Original Article

Abhijan Maity, Bikash Chandra Mondal, Debasish Saha[1], Debasish Sinha Roy

Departments of Orthopaedics and [1]Anesthesiology, Burdwan Medical College, Burdwan, West Bengal, India

Address for correspondence:
Dr. Abhijan Maity,
Department of Orthopaedics,
Burdwan Medical College,
Burdwan, West Bengal, India.
E-mail: abhijan.maity@gmail.com

A prospective randomized, double-blind, controlled clinical trial comparing epidural butorphanol plus corticosteroid with corticosteroid alone for sciatica due to herniated nucleus pulposus

Abstract

Objective: To compare the efficacy of up to 3 epidural butorphanol plus corticosteroid with corticosteroid alone for sciatica due to herniated nucleus pulposus. **Materials and Methods:** In a randomized, double-blind controlled clinical trial, we administered up to 3 epidural injections of either 80 mg (2 mL) of methylprednisolone acetate and 1 mg (1 mL) of butorphanol diluted with 7 mL of isotonic saline or 80 mg (2 mL) of methylprednisolone acetate diluted with 8 mL of isotonic saline by a lumbar interlaminar approach under fluoroscopic guidance to 120 patients (60 patients in each group) with sciatica due to a herniated nucleus pulposus lasting for 4 weeks to 1 year. All patients had scores higher than 30 mm on visual analog scale (VAS). Information on the use of paracetamol, intensity of pain on a VAS ranging from 0 (no pain) to 100 mm (worst pain possible), Schober's test (cm), Straight Leg Raising test, neurologic examination assessing sensory deficits, motor deficits and reflex changes, and Oswestry Low Back Pain Disability Questionnaire were evaluated at 3 weeks, 6 weeks, and 3 months after the first injection. **Results:** There were no significant differences between the 2 groups with regard to baseline characteristics, withdrawals, and complication rate. Three weeks, 6 weeks, and 3 months after the first injection, all the outcome measures in the butorphanol plus corticosteroid group were significantly different from that of the corticosteroid group. **Conclusions:** Epidural butorphanol plus corticosteroid injections, as compared with corticosteroid alone injections, offered marked improvement in pain, reflex, motor and sensory deficits, and functional status and reduced the need for analgesics. **Level of Evidence:** Therapeutic Level I.

Key words: Butorphanol, epidural, sciatica

INTRODUCTION

Sciatica due to a herniated nucleus pulposus is an important health problem.[1] Although 90% of patients are improved with nonsurgical management, 10%–15% need surgical management.[2] Epidural corticosteroid injections have been reported to be used to treat sciatica for the last 50 years. Although used frequently in everyday clinical practice, the use of epidural corticosteroid injections for the treatment of sciatica is controversial. Of 14 controlled trials[3-16] that have been done so far comparing epidural corticosteroid injections with epidural saline injections, convincing evidence of efficacy of epidural corticosteroid injections is lacking.

Butorphanol, a kappa agonist and a weak mu agonist/antagonist with a relatively high lipid-soluble property has

Access this article online

Quick Response Code:

Website: www.picronline.org

DOI: 10.4103/2229-3485.92302

been used effectively to produce long-term postoperative pain relief by the epidural route.[17]

To our knowledge, no published study has compared the efficacy of epidural butorphanol plus corticosteroid with corticosteroid alone for sciatica due to herniated nucleus pulposus.

The aim of our present study was to compare the efficacy of up to 3 epidural butorphanol plus corticosteroid with corticosteroid alone for sciatica due to herniated nucleus pulposus.

MATERIALS AND METHODS

Trial designs

The study was a single-center, prospective, randomized, double-blind controlled clinical trial, conducted in collaboration of Department of Orthopedics and Traumatology and Department of Anesthesiology of our institution from October 2007 to September 2010. The protocol was approved by the ethics committee of our institution. Randomization was done after we had taken written informed consent from the study participants and obtained baseline information. The random assignment scheme was created from a table of random numbers. Opaque prenumbered envelopes containing random assignments were maintained by the hospital pharmacist.

