Randomized Trial

Effect of Addition of Epidural Ketamine to Steroid in Lumbar Radiculitis: One-Year Follow-Up

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Background: Treating sciatica with epidural steroid injection has been a common practice worldwide. N-methyl-D-aspartate (NMDA) receptors are an important component of pain pathways.

Objectives: The aim of this study was to evaluate the safety and efficacy of epidurally administered NMDA receptor antagonists (ketamine) for the treatment of chronic low back pain secondary to radiculopathy and its effect on patients’ quality of life.

Study Design: Randomized, double blind controlled trial.

Setting: Hospital outpatient setting.

Methods: Two hundred participants aged 25 to 50 years old with a diagnosis of lumbar radiculopathic pain secondary to disc herniation were randomized into 2 equal groups. Group I received 80 mg of triamcinolone (2 mL) and 0.25% bupivacaine (3 mL) plus 30 mg (3 mL) of preservative free ketamine. Group II received 80 mg of triamcinolone (2 mL) and 0.25% bupivacaine (3 mL) plus 3 mL of 0.9% saline. Pain scores were obtained before injection, immediately after injection, one week, one month, 3 months, 6 months, 9 months and one year post injection. The Oswestry Low Back Pain Disability Questionnaire was used at baseline and at one month, 3, 6, 9, and 12 months after injection for assessment of quality of life. Patients were asked to report any side effects, particularly those related to ketamine, including nausea, vomiting, visual or auditory hallucinations, and delirium.

Results: Immediately after injection there was no statistically significant difference between Group I and II regarding pain scale scores. After one week of injection, pain relief was significantly better in Group I compared to Group II and then at all evaluation times. The Oswestry Low Back Pain Disability Questionnaire score decreased significantly (P < 0.05) from 72 (range 62- 83) and 70 (range 57- 82) to 8 (range 2 – 12) and 17 (range 9 – 27) at one month; 6 (range 4 – 12) and 18 (range 14 – 22) at 3 months; 12 (range 9 – 16) and 28 (range 22 – 34) at 6 months; 17 (range 9 – 24) and 31 (range 21 – 35) at 9 months; and 17 (range 8 – 22) and 33 (range 20 – 37) at 12 months in the groups, respectively. Six patients in the ketamine group showed short-lasting delusions lasting for 45 ± 12 minutes after injection.

Limitations: The limitations include a lack of placebo control.

Conclusion: Epidurally administered ketamine seems to be a safe and useful adjunct to epidural corticosteroid therapy in chronic lumbar radicular pain.

Key words: Ketamine, epidural, radiculopathic, pain, steroid

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Sciatica is a common problem (1,2). Treatment of sciatica by epidural steroid injection was first used in 1953 (3). Epidural steroid injections are commonly used with multiple effects, including reduction of edema, pressure, inflammation and adhesions on the nerve trunk (2,4-14). N-methyl-D-aspartate (NMDA) receptors are an important component of pain processing (15). Based on recent concepts of pain, during inflammation there is an increase in glutamate and aspartate; its role in central sensitization and wind up has been known. Wind up can magnify responses of dorsal horn neurons up to 20-fold in magnitude and duration (16,17). NMDA receptor antagonists prevent induction and maintenance of the central sensitization process which is usually manifested as a post injury reduction of pain threshold and hypersensitivity of the withdrawal reflexes (18). Ketamine is an NMDA receptor antagonist which has potent anesthetic and analgesic effects (19). Ketamine has been used in pain medicine in recent years with increasing frequency along with multiple publications (20-26).

The aim of this study was to assess the safety and efficacy of epidural ketamine with steroid for treatment of chronic radiculopathic low back pain and its effect on patients’ quality of life.

Methods

This study was carried out on 200 participants who had a diagnosis of lumbar radiculopathic low back pain (extremities pain > back pain) secondary to disc herniation as confirmed by MRI (a herniation of < 25% of the cross-sectional area of the spinal canal). Duration of symptoms was more than 6 months in all participants. Before conducting the study, institutional ethics committee approval and written informed consent from all participants were obtained.

Pre-procedural assessment

A complete physical and neurological examination was performed to reveal defects at specific levels. A neurological examination was performed to reveal any abnormal reflexes. Pain was elicited by straight leg raising when lying or sitting (positive straight leg raising test). There was abnormal sensation in the foot or leg, including dermatome distribution.

The study used a double-blind design. The participants were randomized into 2 equal groups. Two hundred envelopes were prepared with 100 labeled Group I and 100 labeled Group II. The envelopes assigning the participants to a group were opened by a blinded chief nurse. The chief nurse did not participate in the study nor was the nurse involved with the participants’ care. The envelopes and epidural injection bottles containing either ketamine or saline were prepared in cooperation with the hospital’s pharmacy. The postoperative assessors were blinded to the participants’ assignment groups.

