Pain Physician 2011; 14:475-481 • ISSN 1533-3159

Randomized Trial

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

Yasser Mohamed Amr, MD

From: Tanta University Hospital, Tanta, Egypt

Dr. Amr is an assistant professor in the anesthesia department, Tanta University Hospital, Tanta University, Egypt.

Address correspondence:
Yasser Mohamed Amr, MD
Anesthesia Department
Tanta University Hospital
Tanta, Egypt
Postal code: 31527
E-mail:
yasser.amr@gmail.com

Disclaimer: Preliminary results of this study were presented as a poster at the 2009 World Institute of Pain (WIP) conference in New York.
Conflict of interest: None.

Manuscript received: 12/09/2010
Revised manuscript received: 07/27/2011
Accepted for publication: 08/05/2011

Free full manuscript:
www.painphysicianjournal.com

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 administrated 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

Pain Physician 2011; 14:475-481

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 redutction 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 (3mL) 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

Table 1. *Interpretation of Oswestry LowBack Pain Disability Questionnaire*

0% to 20%: minimal disability	The patient can perform most activities. No treatment is needed, except advice on lifting, sitting and exercise.
21%-40%: moderate disability	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
41%-60%: severe disability	Pain is the main problem in this group, but activities of daily living are affected.
61%-80%: crippled	Back pain impinges on all aspects of the patient's life. Intervention is required.
81%-100%:	These patients are either bed-bound or exaggerating their symptoms

