A comparison of the analgesic efficacy of transfominal methylprednisolone alone and with low doses of clonidine in lumbo-sacral radiculopathy

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ABSTRACT

Background: Although transfominal epidural steroid injections under fluoroscopic guidance have become a common mode of treatment of lumbosacral radiculopathy due to herniated disc, the efficacy of steroid with low doses of clonidine has not been compared yet. Objectives: Comparison of the analgesic efficacy of methylprednisolone alone and with low doses of clonidine for transfominal injection in lumbosacral radiculopathy. Study Design: A randomized, double-blind trial. Setting: This study was performed at the Pain Clinic under the Department of Anaesthesiology, Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India. Methods: One hundred and eighty ASA grade I and II patients aged between 18 and 55 years were allocated into groups I, II and III to receive methylprednisolone 60 mg alone or methylprednisolone 60 mg with or without low doses of clonidine (0.5 mcg/kg or 1 mcg/kg) as transfominal epidural injection. Pain relief and patient’s satisfaction were evaluated with the global pain scale. Follow-up visits were advised at 1, 2, 4, 6 and 12 weeks and then at 6 months after injection. Associated complications were recorded. Results: Maximum pain relief was observed at 2 weeks after injection in all the three groups, with no difference in complication rate among the three groups. The most common complication observed was paresthesia in the nerve distribution. Greater than 60% improvement in pain scores was seen in 40% of the patients in group I, 50% of the patients in group II and 75% of the patients in group III. Limitations: This study is limited by the lack of a placebo group. Conclusion: Adding 1 mcg/kg clonidine to 60 mg methylprednisolone in transfominal epidural injections provided better pain relief than 60 mg methylprednisolone with 0.5 mcg/kg clonidine or 60 mg methylprednisolone alone in patients suffering from lumbosacral radiculopathy, with practically no significant side-effects.

Key words: Epidural, lumbosacral radiculopathy, sciatica, transfominal

INTRODUCTION

Sciatica is defined as pain in the distribution of a lumbar nerve root accompanied by neurosensory and motor deficits when, due to a herniated disc, it tends to have a more protracted course, with persistence of symptoms for more than 4-6 weeks in most patients. In about 10% of the patients, surgery is considered after 6 weeks because of persistent pain or progressive neurologic deficit. Although discectomy at the short term produces better pain relief than conventional therapy, its advantage for pain relief after 10 years is not evident.

Epidural steroid injection has been one of the “gold standards” in the management of chronic low back pain and sciatica for over 40 years. Controversy, however, continues regarding its efficacy, with conflicting conclusions found in two systematic reviews. A small but definite beneficial effect in chronic sciatica can be noted, believed to derive mainly from a reduction in inflammation and edema of injured and irritated spinal nerve roots.
A major problem with all those studies was that the commonly used injection techniques did not guarantee that medication actually reached the desired target nerve. Many patients with chronic sciatica and low back pain showed filling defects on epidurography due to the presence of scar tissue, which “shields” the affected nerve from the injectate. More direct application of medication, e.g., via a catheter introduced 10 cm into the epidural space via the sacral hiatus has not resulted in a more favorable outcome in terms of pain relief. Therefore, a transforaminal targeted approach has been advocated for injection of the medication to the affected nerve root.

Clonidine, an α-2 adrenergic agonist, has been traditionally used as an antihypertensive agent. The large expression of α-2 receptors in the central nervous system, i.e., locuscoeruleus and dorsal horn of the spinal cord, has eventually focused the interest of this drug on centrally mediated sedation and analgesia. It, however, has its own set of side-effects, i.e., hypotension, bradycardia, sedation, etc. Recently, there is more emphasis on the use of low doses of clonidine due to a remarkable decrease in the incidence of these side-effects.

The present study was designed to compare the analgesic efficacy of methylprednisolone (a long-acting steroid compound) with or without low doses of clonidine for the treatment of sciatica via transforaminal sleeve root injection.

**METHODS**

After obtaining approval from the institutional ethics committee, this prospective, randomized, double-blinded study was conducted at the Pain Clinic under the Department of Anaesthesiology, Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India, over a period of 2 years, i.e., from April 2010 to March 2012.