Patients

All the patients in the outpatient department of Orthopedics and Traumatology in our institution between October 2007 and September 2010 with sciatica were enrolled in the present study if they had the following inclusion criteria: (i) Sciatica was defined as the presence of pain in one or, both legs, radiating below the knee, with either nerve root compression sign (sensory, motor, or reflex deficits) and/or, nerve root irritation sign (reproduction of radicular pain by elevating the leg) along with computed tomographic (CT) evidence of a herniated nucleus pulposus at a level corresponding to the signs and symptoms; (ii) age 18 years or more; (iii) had a first or, recurrent episode of sciatica lasting for a minimum of 4 weeks and a maximum of 1 year; and/or (iv) pain intensity must have a score higher than 30 mm on VAS.

Patients were excluded if they fulfilled the following exclusion criteria: (i) had signs and symptoms that warrant early surgical intervention (cauda equina syndrome, severe motor deficits, hyperalgesia); (ii) had CT scan evidence of signs and symptoms from causes other than a herniated nucleus pulposus; (iii) had received any previous epidural corticosteroid injections for the present episode; (iv) had undergone lower back spinal surgery; (v) pregnant patients; (vi) had a known allergy to corticosteroid or butorphanol; or (vii) had a known bleeding disorder.

Treatment

The patients received epidural injections of either 80 mg (2 mL) of methylprednisolone acetate and 1 mg (1 mL) of butorphanol diluted with 7 mL of isotonic saline, or 80 mg (2 mL) of methylprednisolone acetate diluted with 8 mL of isotonic saline by a lumbar interlaminar approach under fluoroscopic guidance. The injections were repeated on third and sixth weeks in the patients who continued to have scores higher than 30 mm on VAS. After the first injection, patients were supplied with paracetamol tablets (500 mg) for using as and when required basis.

Blinding

The doctors making the follow-up assessment were unaware of the treatment received, and none of the doctors who administered the injections carried out the follow-up evaluations. Thus both the patients and the assessing doctors were remained unaware of the treatment received throughout the trial.

Follow-up and outcome measure

The patients were re-evaluated as outpatients at 3 weeks, 6 weeks, and 3 months after the first injection. Follow-up assessment of each patient was done by the same doctor throughout the trial. At each follow-up visit, the following information was recorded as outcome measures:

(i) Information on the use of paracetamol; (ii) intensity of pain on a VAS ranging from 0 (no pain) to 100 mm (worst pain possible); (iii) Schober's test (cm); (iv) SLR test; (v) neurological examination assessing sensory deficits, motor deficits, and reflex changes; and (vi) Oswestry Low Back Pain Disability Questionnaire.[18]

Sample size

We selected the visual analog pain score as the primary outcome measure at 3 months. We estimated that, in order to detect a 12 mm difference in the mean visual analog pain score (with a two-sided alpha value of 5%, a statistical power of 80% and a standard deviation of 26, as estimated in an initial study of 50 patients with sciatica) between the 2 groups, at least 48 patients had to be recruited in each group. We therefore planned to enroll 60 patients in each group considering for an expected maximum withdrawal rate of 20%.

Statistical analysis

All statistical analyses were based on an "intention-to-treat" principle; therefore, patients who withdrew from the study, the data at the time of withdrawal were carried forward to all subsequent evaluations. The outcomes

of treatment with the epidural butorphanol plus corticosteroid were compared with those of treatment with the epidural corticosteroid alone with the use of parametric and nonparametric analyses as appropriate for the data. The independent-sample Student *t* tests, Fisher's exact tests, Pearson Chi-square tests, Mann–Whitney *U* test were performed with the use of SAS statistical package (SAS institute, Cary, NC, USA). A *P* value of <0.05 was considered to be statistically significant.

RESULTS

Study group

Between October 2007 and September 2010, 120 patients who satisfy the inclusion and exclusion criteria were enrolled in the study, with 60 patients in the butorphanol plus corticosteroid group and 60 in the corticosteroid group. Randomization was done after we had taken written informed consent from the study participants and obtained baseline information. There were no significant differences between the 2 groups with regard to baseline characteristics [Table 1].

