Original Article

To compare the analgesic efficacy of two different doses of epidural ketamine in chronic low back-pain patients: A randomised double-blind study

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ABSTRACT

Background and Aims: Ketamine, an adjunct to epidural steroid injections (ESI) for chronic back-pain provides better quality and prolonged duration of analgesia. The present study aims to evaluate the analgesic efficacy in terms of pain scores, duration of pain-free period, patient satisfaction score (PSS) and number of repeat injections with 25 mg versus 50 mg ketamine as adjuvants to ESI. **Methods:** In a prospective, randomised, double-blind trial at a tertiary care hospital, 60 patients of chronic low back-pain of either sex, aged 18–65 years, received preservative free 25 mg ketamine in Group I and 50 mg ketamine in Group II as adjunct to 40 mg triamcinolone in total 6 ml volume given epidurally. Baseline data along with follow-ups at 2, 4, 8 and 12 weeks post-procedure included assessment of pain using Visual Analogue Scale (VAS), duration, number of repeat blocks using PSS, Quality of Life (QoL) and side-effects. Categorical data analysed using the Chi-Square test, and continuous data using paired t-test. **Results:** Pain evaluation within the groups over time showed significant improvement from baseline (P = 0.000), and between the groups showed comparable VAS scores at 12 weeks (P = 0.392). The PSS, pain-free duration and number of repeat injections were also statistically comparable. However, the QoL improved more in Group II vs Group I (P = 0.024). The short-lasting side effects were more in Group II, but no features of neurotoxicity were observed in any patient. **Conclusion:** The analgesic efficacy of adjuvant therapy with 50 mg ketamine appeared comparable to 25 mg ketamine. Although, there was a better quality of life and longer pain-free interval with 50 mg ketamine, the side effects were more.

Key words: Chronic pain, epidural, injections, ketamine, low back pain, steroids.

INTRODUCTION

Chronic low back pain (LBP), a multifactorial and multidimensional problem with both sensory and emotional components, is challenging to manage. It is one of the leading causes of chronic pain, that accounts for an annual expenditure of $96 billion in the US.[1] The most frequent cause of LBP is intervertebral disc pathology, ranging from a ligamental tear to disc degeneration, herniation, protrusion and extrusion. Epidural steroid injection (ESI) acts by multiple mechanisms like anti-inflammatory, antinociceptive, decreased capillary permeability and reduced intra-neuronal oedema. The local anaesthetics block Na+ channels to affect nerve transmission and dilute the inflammatory mediators.[2] However, both steroids and local anaesthetics have a short-lasting effect, requiring multiple repeat injections, thereby, causing more side effects such as hypothalamo-pituitary axis (HPA) suppression, low immunity, osteoporosis and glucose intolerance. At the same time, this combination does not address the neuropathic component.[3] Various adjuvants such as clonidine,

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tramadol, ketamine have been tried with good results. Clonidine, although effective, had side effects of hypotension and bradycardia, whereas tramadol caused more nausea and vomiting.

In chronic pains, neuropathic aspect occurs due to NMDA receptor sensitisation at pre-synaptic site resulting in increased glutamate release and its phosphorylation at the post-synaptic site, manifesting as wind up phenomenon. Based on this concept, ketamine, an NMDA receptor antagonist with mild opioid receptor action as well as local anaesthetic properties, has been used in a wide range of doses through epidural and intrathecal routes for acute postoperative and chronic neuropathic pain conditions.[4,5] There is no single effective drug dose recommended in the above-said trials, therefore, the present study was designed to assess the effectiveness of two different doses of preservative-free ketamine, that is 50 mg versus 25 mg, given epidurally as an adjunct to ESI. Evaluation of analgesic efficacy using Visual analogue score(VAS) for pain in patients with chronic LBP was considered as the primary outcome. The secondary outcome included assessment of the quality of life (QOL)scores scores using Revised Oswestry Disability Score (RODS), psychological component by Depression Scores (DS), patient satisfaction using Patient Satisfaction Score (PSS), number of repeat injections and any side effects.

METHODS

The present trial was carried out in a prospective, randomised, double-blind manner at a tertiary care hospital of North India for two years. Informed consent included explaining to the patients in their vernacular language, about all the advantages, side effects and complications of drugs as well as procedure. The trial was approved by the institutional ethics committee (Ref. No. Patho137/18, dated 12/02/18), with a rider to terminate the trial if any of the patients develop neurotoxicity with epidural ketamine. The study was initiated after registration with the Central Trial Registry of Government of India CTRI/2018/08/015209. We followed the Consolidated Standards of Reporting Trials (CONSORT) for this study [Figure 1].