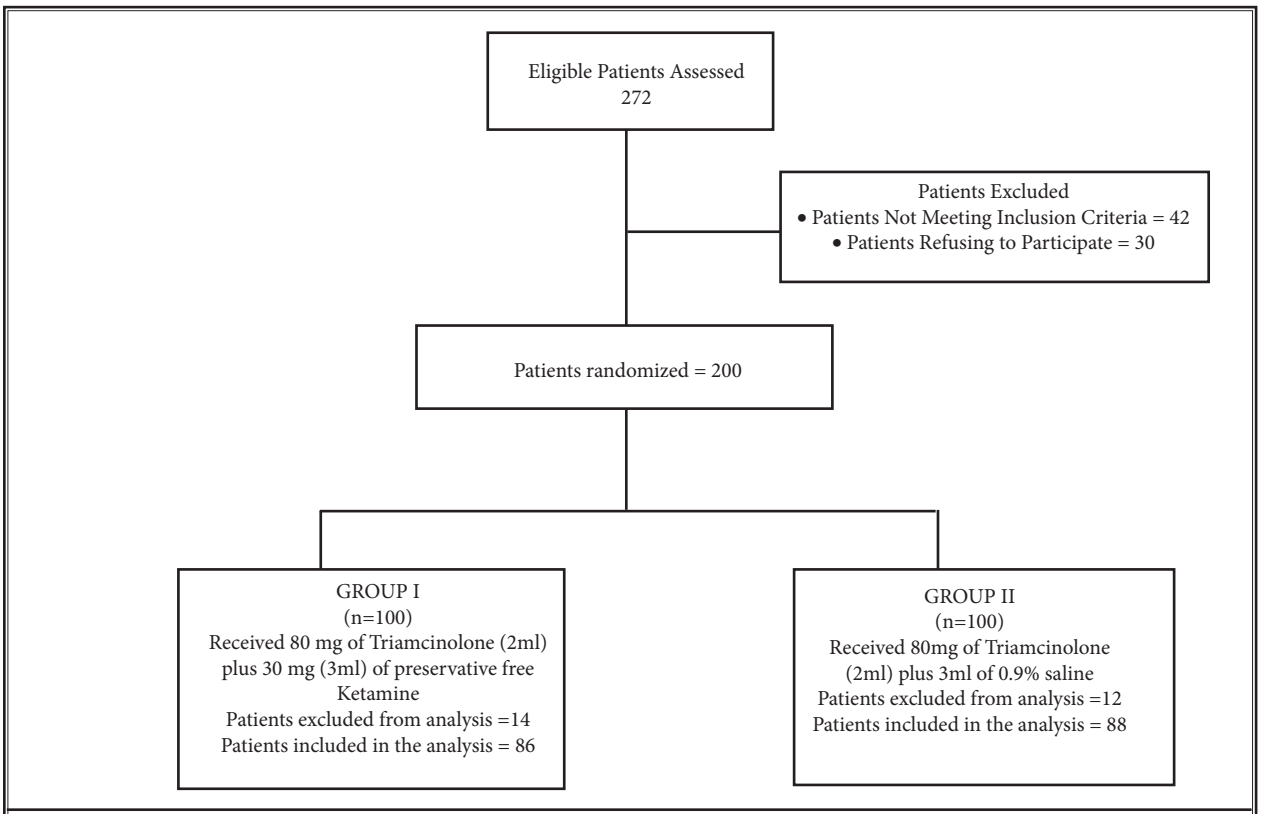

Fig. 1. *Schematic presentation of patient flow through out trial period.*

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 2. *Patient characteristics in both groups .*

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

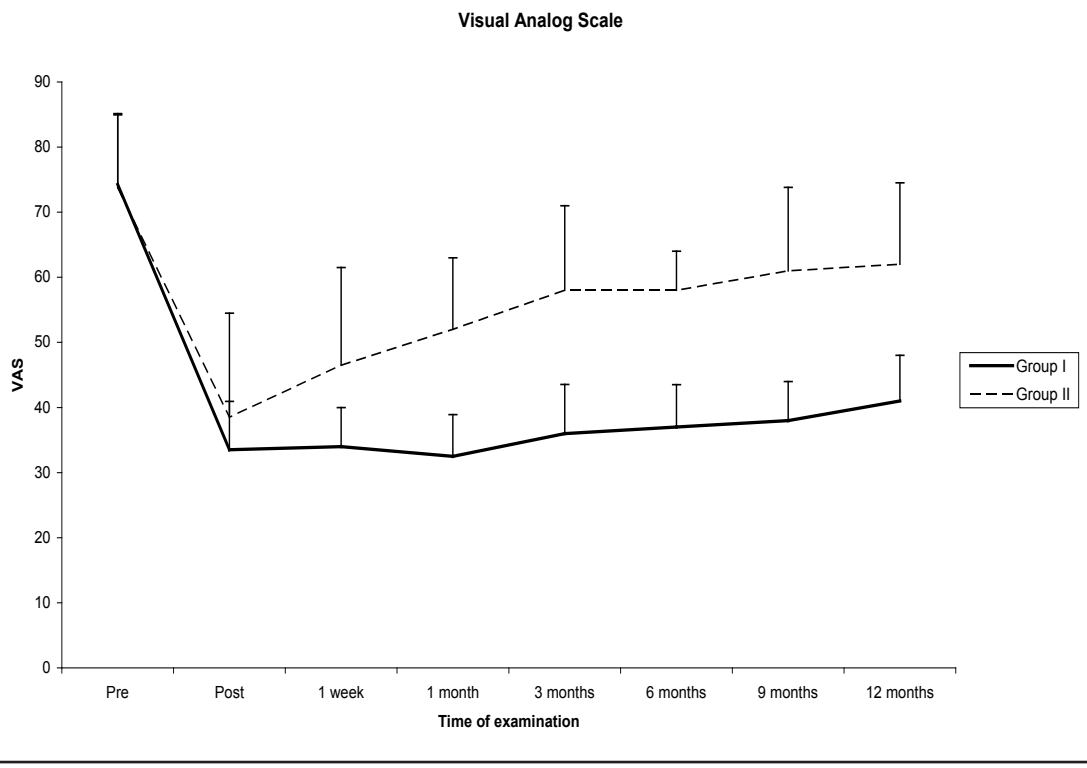

Fig. 2. *VAS (Mean ± SD) of both groups at each time period examined.*

ble regarding age, height, weight, sex, and duration of pain (Table 2).

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.

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 conjugation with MRI findings to assess/diagnose radiculopathy along with clinical correlation. However, this study only utilized MRI findings and clinical examination.