Patients who had a sequestrated disc, prior epidural steroid injections or therapy, a history of opioid analgesia usage, spondylolisthesis, additional spondylolytic changes, neurological deficits, or coagulopathy disorder were excluded from the study. Patients with bilateral radiculopathic low back pain were excluded from the study to avoid misinterpretation of bilateral injection or having to divide the dose bilaterally; others excluded were those who had large disc herniations (a herniation of > 25% of the cross-sectional area of the spinal canal).

All participants were premedicated with intramuscular midazolam 0.05 mg/kg. Basic monitoring with noninvasive arterial blood pressure, electrocardiogram, and pulse oximetry was applied for each participant. The participants were randomized into 2 equal groups. Group I received 80 mg of triamcinolone (2 mL) and 0.25% bupivacaine (3 mL) plus 30 mg (3 mL) of preservative-free ketamine S (+)-enantiomer with no preservatives. Group II received 80 mg of triamcinolone (2 mL) and 0.25% bupivacaine (3 mL) plus 3 mL of 0.9% saline. The procedure was performed under C-arm fluoroscopic guidance with unilateral epidural injection toward the side of pain. The epidural space was identified by the loss of resistance technique for saline and confirmed radiologically by the characteristic longitudinal spread of dye in the epidural space. Pre- and post-injection pain scores were recorded using a visual analog scale (VAS). Pain scores were obtained immediately after injection, one week, one month, 3, 6, 9 and 12 months post-injection. Participants were asked to report any side effects, particularly those related to ketamine, including nausea, vomiting, visual or auditory hallucinations, and delirium.

The Oswestry Low Back Pain Disability Questionnaire (ODI) (26,27) was used for assessment before injection and at one month, 3, 6, 9 and 12 months after injection (Table 1). This questionnaire is divided into 10 sections; each section contains 6 statements. The patient marks the one which most accurately describes his limitation. Each section is scored on a 0-5 scale, with 5 representing the greatest disability. The scores are

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added together and then interpreted as a percentage from this equation: Total score/50 × 100 (1). The ODI has been utilized in multiple pain management studies with its validity established (28-34).

Statistical Analysis
Data were presented in the form of mean ± standard deviation. Comparison of data parameters regarding patient characteristics was performed by Student’s t-test. The Mann-Whitney-U test was used to compare the 2 groups’ pain scores and Oswestry scores. Power of significance was considered significant if P < 0.05.

Results
The study population consisted of 200 participants. Twenty-six did not continue the study follow-up period (14 in the ketamine group and 12 in the saline group) for nonestimated causes. Thus, statistical analysis included 86 patients in the ketamine group and 88 in the control group (Fig. 1). The two groups were compara-

<table>
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<tr>
<th>Interpreted Oswestry Low Back Pain Disability Questionnaire</th>
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<tbody>
<tr>
<td>0% to 20%: minimal disability</td>
<td>The patient can perform most activities. No treatment is needed, except advice on lifting, sitting and exercise.</td>
</tr>
<tr>
<td>21%–40%: moderate disability</td>
<td>The patient has more pain and difficulty in sitting, lifting and standing. Travel and social life are more difficult and patient might be disabled from work. The patient can be managed conservatively</td>
</tr>
<tr>
<td>41%–60%: severe disability</td>
<td>Pain is the main problem in this group, but activities of daily living are affected.</td>
</tr>
<tr>
<td>61%–80%: crippled</td>
<td>Back pain impinges on all aspects of the patient’s life. Intervention is required.</td>
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<tr>
<td>81%–100%:</td>
<td>These patients are either bed-bound or exaggerating their symptoms</td>
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<table>
<thead>
<tr>
<th>GROUP I</th>
<th>GROUP II</th>
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<tbody>
<tr>
<td>(n=100)</td>
<td>(n=100)</td>
</tr>
<tr>
<td>Received 80 mg of Triamcinolone (2ml) plus 30 mg (3ml) of preservative free Ketamine</td>
<td>Received 80mg of Triamcinolone (2ml) plus 3ml of 0.9% saline</td>
</tr>
<tr>
<td>Patients excluded from analysis =14</td>
<td>Patients excluded from analysis =12</td>
</tr>
<tr>
<td>Patients included in the analysis = 86</td>
<td>Patients included in the analysis = 88</td>
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Fig. 1. Schematic presentation of patient flow through out trial period.
Table 2. Patient characteristics in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I N = 86</th>
<th>Group II N = 88</th>
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</thead>
<tbody>
<tr>
<td>Age (years) : Mean (SD)</td>
<td>4.2 (13.2)</td>
<td>47.8 (9.7)</td>
</tr>
<tr>
<td>Height Cm : Mean (SD)</td>
<td>163 (10)</td>
<td>164 (12)</td>
</tr>
<tr>
<td>Weight Kg : Mean (SD)</td>
<td>79 (13)</td>
<td>82 (12)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>47/39</td>
<td>48/40</td>
</tr>
<tr>
<td>Duration of pain (months): Mean (range)</td>
<td>9 (6 – 19)</td>
<td>10 (6 – 21)</td>
</tr>
</tbody>
</table>