Withdrawals

A total of 18 of the 120 patients did not complete the 3 follow-up visits. In the butorphanol plus corticosteroid group, 2 patients did not come after the first injection, 5 patients did not come after the first visit and 3 patients did not come after the second visit. In the corticosteroid group, 2 patients did not come after the first injection, 4 patients did not come after the first visit and 3 patients did not come after the second visit. There were no significant differences between the 2 groups with regard to withdrawals [Table 2]. Mean number of follow-up visits in the butorphanol plus corticosteroid group (2.68 ± 0.77) was not significantly different from that in the corticosteroid group (2.71± 0.74) (independent sample Student *t* test, $P = 0.83$).

Complications

Twelve patients in the butorphanol plus corticosteroid group (20%) and 16 patients in the corticosteroid group (26.67%) experienced a fleeting headache within 24 h after at least one of the epidural injections (Fisher's exact test, $P = 0.52$).

Response to treatment

In the butorphanol plus corticosteroid group, 25 (41.67%) patients received 1 injection, 28 (46.67%) patients received 2 injections, and only 7 (11.67%) patients received 3 injections, as compared with 14 (23.33%), 20 (33.33%), and 26 (43.33%) patients, respectively, in the corticosteroid group. Mean number of injections in the butorphanol group (1.7 ± 0.67) was significantly different from that of the corticosteroid group (2.2 ± 0.8) (independent sample Student *t* test, $P = 0.0003$).

Table 1: Baseline characteristics of 120 patients with sciatica randomly assigned to receive butorphanol plus corticosteroid or corticosteroid alone

Baseline characteristics	Butorphanol plus corticosteroid group (n=60)	Corticosteroid group (n=60)	*P* value
Age† (years)	36.78 ± 8.1	38.15 ± 5.5	0.28‡
Male sex (% of patients)	39 (65)	37 (61.67)	0.85Ψ
First episode of sciatica (% of patients)	23 (38)	27 (45)	0.58Ψ
Acute onset of sciatica (% of patients)	24 (40)	26 (43.33)	0.85Ψ
Radicular level affected on CT scan (% of patients)			
L3–L4	5 (8.33)	6 (10)	1.0Ψ
L4–L5	24 (40)	26 (43.33)	0.85Ψ
L5–S1	31 (51.67)	28 (46.67)	0.71Ψ
Duration of symptoms† (days)	92.43 ± 44.13	90.67 ± 33.16	0.8‡
VAS pain score† (0–100 mm)	63.16 ± 15.14	60.96 ± 13.44	0.4‡
Schober's test† (cm)	2.27 ± 0.9	2.22 ± 0.95	0.77‡
SLR test† (degree)	38.36 ± 13.7	36.7 ± 9.84	0.45‡
Motor deficits (% of patients)	18 (30)	20 (33.33)	0.84Ψ
Sensory deficits (% of patients)	34 (56.67)	32 (53.33)	0.85Ψ
Reflex changes (% of patients)	13 (21.67)	15 (25)	0.83Ψ
Oswestry score† (0–100 mm)	51.67 ± 12.28	53.97 ± 11.38	0.29‡

CT, computed tomography., †The data are given as the mean ± standard deviation., The data are given as the number (%) of patients. ‡Independent-sample Student *t* test. ΨFisher's exact test

Table 2: Withdrawals of the 120 patients with sciatica randomly assigned to receive butorphanol plus corticosteroid or corticosteroid alone

Lost to follow-up	Butorphanol plus corticosteroid group (n=60)	Corticosteroid group (n=60)	*P* value
After the first injectionΨ	2 (3.33)	2 (3.33)	1.0ᵖ
After the first visitΨ	5 (8.33)	4 (6.67)	1.0ᵖ
After the second visitΨ	3 (5)	3 (5)	1.0ᵖ

Ψ The data are given as the number (%) of patients. ᵖFisher's exact test

At each follow-up visit, patients were re-evaluated by recording the various outcome measures. Three weeks after the first injection, all the outcome measures in the butorphanol plus corticosteroid group were significantly different from that of the corticosteroid group [Table 3]. The results at 6 weeks and 3 months after the first injection

were also similar to those at 3 weeks after the first injection [Tables 4 and 5].