Inclusion criteria

The study group consisted of patients in the age group of 18–70 years, either sex, American Society of Anesthesiologists physical status I and II, with a complaint of LBP of at least three months duration with or without referred leg pain. Patients with a pain score of ≥40 on VAS (0-100 cm on a linear scale; 0-30 mild; 40-70 moderate and 80-100 severe pain); with mild to moderate depression due to chronic pain, primary sensory component with minimal or no motor involvement, conservative treatment failure and magnetic resonance imaging (MRI) showing intervertebral disc pathology such as ligamental tear, degeneration, protrusion or extrusion were included in this study.

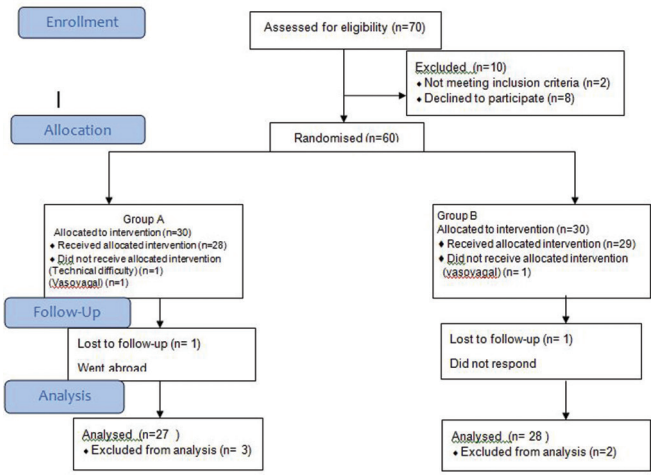

Figure 1: Consort flow diagram

The exclusion criteria comprised contraindications for epidural injection, such as local infection, generalised septicaemia, increased intracranial pressure and platelet and clotting factor abnormalities, significant neurological diseases, systemic steroid therapy, facet joint arthropathy, a known history of allergy to study drugs, a history of severe depression with suicidal tendencies, history of spine surgery, cauda-equina syndrome, epidural lipomatosis, tumours, fracture spine, pregnancy and lactation.

Sixty selected patients were randomly allocated to two groups of 30 each as per computer-generated random number slips by a trained registered nurse practitioner (RNP) who did not participate in the assessment of the patients.

Group I: received epidural ketamine 25 mg.

Group II: received epidural ketamine 50 mg.

In each group, the drug solution was prepared with preservative-free ketamine (Aneket, Neon

Laboratory Limited, India) (50mg/1 ml), 1 ml of triamcinolone (40 mg), 2 ml of bupivacaine 0.5% and made upto 6 ml with normal saline and given epidurally in study patients.

The same pain physician performed the procedure in all the patients and the same assessor carried out the pre and post-procedural assessment. Patients and assessors were unaware of group allocation.

The pre-assessment included history, physical examination, neurological evaluation along with various scores; VAS for pain, RODS for QOL and DS for QOL.[6,7] The MRI lumbosacral spine was advised in every case and other investigations ordered according to the clinical condition of the patients.

For the procedure in the operating room, standard monitors were applied and after securing intravenous line, 2mg midazolam administered, ten minutes before the procedure. After putting the patient in a prone position, the area was cleaned and draped under all aseptic conditions. Then, epidural injection was performed under fluoroscopic guidance through an interlaminar approach using 18G Touhy's needle at the level decided by MRI report and clinical symptoms. On achieving the loss of resistance to air, a non-ionic contrast medium (Injection Omnipaque 300 GE USA) was injected while observing its epidural spread in the lateral fluoroscopic view. The study drug solution was administered as per group allotment. The contrast was re-injected to confirm the final findings of the placement of the drug. Assessor anaesthesiologist was summoned after completion of the block. Patients were shifted to post anaesthetic care unit (PACU), observed for two hours for any adverse effects and then discharged.

The post-procedure prescription included pharmacological treatment like analgesics, tricyclic antidepressants with or without anticonvulsants and therapeutic exercise programme. Post-injection evaluation at 2, 4, 8 and 12 weeks included VAS, PSS, RODS and DS. Twelve weeks was considered the endpoint. The PSS was used as a criteria to repeat the block (PSS-1 as good response, no-repeat block required; PSS-2 patient has improved but repeat block required; PSS-3 as no effect of epidural). Additionally, at each follow-up, side effects as well as the signs of neurotoxicity such as ataxia, dizziness, trismus, muscular rigidity, weakness of legs, difficulty in walking and seizure were looked for.