**Participants**

The study was conducted on 180 patients of either sex, with age ranging from 18 years to 55 years, with body weight between 40 and 70kg, ASA grade I or II, suffering from sciatica due to disc herniation [lumbar spine magnetic resonance imaging scan documenting a herniated nucleus pulposus (HNP) at not more than two levels, i.e., L3-L4, L4-L5 or L5-S1] and symptomatic for more than 6 weeks. The exclusion criteria were a large HNP with severe central or foraminal stenosis on magnetic resonance imaging, progressive neurologic deficits, cauda-equina syndrome, blood coagulation disorder, valvular heart diseases, hypotension, emotional instability, known history of allergy to local anesthetics, corticosteroids or clonidine or received prior epidural steroid injection or lumbar surgery. Apart from the magnetic resonance imaging (MRI) of the lumbosacral spine, all the patients were advised to get their complete hemogram, renal function tests, blood sugar and coagulation profile reported.

**Randomization**

After taking a written informed consent, the patients were randomly allocated into one of the three groups of 60 patients each using a computer-generated randomization schedule. Patients belonging to group I received methylprednisolone 60 mg as transforaminal injection, while those of group II received methylprednisolone 60 mg and clonidine 0.5 mcg/kg and those of group III received methylprednisolone 60 mg and clonidine 1 mcg/kg. The total volume of injected medication in each group was kept constant at 1.5 mL with the addition of normal saline.

**Pre-procedure assessment**

All the patients were assessed at least 1 week prior to the procedure and a standard treatment protocol was advised to them, i.e., combination of oral tramadol 37.5 mg + paracetamol 325 mg and gabapentin 300 mg three times a day. The patients were given a pain diary to note down the global pain scale scores twice a week (Monday and Thursday) beginning 7 days before the day of treatment up to 6 weeks after treatment.

**Technique**

The procedure was performed with the patient in the prone position on an X-ray translucent table. Fluoroscopy was used to identify and mark the essential bony landmarks. No sedation was given. Baseline pulse rate, blood pressure and respiratory rate were recorded before undertaking the procedure.

Lumbar transforaminal approach was performed by placing the needle in the neural foramen, ventral to the nerve root. The needle was directed in an oblique approach toward a target point on the upper margin of an imaginary triangle, the “safe triangle,” with the three sides corresponding to the horizontal base or the pedicle, the outer vertical border of the intervertebral foramen and the connecting diagonal nerve root and dorsal ganglion. The image was adjusted until the superior articulating process was visualized between the anterior and the posterior edge of the vertebral body and the base of the articulating process was in line with the pedicle above.

After sterile preparation, draping and anesthetising the skin and the overlying tissues with 2% lidocaine, a 12-cm-long, 22-gauge spinal needle was inserted just above the superior articulating process and directed toward the base of the pedicle, and advanced slowly until the bone was contacted.
just below the pedicle. The needle was then slightly withdrawn and redirected inferiorly into the targeted spinal nerve canal. Advancement was made under lateral and anteroposterior (AP) views to provide a 3-dimensional spatial representation. The AP view was taken to verify that the needle was not medial to the 6-o clock position of the pedicle; on the lateral view, the needle was positioned just below the pedicle in the ventral aspect of the intervertebral foramen.[14]

The first sacral (S1) foramen was best seen by directing the X-ray beam in a cephalocaudad direction so that the anterior and posterior foramina align, appearing as a small radiolucent circle just below the oval S1 pedicle.[15] The needle was inserted slightly lateral and inferior to the S1 pedicle and advanced slowly through the posterior foramen to the medial edge of the pedicle and the appropriate depth was gauged by first striking the posterior sacral bone just above the posterior S1 foramen before directing the needle tip into the S1 neural canal.

Non-ionic contrast dye (iohexol) 0.5-1 mL was injected very slowly (at about 1 mL in 20 s) and the dye pattern was assessed. If leg paraesthesias were noted as the needle approached the neural foramen, the needle was withdrawn slightly and the dye was injected. A positive image of the nerve root on fluoroscopy indicated that the needle had penetrated the epidural membrane. After an adequate dye pattern was observed, 1.5 mL of the mixture prepared was injected (maximum volume of 2 mL of injectate is necessary to preserve selectivity of single nerve block). The injection was given at two levels depending upon the level of disc herniation.

All patients were observed for any change in pulse rate, blood pressure and respiratory depression throughout the procedure. The level of sedation was assessed using a four-point scale,[16] 1 = responds readily to name spoken in a normal tone, 2 = lethargic response to a name spoken in a normal tone, 3 = responds only after name is called loudly and 4 = responds only after mild prodding or shaking.

The patients were discharged from the recovery room after they were fully awake and oriented (sedation scale = 1) and no adverse effects noted for 6 h after the injection of the drugs under study. The subjects were allowed to take oral tramadol 37.5 mg and paracetamol 325 mg combination as and when required during the study period with a minimum interval of 6 h between two doses. Gabapentin 300 mg three times a day, however, continued as in the pre-treatment period. An overall improvement in the patients’ condition was assessed in the follow-up visits at 1, 2, 4, 6 and 12 weeks after injection, the basis being a reduction of scores on global pain scale.

