Section: Anesthesiology

Original Research Article

COMPARISON OF THE EFFICACY OF EPIDURAL KETAMINE VS ORAL GABAPENTIN FOR ANALGESIA IN CHRONIC PAIN DUE TO SPINAL INJURIES

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Abstract

Background: A key management challenge for those involved in patient care is chronic, severe neuropathic pain following spinal cord damage. A comparison of the efficacy of epidural ketamine vs oral gabapentin for the treatment of chronic pain associated with post-spinal cord injury was the goal of this study. **Materials and Methods:** In this prospective, randomised, double-blinded study, 40 patients were randomized into two groups. Group 1 (20 patients) received 0.2mg/kg (2ml) of preservative-free ketamine single bolus through epidural injection. Group 2 (20 patients) received a single bolus epidural injection of 2ml 0.9% normal saline (placebo) and, after the procedure, was given oral gabapentin 300 mg to be taken three times daily for 45 days. A general physical examination, basic blood tests, and spine-specific Magnetic Resonance Imaging (MRI) were performed. **Result:** There was no significant difference in gender, age, weight, diagnosis, comorbidities, and variations in the patient's vitals between groups. In the Epidural placebo group, the pain score decreased to a mean VAS of 5.7 at around seven days of oral gabapentin daily. The pain decreased to a mean VAS of 5.3 at 21 days and remained at 5.3 throughout the remaining study period. In the EPI-Ketamine group, the pain was reduced after half an hour of the epidural injection. The analgesia lasted throughout the study with a mean VAS of 2.9 at 60 days. There was a significant difference in adverse effects between groups. **Conclusion:** Compared to oral gabapentin, epidural ketamine has significantly fewer side effects and offers noticeably greater analgesia in chronic pain related to spinal injury.

INTRODUCTION

Spinal cord injury occurs due to cauda equina and spinal cord damage. No matter where or how the pain is felt, most individuals who suffer from spinal cord damage acquire chronic pain. In most cases, the pain is excruciating, significantly lowering one's quality of life. Unfortunately, little is known about the mechanisms causing pain following spinal cord damage. After spinal cord injury, persistent, severe neuropathic pain poses a significant management challenge for those involved in patient care. The exact cause of post-spinal cord injury neuropathic pain is yet unknown.[1]

Recent clinical studies have shown that the excitatory amino acids glutamate and aspartate, which act at the N-methyl-D-aspartate (NMDA) receptors, are partially responsible for central sensitization of the nociceptive input.[2] These compounds have been theorized to contribute to a chronic hyperexcitability state in the pain pathway. Increased neurokinin synthesis in the sensory ganglion, increased glutamate and aspartate release in the spinal dorsal horn, and enhanced neurokinin transport and release in the spinal cord all occur after inflammation or injury and promote central sensitization and wind up.[3]

Wind-up can 20 times increase the size and duration of a dorsal horn neuron's reaction. This level of hyperexcitability in the brain can be thought of as the temporal summation of excitatory postsynaptic potentials and may persist even after the peripheral input has stopped. Neuropathic pain is frequently treated with gabapentin.[3,4] Neuropathic pain has been treated with anticonvulsants, antidepressants, analgesics, and cannabinoids. Despite the drug

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therapy's modest short-term benefits, the balance between long-term benefits and harm has been disregarded. A drug efficacy and safety comparison is valuable because clinical decision-makers and pharmaceutical companies are interested in whether a treatment is appropriate for pain.[4] Therefore, the present study aimed to compare the efficacy of epidural ketamine vs oral gabapentin for analgesia in chronic pain of spinal cord injuries.

MATERIALS AND METHODS

This prospective, randomised, double-blinded study was conducted at Government Rajaji Hospital, Madurai medical college, from November 2019 to October 2020.

Inclusion Criteria

Patients aged between 18 to 50 of both sexes and patients diagnosed with chronic low back pain radiating to lower limbs for more than six months secondary to traumatic injury of the lower dorsal and lumbar spine (from T10 to L4) were included. This diagnosis was confirmed by magnetic resonance imaging (MRI), showing injury to the spinal cord's nerve roots and dorsal horn and signs of lumbar radiculopathy.

Exclusion Criteria

Patients with focal neurological impairments, renal and hepatic illness, and uncontrolled type 2 diabetes mellitus were eliminated, as were coagulation problems. Patients with anatomical spinal malformations, back skin infections, bed sores, pregnant and nursing moms, and patients who lost follow-up were also disqualified.

Forty patients were randomized into two equal groups. Group 1 (20 patients) received 0.2mg/kg (2ml) of preservative-free ketamine single bolus through epidural injection. After the procedure, the patient was given an oral placebo to be taken thrice daily for up to 45 days. Group 2 (20 patients) received a single bolus epidural injection of 2ml 0.9% normal saline (placebo) and, after the procedure, was given oral gabapentin 300 mg to be taken three times daily for a period of up to 45 days. Ethical approval was obtained from the institutional ethics committee. The study only included patients who met the inclusion and exclusion criteria. Before signing consent, the patient received an explanation of the procedure, its goals, and any potential adverse effects.