The sample size calculated using G Power version 3.1.9.2.from the results of the pilot study conducted on ten patients in each group, to detect 20% difference of VAS between the two groups taking alpha error 0.05 and beta error 0.80, was found to be 26 patients in each group. Considering a 10% dropout rate, a total of 30 patients were included in each group.

At the end of the study, the data thus obtained was decoded, compiled, compared and analysed statistically using Statistical Package for Social Sciences (SPSS) software 20. The observations thus made were tabulated as mean ± standard deviation (SD) with 95% Confidence Interval (CI). Categorical data was analysed using the Chi-Square test, whereas continuous data compared using paired t-test and the pain-free survival period evaluated using Kaplan Meier Survival Functional analysis. The level of significance was determined as its '*P*' value with $P < 0.05$ as significant.

RESULTS

In group I, three patients were excluded from the results, due to technical difficulty in one patient, severe bradycardia in second and third lost to follow-ups; whereas in group II, two patients were excluded, one due to vasovagal syncope with vomiting and bradycardia and second lost to follow-ups. Thus, the demographic profile included all sixty patients, while 27 patients in Group I and 28 in group II were analysed [Figure 1].

The two groups were comparable demographically in terms of age and sex [Table 1]. The analgesic efficacy measured by VAS scores was significantly improved from baseline at various time intervals in both the groups but comparable between the groups at 12 weeks [Table 2]. However, on plotting Kaplan Meier Analysis survival function graph, the probability of pain-free interval appeared more in group II compared to group I ($P = 0.022$) [Figure 2]. Patient satisfaction score (PSS) and number of repeat injections were comparable between the groups at all time intervals [Table 3]. Seven patients out of eighteen with PSS-2 in group I did not consent for repeat block, rather opted for conservative management.

A significant improvement from the baseline was observed in RODS at all follow-ups ($P = 0.000$). However, at 12 weeks the improvement in QoL was significantly more in group II than group I ($P = 0.024$) [Table 4].

DS also improved significantly from baseline at all follow-ups but remained comparable on intergroup comparison at 12 weeks ($P = 0.559$) [Table 5].

The incidence of transient side effects such as increased systolic blood pressure was more in group II vs I (28.57% vs 3.7%) ($P < 0.05$), whereas post-injection tachycardia in group II vs I (10.71% vs 3.70%) was comparable ($P > 0.05$). Hallucinations observed were also more in group II vs I (57.14% vs 33.33%) ($P < 0.05$) and these required an additional dose of midazolam. One patient in group I additionally experienced nausea immediately post-procedure. No features of neurotoxicity were observed in any of the patients [Figure 3].

Table 1: Demographic profile

	GROUP I (*n*=30)	GROUP II (*n*=30)	*P*
Age (years)	47.92±15.42	48.82±15.80	0.223
Weight (kg)	67.4±4.93	69.43±8.29	0.448
Height (cm)	153.8±2.13	153±1.79	0.518
Male	16	15	0.089
Female	14	15	

Data are Mean±SD, *n* - number of patients

Table 2: VAS scores at various time intervals in the study groups

	GROUP I	*P* w.r.t.b	GROUP II	*P* w.r.t.b	*P* Intergroup
Baseline	75.56±13.11		81.79±10.2		0.054
2 Weeks	45.56±9.13	0.000†	53.39±15.52	0.000†	0.027*
4 Weeks	45.93±12.41	0.000†	42.86±14.36	0.000†	0.401
8 Weeks	37.04±17.11	0.000†	32.43±13.58	0.000†	0.273
12 weeks	32.22±14.3	0.000†	29.18±11.75	0.000†	0.392

Data are Mean±SD, w.r.t.b- with respect to baseline, *Significant, †highly significant