DISCUSSION

In the present study, we administered up to 3 epidural butorphanol plus corticosteroid injections or epidural corticosteroid alone for sciatica due to herniated nucleus pulposus. Although 14 controlled trials[3-16] have been done so far to evaluate the efficacy of epidural corticosteroid injections for sciatica due to herniated nucleus pulposus, it is very difficult to compare between them because: (i) only 7 studies consist of more than 20 patients in each group; and (ii) injection volume, number of injections, route of injection, and schedule of injection differ in various studies. Of these 14 studies, only 5 shows significant difference in favor of epidural corticosteroid injections[3-5,7,8] and 9 found no significant difference in favor of corticosteroid injections.[6,9-16] In a randomized double-blind controlled clinical trial of 100 patients treated with either epidural corticosteroid injections or with placebo, Dilke *et al*[3] found statistically significant differences in terms of relief of pain and return of normal daily activity in favor of the corticosteroid group. In a review of 39 patients, Ridley

Table 3: Comparative outcome measures at 3 weeks after the first injection in both groups

Outcome measure	Butorphanol plus corticosteroid group^{v} (n=60)	Corticosteroid only group*(n=60)	*P* value
VAS pain score (0–100 mm)†	35.15 ± 14.49	44.58 ± 13.35	<0.001‡
Schober's test (cm)†	3.25 ± 0.68	2.9 ± 0.73	<0.001‡
SLR test (degree)†	52.1 ± 10.63	45.35 ± 9.16	<0.001‡
Motor deficits (% of patients)	6 (10)	16 (27)	0.03$^{\Psi}$
Sensory deficits (% of patients)	18 (30)	24 (40)	0.03$^{\Psi}$
Reflex changes (% of patients)	4 (7)	13 (22)	0.03$^{\Psi}$
Oswestry score (0–100 mm)†	29.33 ± 9.23	40.8 ± 8.93	<0.001‡
No. of paracetamol tablets taken at 3 weeks†	39.7 ± 14.9	53.41± 16.7	<0.001‡

†The data are given as the mean ± standard deviation, The data are given as the number (%) of patients, ‡Independent-sample student t test. $^{\Psi}$Fisher's exact test, ^{v}Data were missing for 2 patients. *Data were missing for 2 patients, Missing data at the time of withdrawal were carried forward to all subsequent evaluations

Table 4: Comparative outcome measures at 6 weeks after the first injection in both groups

Outcome measure	Butorphanol plus corticosteroid group† (n=60)	Corticosteroid only group*(n=60)	*P* value
VAS pain score (0–100 mm)$^{\pi}$	21.81± 12.16	31.78 ± 13	<0.001‡
Schober's test (cm)$^{\pi}$	3.93 ± 0.72	3.39 ± 0.63	<0.001‡
SLR test (degree)$^{\pi}$	59.65 ± 10.14	50.41 ± 9.1	<0.001‡
Motor deficits (% of patients)	3 (5)	12 (20)	0.02$^{\Psi}$
Sensory deficits (% of patients)	9 (15)	20 (33)	0.03$^{\Psi}$
Reflex changes (% of patients)	2 (3)	10 (17)	0.03$^{\Psi}$
Oswestry score (0-100 mm)$^{\pi}$	23 ± 9.46	34.33 ± 8.2	<0.001‡
No. of paracetamol tablets taken between 3 and 6 weeks$^{\pi}$	28 ± 13.53	39 ± 12.66	<0.001‡

†Data were missing for 2 patients after the first injection and 5 patients after the first follow-up visit, *Data were missing for 2 patients after the first injection and 4 patients after the first follow-up visit, Missing data at the time of withdrawal were carried forward to all subsequent evaluations, $^{\pi}$The data are given as the mean ± standard deviation, The data are given as the number (%) of patients, ‡Independent-sample student t test. $^{\Psi}$Fisher's exact test

Table 5: Comparative outcome measures at 3 months after the first injection in both groups