At all time periods examined, pain scores were significantly lower in both groups than pre-injection (P value was < 0.05). Pain scores were significantly lower in Group I than in Group II at one week, one month, 3, 6, 9 and 12 months after treatment (P < 0.0001) (Fig. 2). There was no significant difference between both groups at post-injection (P = 0.4).

The Oswestry score was decreased significantly (P < 0.05) from 72 (range 62-83) and 70 (range 57-82) to 8 (range 2 – 12) and 17 (range 9 – 27), at one month; 6 (range 4 – 12) and 18 (range 14 – 22) at 3 months; 12 (range 9 – 16) and 28 (range 22 – 34) at 6 months; 17 (range 9 – 24) and 31 (range 21 – 35) at 9 months; and 17 (range 8 – 22) and 33 (range 20 – 37) at 12 months in the groups, respectively. The Oswestry scale decreased significantly in Group I versus Group II, (P < 0.0001).

No side effects related to ketamine were reported, except 6 patients in the ketamine group showed short-lasting delusions (lasting for 45±12 minutes) after injection. None of them required intervention.

![Fig. 2. VAS (Mean ± SD) of both groups at each time period examined.](image-url)
Epidural Ketamine in Lumbar Radiculitis

Discussion

Although the efficacy of this treatment is controversial, epidural steroid agents are commonly used in the treatment of low back pain and sciatica (2,6-11,28-37). However, there is continued debate about the effectiveness of epidural injections with or without steroids and the frequency and number of injections to be provided in various types of lumbar problems including disc herniation and radiculitis (2,4-11,35-41).

In an assessment of 209 patients, an increased risk of treatment failure at 2 weeks after one to 3 injections was associated with chronic pain (37,42).

The author postulated that adding NMDA blockers to epidural steroid could prolong its efficacy. In the present study, the analgesia induced by adding ketamine to steroids was better and more sustained when compared to that with corticosteroids alone. The Oswestry assessment revealed a significant improvement in daily life activity and quality of life post-injection in both groups, but with more significant improvement in the ketamine group compared to the steroid group. However, epidural saline, which had been used in the control group, may have a greater therapeutic benefit than placebo, thus underestimating ketamine efficacy (39-41,43-45).

The long potency was explained by blocking of dorsal horn wind up by NMDA antagonists. Temporal summation of secondary pain in humans appear to be selectively attenuated by NMDA receptor antagonists (46). Lauretti et al (47), in a study carried out by inserting an epidural catheter in patients with low back pain, gave ketamine 3 times a day for 3 weeks, reported that epidural ketamine adjuvant to lidocaine was efficacious for control of refractory chronic low back pain.

Comparing the post-injection to pre-injection VAS scores in Lauretti’s study, the VAS was maintained at 0-3 cm during the epidural ketamine administration and continued for 2 to 5 weeks later. The shorter duration of potency than the current study could be explained by using ketamine alone without corticosteroids.

In the present study, 6 participants in the ketamine group showed short-lasting delusions shortly after administration of ketamine, but none of them required intervention.

In an experimental study by Benrath et al (48), it was reported that mechanical allodynia is reduced after administration of intrathecal ketamine; the reduction sustained for 2 weeks further in a rat model. Several experimental studies have shown that administration of NMDA receptor antagonists inhibits the spinal processing of the pain input (13).

Racemic ketamine is not recommended for epidural administration because of the neurotoxic effects of the preservatives (49). However, this study used ketamine active enantiomer S(+) ketamine which has been used intrathecally and epidurally for the management of perioperative pain in many clinical studies (50-55). Compared with racemic ketamine, the S (+)-enantiomer has a twofold higher analgesic potency and S (+)-ketamine is commercially available without preservatives added (56).

Electrodiagnostic studies (electromyogram/nerve conduction study) would be a better standard in conjunction with MRI findings to assess/diagnose radiculopathy along with clinical correlation. However, this study only utilized MRI findings and clinical examination.

Conclusion

Epidurally administered ketamine seems to be a safe and useful adjunct to epidural corticosteroid therapy in chronic radiculopathic pain.

References


Epidural Ketamine in Lumbar Radiculitis