Sample size and statistical analysis
Sample size was calculated based on a pilot study conducted on 15 patients for an improvement of at least 60% in visual analogue scale (VAS). The minimum sample size turned out to be 48 for \( \alpha = 0.05 \) with power of 80%. Considering any loss of subjects during follow-up, 60 patients were enrolled in each group. Data from subjects of the pilot study were also included in the study. Demographic data and side-effects were analyzed using Fisher’s exact test. Pain relief and other parameters on the global pain scale were assessed using the Analysis of Variance (ANOVA) test. Results were considered statistically significant if the P value was less than 0.05.

RESULTS
Study design and participant flowchart [Figure 1].

Baseline characteristics
The three study groups were similar in terms of their age, gender, weight and duration of pain [Table 1].

The baseline hemodynamic and respiratory parameters, i.e., pulse rate, mean arterial pressure (MAP), respiratory rate and oxygen saturation, were also compared among the three study groups. Although small differences were observed, they were found to be statistically insignificant (P > 0.05).

![Figure 1: Study design and participant flowchart](image-url)
Efficacy of treatment

Visual analogue scale

The extent of pain was evaluated in terms of VAS scores, a component of the global pain scale. As observed, the baseline pain scores were similar in the three study groups (P > 0.05). Significant pain relief was observed after treatment in all three study groups, with maximum relief 2 weeks after treatment. However, post-treatment pain scores showed a significant difference among the three groups at all the follow-up visits. Statistical analyses depicted that the extent of pain relief among the three study groups after the same duration of treatment was significantly different, the best relief being in patients belonging to group III [Table 2 and Figure 2].

Analgesic requirement

The analgesic requirement (mean ± SD) of patients in all the three treatment groups decreased significantly after the treatment as compared with the pre-treatment requirements. At the same time, the difference in analgesic requirement among the three study groups was significant in all follow-up visits, with a maximum reduction in analgesic requirement seen in patients belonging to group III [Figure 3].

Quality of sleep

The changes observed in the quality of sleep after treatment showed a significant improvement from the baseline values. On statistical analysis, the inter-group difference after treatment was also significant [Table 3].

Global pain scale scores

Patient’s overall comfort was evaluated in terms of global pain scale score. Analysis showed that the three study groups had significant relief of symptoms after treatment in all the follow-up visits. At the same time, relief observed in group III patients was significantly better than that seen in the patients of groups I and II [Figure 4].

Complications

None of the patients developed any serious complication. The only complication observed in the study was transient paresthesia in the nerve distribution, which began during the procedure and resolved within 24 h without any sequelae. There was no difference in complication rate among the three study groups [Table 4].

### Table 3: Changes in quality of sleep

| QS p  | Very poor | Poor | Satisfactory | Well | Very well |
|-------|-----------|------|--------------|------|-----------|
| Group I | 15 | 15 | 25 | 5 | 0 |
| Group II | 18 | 13 | 24 | 2 | 0 |
| Group III | 17 | 15 | 23 | 4 | 0 |

### Table 4: Complications

| Complications | Group I (n=60) | Group II (n=58) | Group III (n=59) |
|---------------|---------------|----------------|-----------------|
| Bradycardia   | 0             | 0              | 0               |
| Hypotension/fainting | 0 | 0 | 0 |
| Sedation      | 0             | 0              | 0               |
| Respiratory depression | 0 | 0 | 0 |
| Nausea/vomiting | 0 | 0 | 0 |
| Paresthesia   | 3             | 5              | 4               |
| Others        | 0             | 0              | 0               |
DISCUSSION

In modern times, lumbosacral radiculopathy has become one of the most costly and ubiquitous medical problems, especially in Western Europe and North America.\(^{[17]}\) However, the exact data on incidence and prevalence of sciatica are lacking and the annual prevalence of disc-related sciatica in the general population is estimated to be roughly at 2.2%\(^{[18]}\).

MRI, introduced in the early 1970s, stands today as an excellent tool for the screening of patients with radicular pain.

In the present study, diagnosis of sciatica was primarily made on the basis of history taking and physical examination. The level of disc herniation was, however, reconfi rmmed before transforaminal block with the help of an MRI. MRI was also performed to exclude severe canal stenosis, infective cause of radicular pain and massive disc protrusion, wherein the patients were excluded from the study.