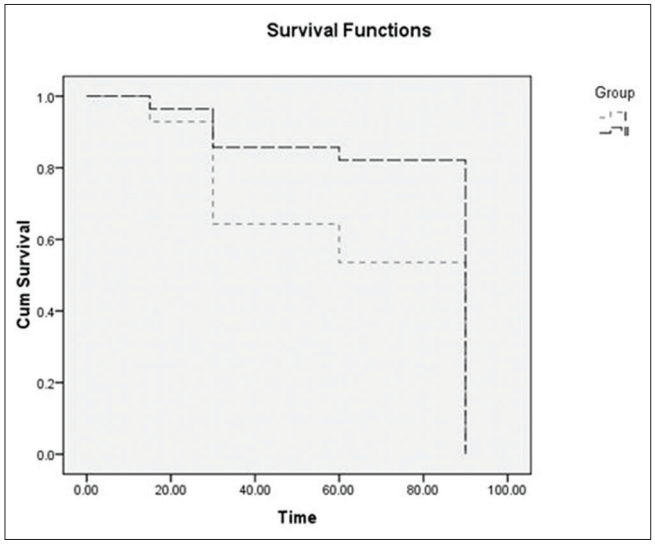

Figure 2: Kaplan Meier graph showing survival function for the two interventions. $P = 0.022$ significant

DISCUSSION

Intradiscal pathology is the most prevalent cause of LBP. ESI is the most common procedure performed for relieving pain, due to its anti-inflammatory action; usually lasting up to 3-4 weeks. The more number of repeat blocks thus required, increase the risk of steroid-induced side effects. Various adjuvants like clonidine, tramadol, ketamine etc., have been used as an adjunct with ESI to improve both the quality of analgesia and duration of pain relief.[4,5] Ketamine due to its NMDA antagonist activity, exhibits amnesia, psycho-sensory, as well as analgesic properties, thereby, prolonging the duration of analgesia and reducing steroid-induced side effects. It helps in controlling chronic and neuropathic pain via multi-receptor modulation.[4,5,8-12] Nevertheless, it also causes transient side effects such as hallucinations, hypertension and tachycardia usually lasting up to two hours.

Basuni *et al*. observed neurotoxicity with a dose of >25 mg when used intrathecally in obstetric patients, but, other researchers including Khezri MB *et al*. used it intrathecally in patients with no such side effects.[13-15] Despite the concerns raised by the above study and FDA announcement regarding intrathecal use of ketamine, some authors still favour its use for lumbar epidural or intrathecal administration.[4,5,8,9]

Various authors have described ketamine usage in different doses for acute postoperative pain.[8,16,17] For neuropathic and chronic pain, 0.2–0.5 mg/kg or a single dose of 30 mg or 50 mg used through intravenous or spinal/epidural route was found useful in relieving pain.[4,5,8-15] Xie *et al*. reported more significant pain relief

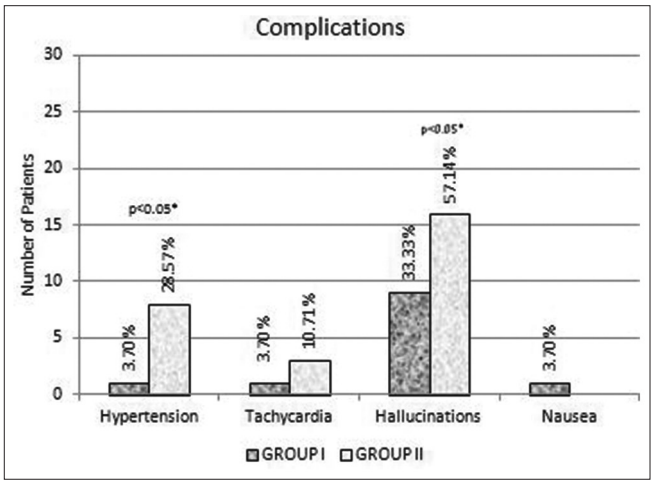

Figure 3: Complications observed in the two groups. The data shows number of patients with percentages (%), $P < 0.05$ *significant

Table 3: Patient satisfaction score at various time intervals and repeat injections performed in the study groups

PSS Score	Group I (*n*=27)				Group II (*n*=28)				*P*
	2nd week	4th week	8th week	12th week	2nd week	4th week	8th week	12th week	
1	21	18	22	24	27	24	27	27	0.487
2	4	8	3	3	1	2	1	1	0.383
3	2	1	2	0	0	2	0	0	0.508
Pts receiving repeat blocks	0	8	3	0	1	3	1	1	
Repeat block	11 (40.74%)				6 (21.43%)				0.00

n - number of patients, *P*>0.05 insignificant, Pts=Patients

Table 4: Revised oswestry disability score for assessment of quality of life at various time intervals in the study groups.

