decreased by 3.45% from 0.87 at 1 month to 0.84 with SD $\pm$ 0.93 and range from 0 to 4. As compared to Pre-Injection, mean VASL had reduced by 88.77%. This improvement is statistically significant (p < 0.001) (Table 2, Fig. 3).

Modified Oswestry Disability Index Score: At 2 weeks follow up, mean ODI decreased by 79.04% to 13.43 with standard SD of $\pm$ 5.17 and range from 4.8% to 23.8%. This improvement in disability was clinically and statistically significant with p value <0.001. At 1 month follow up assessment, mean ODI had further decreased by 5.81% from 13.43 at 2 weeks to 12.65 with SD $\pm$ 5.34 and range from 1.3% to 23%. As compared to Pre-Injection, mean ODI had reduced by 80.25%. This improvement is statistically significant (p < 0.001). At 3 months follow up, mean ODI had further decreased by 0.79% from 12.65 at 1 month to 12.55 with SD $\pm$ 5.08 and range from 4.0% to 23.8%. As compared to Pre-Injection, mean ODI had reduced by 80.41%. This improvement is statistically significant (p < 0.001) (Table 3, Fig. 4).

None of the patients underwent surgery during the 3-month follow-up period. No immediate or delayed adverse drug reactions and no adverse effects related to Etanercept were observed during study.

4. Discussion

The basis of treating sciatica with the monoclonal antibody against TNF alpha, Etanercept, is based on findings that autologous

Fig. 2. Comparison of VASB at different time points from baseline during study.

Fig. 3. Comparison of VASL at different time points from baseline during study.

Fig. 4. Comparison of mean ODI at different time points from baseline during study.

nucleus pulposus can induce nerve root injury even without mechanical nerve compression,²³ and that patho-physiological effects of nucleus pulposus seems to be mediated via TNF alpha.^{10,30}

This study showed clinical efficacy of transforaminal epidural Etanercept for PIVD induced sciatica by demonstrating clinically and statistically significant reduction in VASB, VASL and ODI, 2 weeks after treatment with two transforaminal epidural injections of TNF alpha inhibitor, Etanercept. These results were sustained at 3 month follow up assessment. These findings suggest that 2 transforaminal injections of 2 mg of Etanercept provided substantial reduction in VASL and VASB for the majority of treated subjects, persisting for 3 months after treatment.

No adverse drug effects were encountered during study. The safety data in our study suggest that transforaminal epidural Etanercept injections, in the dose and concentration ranges tested, should not be associated with any side effects. But, because of the small number of patients studied, these results could not be generalized and there remains a chance that adverse effects could occur if transforaminal Etanercept were used in a larger cohort. So the further studies should heed this possibility and monitor patients for signs of toxicity. The other unanswered aspect is the duration of benefit. As our follow up period was limited to 3 months and discogenic radiculopathy tends to be a recurring phenomenon characterized by frequent bouts of remissions and exacerbations^{6,14,34} longer follow up studies are required.

5. Conclusion

In conclusion, anti-TNF alpha therapy is an encouraging treatment option for sciatica that seems to decrease pain and subjective disability and perhaps obviate the need for back surgery. Further areas for investigation include studies to definitively establish efficacy and further evaluate safety, ascertainment of whether or not the analgesic effects of TNF inhibitors are time-dependent and identification of the optimal candidates, drugs, dose ranges, and injection intervals for treatment.

There is an urgent need for a randomized controlled trial to evaluate whether these promising early results can be confirmed. Before these results are confirmed in a randomized controlled trial and long-term safety is documented, we do not recommend the use of anti-TNF alpha therapy for sciatica outside a trial setting.

Conflicts of interest

The authors have none to declare.

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