Outcome measure	Butorphanol plus corticosteroid group (n=60)†	Corticosteroid only group* (n=60)	*P* value
VAS pain score (0–100 mm)$^{\pi}$	18.2 ± 12.35	26.83 ± 12.1	<0.001‡
Schober's test (cm)$^{\pi}$	4.37 ± 0.78	3.74 ± 0.64	<0.001‡
SLR test (degree)$^{\pi}$	63.21 ± 9.64	54.23 ± 9	<0.001‡
Motor deficits (% of patients)	2 (3)	10 (17)	0.03$^{\Psi}$
Sensory deficits (% of patients)	5 (8)	17 (28)	0.01$^{\Psi}$
Reflex changes (% of patients)	2 (3)	10 (17)	0.03$^{\Psi}$
Oswestry score (0–100 mm)$^{\pi}$	19.33 ± 9.67	28.9 ± 8.17	<0.001‡
No. of paracetamol tablets taken between 6 weeks and 3 months$^{\pi}$	20.15 ± 10.46	28.46 ± 10.35	<0.001‡

†Data were missing for 2 patients after the first injection, 5 patients after the first follow-up visit and 3 patients after the second follow-up visit, *Data were missing for 2 patients after the first injection, 4 patients after the first follow-up visit and 3 patients after the second follow-up visit. Missing data at the time of withdrawal were carried forward to all subsequent evaluations, $^{\pi}$The data are given as the mean ± standard deviation, The data are given as the number (%) of patients, ‡Independent-sample Student *t* test. $^{\Psi}$Fisher's exact test

et al[7] reported significant pain relief in corticosteroid group within 2 weeks after the first injection. But, this benefit disappeared for 6 (35%) patients at 6 months follow-up visit, whereas 11 (65%) patients retained this benefit up to this time. They conclude that although epidural corticosteroid injections offer short-term pain relief, their long-term effect is doubtful. Similarly, in a study of 23 patients, Bush *et al*[8] found significant pain relief and significant increase in mobility in steroid group at 4 weeks, but, at 1 year this difference was only significant in terms of objective measurement (SLR). Snoek *et al*,[10] Cuckler *et al*,[12] and Valat *et al*[16] who addressed the same clinically relevant question failed to demonstrate significant difference in favor of corticosteroid group. In a study of 158 patients, Carette *et al*[15] conclude that although epidural corticosteroid injections provide short-term pain relief, it does not provide significant functional improvement nor does it reduces the need for surgery.

Watts *et al*[19] performed a meta-analysis using pooled data of 907 patients from 11 previous randomized trials. They found that epidural corticosteroid injections were effective in the management of lumbosacral radicular pain. Although results of our study are not consistent with the results of this meta-analysis, this meta-analysis study has some limitations that need to be considered. The major limitation is that, the study was based on a collection of small trials. According to Bogduk *et al*,[20] overdependence on the results of meta-analysis that are based on the results of small trials should be avoided and should be considered with caution, even when the pooled data shows a statistically significant result. Whenever possible, a larger trial with sufficient power needs to be conducted to confirm the results of these meta-analyses that are based on a collection of small trials. In a recent large randomized double-blind controlled trial of 158 patients treated with either epidural corticosteroid injections or with placebo, Carette *et al*[15] found that, although epidural corticosteroid injections provide short-term pain relief, it does not provide significant functional improvement nor does it reduce the need for surgery. The results of our study are consistent with the results of this larger trial with sufficient power.

So, convincing evidence of efficacy of epidural corticosteroid injection for sciatica due to herniated nucleus pulposus is lacking in various literature overviews. In the present study, we found statistically significant difference in favor of epidural butorphanol plus corticosteroid injections than corticosteroid alone.

The major strength of the present study is its prospective randomized, double-blind design. Both the patients and the assessing doctors were remained unaware of the treatment received throughout the trial. All the patients in each group were received epidural injections under fluoroscopic guidance. So, correct positions of the needle within the epidural space were confirmed intraoperatively under fluoroscopic guidance. A follow-up assessment of each patient was done by the same doctor throughout the trial. The follow-up assessment of each patient was done with the use of various outcome measures at regular standardized intervals.

However, the present study has some limitations. The major limitation is that, although we have successfully used combined epidural butorphanol plus corticosteroid injections, far larger numbers of patients are necessary to definitely conclude the safety and efficacy of this new therapeutic modality. Another weakness of our study is the number of patients who did not complete the 3 follow-up visits. However, as the rate of the patients lost to follow-up in our study is comparable with that in other studies, we do not believe that it hampers our results.