Conclusion

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

References

1. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
2. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJE, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. P*ain Physician* 2009; 12:699-802.
3. Loy TT. Epidural steroid injection for Sciatica: An analysis of 526 consecutive cases with measurements and the Whistle test. J of Orthop Surg (Hong Kong) 2000; 8:39-44 .
4. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in Medicare population: A 10-year evaluation from 1997 to 2006. *Pain Physician* 2009; 12:9-34.
5. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: A comparative evaluation of 1997, 2002, and 2006 data. *Pain Physician* 2010; 13:199-212.
6. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phi-*

la Pa 1976) 2009; 34:49-59.

7. Conn A, Buenaventura R, Datta S, Abdi S, Diwan S. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2009; 12:109-135.
8. Parr AT, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: A systematic review. *Pain Physician* 2009; 12:163-188.
9. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; 12:137-157.
10. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. Pain Physician 2009; 12:233-251.
11. Chou R, Huffman L. Guideline for the Evaluation and Management of Low Back Pain: Evidence Review. American Pain Society, Glenview, IL, 2009.
12. Bogduk N. Spine update – Epidural steroids . *Spine* 1995; 7:845-848.
13. Park IK, Kim TH, Shin YH. The effective steroid dose of caudal epidural injection with unilateral epidural catheter position in patients with symptomatic herniated nucleus pulposus. *Reg Anesth Pain Med* 2008; 33:e30.
14. Lee IS, Kim SH, Lee JW, Hong SH, Choi JY, Kang HS, Song JW, Kwon AK. Comparison of the temporary diagnostic relief of transforaminal epidural steroid injection approaches: Conventional versus posterolateral technique. *ANJR Am J Neuroradiol* 2007; 28:204-208.
15. Subramania K, Subramania B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: A quantitative and qualitative systematic review. *Anesth Anal* 2004; 99:482-495.
16. Pocket S. Spinal cord synaptic plasticity and chronic pain. *Anesth Analg* 1995; 80:173 -179.
17. Sandkuhler J. Learning and memory in pain pathways. *Pain* 2000; 88:113-118.
18. Liu XG, Sandkuhler J. Long term potentiation of C fibres evoked potentials in the rat spinal dorsal horn is prevented by spinal N-methyl-D- aspartic acid receptor blockage. *Neurosci Lett* 1995; 191:43–46.
19. Woolf CJ ,Thompson SWN. The induction and maintenance of central sensitization is dependant on N-methyl-D-aspartic acid receptor activation: Implications for the treatment of post injury pain and hypersensitivity states. *Pain* 1991; 44:243-299.
20. Gomes LM, Garcia JB, Rimamar JS, Nascimento AG. Neurotoxicity of subarachnoid preservative-free S (+)- ketamine in dogs. Pain Physician 2011; 14:83-90.
21. Smith HS. Ketamine-induced urologic insult (KIUI). Pain Physician 2010; 13:E343-E346.
22. Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic pain patients wiht high opioid requirements. Pain Physician 2010; 13:389-394.
23. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Pharmacodynamic profiles of ketamine (RP- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. *Pain Physician* 2010; 13:379-387.
24. Nama S, Meenan DR, Fritz WT. The use of sub-anesthetic intravenous katamineand adjuvant dexmedetomidine when treating acute pain from CRPS. *Pain Physician* 2010; 13:365-368.
25. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin ni spinal cord injury related chronic pain: A prospective, randomized, double blind trial. *Pain Physician* 2010; 13:245-249.
26. Childs JD, Piva SR. Psychometric properties of the functional rating index in patients with low back pain. *Eur Spine J* 2007; 14:1008-1012.
27. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Phys Ther* 2001; 81:776-788.
28. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 3. Post surgery syndrome. *Pain Physician* 2008; 11:817-831.
29. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 1. Discogenic pain without disc herniation or radiculitis. *Pain Physician* 2008; 11:785-800.
30. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin RM. The preliminary results of a comparative effectiveness evaluation of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E341-E354.
31. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E355-E368.
32. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
33. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.p
34. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
35. Dashfield AK, Taylor MB, Cleaver JS, Forrow D. Comparison of caudal steroid epidural with targeted steroid placement during spinal endoscopy for chronic sciatica: A prospective, randomized double blind trial. *Br J Anaesth* 2005; 44:514-519.
36. Riew KD, Yin Y, Gilula L, Bridwell KH, Lenke LG, Lauryssen C, Goette K. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000; 82-A:1589-1593.
37. Hopwood MB, Abram SE. Factors associated with failure of lumbar epidural steroids. *Reg Anesth* 1993;18:238–243.
38. Manchikanti L, Helm S, Singh V, Benyamin RM, Datta S, Hayek S, Fellows B, Boswell MV. An algorithmic approach for clinical management of chronic spinal pain. *Pain Physician* 2009; 12:E225-E264.
39. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guide-

lines for interventional techniques: Part 2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E264.