The modern era of treatment of sciatica initially focused primarily on surgery. However, in recent years, numerous studies have shown that a disc herniation may decrease in size or disappear in the course of a few months, no matter whether it is contained, extruded or migrated or of a small or large size\(^{[19-21]}\).

Saal and Saal\(^{[22]}\) also emphasized the effectiveness of conservative management of disc herniation. Fifty-eight patients on treatment with analgesics, anti-inflammatory medication (NSAIDs), epidural injection of steroids, at a low back school or by exercises were followed for a mean period of 31 months. Only 10% of the patients required surgery due to failure of resolution of symptoms. Majority of patients with lumbar radicular pain who avoid an operation for at least 1 year after receiving a nerve root injection will continue to avoid operative intervention for a minimum of 5 years\(^{[23]}\).

The lumbar transforaminal injection technique using fluoroscopic control ensures the corticosteroid preparation to be delivered precisely to the target site, i.e., the ventral aspect of the lumbar nerve root as well as the dorsal root ganglion, and the efficacy of radio-guided transforaminal epidural corticosteroid injections is higher than that obtained with blindly performed interspinous injections.\(^{[8,24]}\) Furman et al.\(^{[25]}\) emphasized the need for contrast injection apart from fluoroscopic guidance in lumbosacral transforaminal epidural steroid injection (TFESI). They observed that a flash or blood aspiration to predict an intravascular injection is not sensitive and, therefore, a negative flash or aspiration is not reliable. Thus, procedures without contrast confirmation may
instill medications intravascularly and therefore not into the desired epidural location.

The efficacy of transforaminal steroid injection has been emphasized in a number of studies, clearly proving the adequacy of this method. One of the earliest studies comparing the efficacy of epidural, perineural, single shot steroid injection with the conventional interlaminar epidural steroid injection in patients with lumbar radicular pain syndromes was performed by Kraemer et al.,[26] who found that patients with perineural selective nerve root steroid injections showed significantly better results than conventional epidural steroid injections.

TFESI is a relatively simple, effective and low-risk alternative to surgical decompression for the treatment of lumbar disc herniation in selected cases. The procedure significantly alleviates the severity of sciatica due to a herniated disc and improves the patient’s daily activity, reducing the need for surgical decompression.[27]

The steroid used in this study, methylprednisolone acetate (MPA), is a long-acting steroid compound manufactured as an injectable preparation. MPA temporarily blocks nociceptive C-fiber transmission.[28] Also, ectopic discharge from injured nerves appears to be suppressed by stabilization of axonal membranes by steroids, and this has been shown to correlate with their local anesthetic effect.[29,30] Epidural injection of MPA seems to be associated with little risk of serious neurological damage. Even after a single accidental subarachnoid injection, the possibility of a serious complication is probably very low.[31] Epidural administration of clonidine was shown to produce post-operative analgesia as early as 1989 by Eisenach et al.[32] the mechanism being activation of alfa-2 adrenoceptors found concentrated near sites of peripheral nerve injury or inflammation. Clonidine has been shown to produce analgesia when given as perineural injection. This analgesia is further enhanced in cases of persistent neuritis.[33]

One of the inclusion criteria of patients in this study was that they were suffering from the radicular pain for at least 6 weeks, making the condition persistent in nature. Hence, anticipation of efficacy of clonidine in our patients can be further justified.

Clonidine has been used as targeted injection in sciatica with methylprednisolone and hyaluronic acid after diagnostic epiduroscopy. Adhesions unreported in MRI were mechanically mobilized under direct vision, and this targeted medication resulted in substantial and prolonged pain relief.[34]

Burgher et al.[35] have used clonidine in transforaminal injections along with lidocaine and compared its efficacy with lidocaine and steroid group in their study on 26 patients who underwent up to three lumbar transforaminal epidural steroid injection (TFESIs) with 2% lidocaine and either triamcinolone (40 mg) or clonidine (200 or 400 μg) for acute lumbar radicular pain treatment. Their prime objective was to find an effective alternative to steroids for transforaminal injections. Both groups showed statistically significant improvements at 2 weeks and 1 month post-enrollment, but the steroid group noted greater improvement.

A deduction can thus be made from these studies that clonidine as an adjuvant to steroid would provide better pain relief than steroid alone.

An analysis of complications associated with fluoroscopically guided lumbar transforaminal epidural steroid injections shows that there are no major complications reported and that the minor complications found also resolve without sequelae.[36-39]

Injury to the nerve root with the sharp tip of the spinal needle is a potential complication of TFESI.[40] Huston et al.[41] reported increased radicular pain in 8.8% of the patients while Manchikanti et al.[41] reported increased radicular pain in 1% and Botwin et al.[42] in 0.6% of the patients after TFESI. Some authors have proposed a retrodiscal[42] or retroneural[43] approach as an alternative to the conventional sub-pedicullar safe triangle approach to minimize the risk of this complication.