Revised Oswestry Disability Score					
	Group I	*P* w.r.t.b	Group II	*P* w.r.t.b	*P* Intergroup
Baseline	54.29±14.21		57.78±18.32		0.435
2 weeks	39.92±12.83	0.000†	35.89±14.77	0.000†	0.285
4 weeks	35.03±13.16	0.000†	31.32±15.27	0.000†	0.339
8 weeks	32.51±12.98	0.000†	25.96±15.36	0.000†	0.094
12 weeks	27.40±13.21	0.000†	20.17±9.69	0.000†	0.024*

Data are Mean±SD, w.r.t.b- with respect to baseline, *significant, †highly significant

Table 5: Depression score at various time intervals in the study groups

Depression Score					
	Group I	*P* w.r.t.b	Group II	*P* w.r.t.b	*P* Intergroup
Baseline	7.70±5.16		8.85±8.11		0.534
2 weeks	6.03±5.26	0.000†	6.10±5.25	0.001†	0.961
4 weeks	5.18±4.87	0.000†	4.46±3.45	0.000†	0.529
8 weeks	5.00±4.59	0.000†	4.00±3.41	0.000†	0.363
12 weeks	4.25±3.57	0.000†	3.71±3.29	0.000†	0.559

Data are Mean±SD, w.r.t.b with respect to baseline, *significant, †highly significant

with a single low dose of epidural ketamine (0.5 mg/kg) as compared to its intravenous use (0.5 mg/kg).[18] So, we considered to investigate the lower dose of ketamine, that is 25 mg in group I. The addition of 50 mg ketamine to ESI showed better results than 75 μg clonidine in terms of VAS and pain-free interval in LBP ($P < 0.05$).[9] Thus, the idea of comparing 50mg epidural ketamine with 25 mg was conceived.

VAS scores improved from baseline and were comparable in both the groups, thus indirectly indicating the effectivity of the procedure. This 'Analgesic Efficacy', could probably be explained by anti-inflammatory effects of steroids and NMDA receptor antagonism of ketamine. PSS used to assess the subjective feelings of a patient objectively and taken as criteria for repeating a block; was comparable between the groups. Manchikanti *et al*. in their review on the role of steroids in LBP analysed that steroids were more effective than local anaesthetics and between steroids, triamcinolone showed better results than dexamethasone. ($P = 0.000$).[19,20]

Further, the probability of the pain-free period was statistically more in group II vs I ($P = 0.022$), which could be due to high lipid-solubility of ketamine resulting in slow release from epidural space, thus, maintaining stable plasma concentration and hence, longer duration of action.[9]

Chronic low back-pain has a significant impact on the patient's day to day occupational and social capabilities. RODS used as a tool to measure the quality of life showed a significant reduction from baseline in both the groups, however, when compared between the groups at the end of study period, group II was better than group I. Amr YM observed in his study that epidural ketamine (30 mg) significantly improved quality of life for one year compared to normal saline ($P < 0.0001$).[5]

Additionally, chronic LBP has negative impact on the patient's psychological health, both direct as well as an indirect vicious cycle of pain associated disability and handicap. The chronic usage of steroids itself can lead to depression, whereas ketamine acts as a rapid-acting antidepressant that mediates via rapamycin pathway activation. This explains the significance of ketamine in reduction of DS from baseline, which was comparable between the groups. Studies showed that 30 mg ketamine also caused reduction in depression scores from baseline.[4,21]

The increased incidence of tachycardia and hypertension in group II vs I, even though transient, could be a cause of concern in patients with co-morbidities. However, some authors observed no such effects with lesser dose of ketamine.[10,11,14] The short-lasting hallucinations were observed in both groups, and increased in a dose dependent manner. Amr YM (six out of 86) and Gupta R *et al*. (20 patients out of 30) also observed these hallucinations after

epidural ketamine.[4,5] A significant concern was the neurotoxic effects of ketamine, which were not observed in any of our patients.

Limitation of the study

There was no placebo group; since it is unethical to deprive the patient of a chance to be pain-free. Moreover, hallucinations occurring with ketamine would have affected the blinding of the placebo/active control study.

CONCLUSION

Ketamine, when used as an adjunct to ESI in chronic LBP, provides good analgesic efficacy, improvement in the quality of life, and reduction in depression. However, 50mg ketamine produced comparable analgesia to 25 mg ketamine along with adequate patient satisfaction and similar repeat injections at 12 weeks. The probability of pain-free interval as well as quality of life was better with higher dose of epidural ketamine (50 mg), however, it was associated with more side effects. Therefore, in patients with co-morbidities, the dose of ketamine should be chosen depending upon the risk-benefit ratio.

Disclosures

Nil.

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Conflicts of interest

There are no conflicts of interest.

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