In conclusion, we found that epidural butorphanol plus corticosteroid injections, as compared with corticosteroid alone injections, offered marked improvement in pain, reflex, motor, and sensory deficits, and functional status and reduced the need for analgesics.

REFERENCES

1. Frymoyer JW. Back pain and sciatica. N Engl J Med 1988;318:291-300.
2. Bush K, Cowan N, Katz DE, Gishen P. The natural history of sciatica associated with disc pathology: A prospective study with clinical and independent radiologic follow-up. Spine 1992;17:1205-12.
3. Dilke TF, Burry HC, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. BMJ 1973;2:635-7.
4. Breivik H, Hesla PE, Molnar I, Lind B. Treatment of chronic low back pain and sciatica: comparison of caudal epidural injections of bupivacaine and methylprednisolone with bupivacaine followed by saline. In: Bonica JJ, Albe-Fessard DG, editors. Advances in pain research and therapy. Vol. 1. New York: Raven Press; 1976. p. 927-32.
5. Yates DW. A comparison of the types of epidural injection commonly used in the treatment of low back pain and sciatica. Rheumatol Rehabil 1978;17:181-6.
6. Mathews JA, Mills SB, Jenkins VM, Grimes SM, Morkel MJ, Mathews W, *et al*. Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. Br J Rheumatol 1987;26:416-23.
7. Ridley MG, Kingsley GH, Gibson T, Grahame R. Outpatient lumbar epidural corticosteroid injection in the management of sciatica. Br J Rheumatol 1988;27:295-9.
8. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. Spine 1991;16:572-5.
9. Beliveau P. A comparison between epidural anesthesia with and without corticosteroid in the treatment of sciatica. Rheumatol Phys Med 1971;11:40-3.
10. Snoek W, Weber H, Jorgensen B. Double blind evaluation of extradural methyl prednisolone for herniated lumbar discs. Acta Orthop Scand 1977;48:635-41.
11. Klenerman L, Greenwood R, Davenport HT, White DC, Peskett S. Lumbar epidural injections in the treatment of sciatica. Br J

Rheumatol 1984;23:35-8.
12. Cuckler JM, Bernini PA, Wiesel SW, Booth RE Jr, Rothman RH, Pickens GT. The use of epidural steroids in the treatment of lumbar radicular pain: A prospective, randomized, double-blind study. J Bone Joint Surg Am 1985;67:63-6.
13. Rocco AG, Frank E, Kaul AF, Lipson SJ, Gallo JP. Epidural steroids, epidural morphine and epidural steroids combined with morphine in the treatment of post-laminectomy syndrome. Pain 1989;36: 297-303.
14. Serrao JM, Marks RL, Morley SJ, Goodchild CS. Intrathecal midazolam for the treatment of chronic mechanical low back pain: A controlled comparison with epidural steroid in a pilot study. Pain 1992;48:5-12.
15. Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St Pierre A, *et al*. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med 1997;336:1634-40.
16. Valat JP, Giraudeau B, Rozenberg S, Goupille P, Bourgeois P, Micheau-Beaugendre V, *et al*. Epidural corticosteroid injections for sciatica: A randomized, double blind, controlled clinical trial. Ann Rheum Dis 2003;62:639-43.
17. Tan PH, Chou AK, Perng JS, Chung HC, Lee CC, Mok MS. Comparison of epidural butorphanol plus clonidine with butorphanol alone for postoperative pain relief. Acta Anaesthesiol Sin 1997;35:91-6.
18. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980;66:271-3.
19. Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. Anaesth Intensive Care 1995;23:564-9.
20. Bogduk N, Brazenor G, Christophidis N, Cherry D, Fraser R, Jenkins J, *et al*. Epidural use of steroids in the management of back pain and sciatica of spinal origin. National Health and Medical Research Council (NHMRC) 1994.

How to cite this article: Maity A, Mondal BC, Saha D, Roy DS. A prospective randomized, double-blind, controlled clinical trial comparing epidural butorphanol plus corticosteroid with corticosteroid alone for sciatica due to herniated nucleus pulposus. Perspect Clin Res 2012;3:16-21.

Source of Support: There was no source of external funding in support of this study. **Conflict of Interest:** None declared.