The question regarding use of corticosteroids is due to the potential for their adverse/side-effects. These may be due to their local action or systemic effects. Although the different preparations of steroids used for epidural injections, e.g. methylprednisolone acetate (used in this study), triamcinolone acetonide, betamethasone acetate and phosphate, have not been found to cause any serious complications after TFESI, accidental injections of particulate matter of steroids into the artery of Adamkeiwicz, the major supplier of the anterior spinal artery in the thoracolumbar region of the spinal cord[44] that may arise in a minority of patients near the lower lumbar vertebrae[45] can lead to a catastrophic outcome, i.e., paraplegia resulting from profound spinal cord infarction as a result of interruption of blood flow.[46] A non-particulate preparation of steroid, i.e., dexamethasone sodium phosphate, was found to be safer as compared with other steroids,[47] but this preparation is not available in the Indian market yet.

Systemic side-effects of corticosteroids were extremely rare after TFESI as the doses of steroids used was very small (20-40 mg) compared with conventional...
interlaminar epidural injections. A temporary elevation of blood sugar levels in an insulin-dependent diabetic has been reported by Botwin et al. A small number of patients have also complained of flushing of face after TFESI, which was presumed to be an IgE-mediated reaction in response to steroids. Patients with congestive heart failure should be aware of possible fluid retention. Studies with other agents, which can be used as alternatives to steroids in transforaminal injections, are hence being conducted, and it is likely that drugs blocking tumour necrosis factor (TNF)-α and other similar candidate compounds could emerge as potential treatments for sciatica.

The primary concerns with the use of clonidine are regarding its adverse effects and possible neurotoxicity. Bradycardia and hypotension associated with epidural clonidine have been reported, but the doses used in this study are significantly lower than those found to be associated with these complications. Moreover, the use of clonidine as an adjuvant to steroids in transforaminal injections has not been reported till date. Burgher et al. have used clonidine as an alternative to steroids in TFESI giving 2% lidocaine and either clonidine (200 or 400 mcg) or triamcinolone (40 mg). A rapid improvement in radicular pain was observed in both treatment groups, but with greater functional improvement in those patients receiving steroids. There was no difference in side-effects and no serious complication was reported. Differences in analgesia were unclear. As target enrolment determined by power analysis was not achieved in this study, the outcome cannot be generalized.

This prospective study, wherein patients suffering from lumbosacral radiculopathy received transforaminal epidural injection of methylprednisolone alone or with 0.5 mcg/kg or 1 mcg/kg of clonidine showed that although there was effective pain relief in all three study groups, maximum relief was noted in patients who received methylprednisolone with 1 mcg/kg of clonidine. Data of multiple previous studies can be analyzed and their inferences extended to concur with this conclusion.

None of the patients of the present study suffered from bradycardia, hypotension, hypoxaemia or sedation. The only complication observed in our study was transient paresthesia in the nerve distribution, which occurred only in 12 patients (6.67% patients), with no difference of complication rate among the three groups. At the same time, the complication resolved in all the patients within 24 h without any sequelae.

Thus, clonidine, when used as an adjuvant to methylprednisolone in transforaminal injection at 0.5 mcg/kg and 1 mcg/kg, showed a dose-dependent increase in the quality of analgesia. No side-effect could be attributed to transforaminal clonidine in a dose of up to 1 mcg/kg.

**CONCLUSION**

The results of this randomized, double-blind trial of fluoroscopy-guided transforaminal methylprednisolone alone and with low doses of clonidine (0.5 mcg/kg and 1 mcg/kg) in persistent pain of lumbosacral radiculopathy due to herniated intervertebral disc have demonstrated pain relief in 75% of the patients receiving methylprednisolone with 1 mcg/kg clonidine over the course of 6 months, with superior results compared with the methylprednisolone alone and with 0.5 mcg/kg clonidine.

Thus, it can be said that transforaminal injection of clonidine as an adjuvant to steroid, methylprednisolone acetate, may be an effective treatment for sciatica due to disc herniation. Clonidine is found to be a more effective adjuvant at doses of 1 mcg/kg as compared with 0.5 mcg/kg with practically no significant side-effect or complication. A longer duration of follow-up may be necessary to assess whether there is a difference in the duration of analgesia between the study groups.

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