40. Manchikanti L, Singh V, Falco FJ, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820.
41. Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Comparative outcomes of a 2-year follow-up of cervical medial branch blocks in management of chronic neck pain: A randomized, double-blind controlled trial. *Pain Physician* 2010; 13:437-450.
42. Jamison RN, VadeBoncouer T, Ferrante FM. Low back pain patients unresponsive to an epidural steroid injection: Identifying predictive factors. *Clin J Pain* 1991; 7:311–317.
43. Wittenberg RH, Greskotter KR, Steffen R, Schoenfeld BL. Is epidural injection treatment with hypertonic saline solution in intervertebral disk displacement useful? (The effect of NaCl solution on intervertebral disk tissue). *Z Orthop Ihre Grenzgeb* 1990; 128:223–226.
44. Bhatia MT, Parikh LCJ. Epidural saline therapy in lumbo-sciatic syndrome. *J Indian Med Assoc* 1966; 47:537-542.
45. Gupta AK, Mital VK, Azmi RU. Observations of the management of lumbosciatic syndromes (sciatica) by epidural saline. *J Indian Med Assoc* 1970; 54:194-196.
46. Warnke T, Stubhaug A, Jorum E. Ketamine, an NMDA receptor antagonist suppresses spatial and temporal properties of burn induced hyperalgesia in man: A double blind, cross over comparison with morphine and placebo *Pain* 1999; 76:357-363 .
47. Lauretti GR, Rodrigues AM, Reis MP. Epidural Ketamine versus epidural clonidine as therapeutics for refractory chronic low back pain. *Reg Anesth Pain Med* 2001; 26:88 .
48. Benrath J, Brecntel C, Stark J, Sandkuhler J. Low dose of S (+) Ketamine prevents long term potentiation in pain pathways under strong opioid analgesia in the rat spinal cord in vivo. *Br J Anaesth* 2005; 95:518-535.
49. Gebhardt B. Pharmacology and clinical results with peridural and intrathecal administration of ketamine. *Anesthetist* 1994; 43:34-40.
50. Subramaniam K, Subramaniam B, Pawar DK, Kumar L. Evaluation of the safety and efficacy of epidural ketamine combined with morphine for postoperative analgesia after major upper abdominal surgery. *J Clin Anesth* 2001; 13:339-344.
51. Koinig H, Marhofer P, Krenn CG, Klimsca W, Wildling E, Erlacher W, Nikolic A, Turnheim K, Semsroth M. Analgesic effects of caudal and intramuscular S(+)-ketamine in children. *Anesthesiology* 2000; 93:976-980.
52. Pattar A, Silomon M, Werth M, Ziegeler S. Epidural vs. subcutaneous application of s-ketamine for postoperative pain management after total knee replacement: 14AP5-6. *Eur J Anaesth* 2010; 27:205.
53. Ozyalcin NS, Yucel A, Camlica H, Dereli N, Andersen OK, Arendt-Nielsen L. Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: Comparison of epidural and intramuscular routes. *Br J Anaesth* 2004; 93:356-361.
54. Marhofer P, Krenn CG, Plöchl W, Wallner T, Glaser C, Koinig H, Fleischmann E, Höchtl A, Semsroth M. S(+)-ketamine for caudal block in paediatric anaesthesia. *Br J Anaesth* 2000; 84:341-345.
55. Lauretti GR, Rodrigues AM, Paccola CA, Mattos AL. The combination of epidural clonidine and S(+)-ketamine did not enhance analgesic efficacy beyond that for each individual drug in adult orthopedic surgery. *J Clin Anesth* 2005; 17:79-84.
56. Adams HA, Werner C. From the racemate to the eutomer: (S)-ketamine. Renaissance of a substance? *Anaesthesist* 1997; 46:1026-1042.