A general physical examination was performed with a history of the presenting ailment and any coexisting diseases. Basic blood tests and spine-specific Magnetic Resonance Imaging (MRI) were performed. The patients were moved to the operating room, where conventional monitoring procedures, including electrocardiography, non-invasive blood pressure monitoring, and pulse oximetry, were carried out.

According to earlier MRI imaging, the epidural injection was administered in the afflicted lower dorsal or lumbar spine interspace. The loss of resistance technique recognized the epidural space. C-arm radiologically confirmed it by looking at the distinctive longitudinal vacuolated spread of dye in the epidural space, after which the respective drugs were injected. Throughout the procedure and two hours after, pulse oximetry every 15 minutes, blood pressure, and pulse rate were evaluated. Continuous ECG monitoring was done till the end of the procedure. The use of anxiolytics and anti-emetics, if required, was mentioned.

The Visual analogue pain score measured the pain level before the epidural injection. Pain scores at 7 days, 15 days, 30 days, and 45 days post-injection. Side effects include increased blood pressure, increased heart rate, vomiting, mental/mood changes, blurred vision or drowsiness (related to ketamine) and effects such as dizziness, lack of coordination, and weakness (related to gabapentin) were recorded.

The information gathered from the selected cases was noted in the master chart. The collected data were analysed with IBM SPSS software 23.0 Version. Descriptive statistics were utilised for categorical variables, frequency analysis, and percentage analysis. For continuous variables, the mean and SD were used. To determine the significant difference between the bivariate samples in independent groups, the Unpaired Sample T-test was employed for normal data and the Mann-Whitney U test for skewed data. The significance of categorical data was determined using the Chi-Square test. All statistical tools consider a probability value of 0.05 to be a significant level.

RESULTS

Among 40 patients, most were males in both groups, and there was no significant difference in gender between groups (0.658). Most patients were between 36-45 years (45% in the Epidural placebo Group and 60% in the EPI-Ketamine Group). There was no significant difference in age between groups (p=1).

Table 1: Demographic data of the study

		Epidural placebo with oral gabapentin group	Epidural Ketamine group	P-value
Gender	Male	18 (90%)	16 (80%)	0.658
	Female	2 (10%)	4 (20%)	
Age group	<35	5 (25%)	3 (15%)	1
	36-45	9 (45%)	12 (60%)	
	>45	6 (30%)	5 (25%)	

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Weight	≤65	8 (40%)	8 (40%)	0.325
	66-75	7 (35%)	10 (50%)	
	>75	5 (25%)	2 (10%)	
Diagnosis	Degenerative spinal stenosis L1	3 (15%)	5 (25%)	0.758
	L1 Burst	8 (40%)	7 (35%)	
	L3spondylolisthesis	4 (20%)	5 (25%)	
	L4spondylolisthesis	5 (25%)	3 (15%)	
Comorbidities	SHT	6 (30%)	3 (15%)	0.224
	T2DM+SHT	1 (5%)	2 (10%)	
	T2DM	0	3 (15%)	
	Nil	13 (65%)	12 (60%)	

The diagnoses include degenerative spinal stenosis L1 (15% in the Epidural placebo group and 25% in the EPI-Ketamine group) and L1 Burst (40% in the Epidural placebo group and 35% in the EPI-Ketamine group).
The comorbidities include SHT (30% in the Epidural placebo group and 15% in the EPI-Ketamine group), T2DM SHT (5% in the Epidural placebo group and 10% in the EPI-Ketamine group), and T2DM (15% in EPI-Ketamine group). There was no significant difference in weight, diagnosis, and comorbidities between groups [Table 1].

Table 2: Vitals during the epidural injection between groups

		Mean STD				**P-value**
		Epidural placebo with oral gabapentin group		**Epidural Ketamine group**		
Baseline values	SBP	130.10	11.15	130.10	11.15	1.00
	DBP	79.50	2.24	79.50	2.24	1.00
	PULSE	83.15	4.91	83.15	4.91	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00
After 5 minutes	SBP	130.40	10.44	130.40	10.44	1.00
	DBP	81.00	4.47	81.00	4.47	1.00
	PULSE	83.10	4.25	83.10	4.25	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00
After 15 minutes	SBP	130.30	8.42	130.30	8.42	1.00
	DBP	80.00	4.59	80.00	4.59	1.00
	PULSE	83.15	3.88	83.15	3.88	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00
After 30 minutes	SBP	129.80	9.22	129.80	9.22	1.00
	DBP	78.00	5.23	78.00	5.23	1.00
	PULSE	81.15	3.33	81.15	3.33	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00
After 1 hour	SBP	130.30	8.32	130.30	8.32	1.00
	DBP	79.00	3.08	79.00	3.08	1.00
	PULSE	80.85	2.18	80.85	2.18	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00
After 2 hours	SBP	127.90	6.85	127.90	6.85	1.00
	DBP	79.50	2.24	79.50	2.24	1.00
	PULSE	80.90	2.47	80.90	2.47	1.00
	SPO2	99.00	0.00	99.00	0.00	1.00

There was no significant difference or variations in the patient's vitals in both groups during the procedure [Table 2].

Table 3: VAS pain score between groups

	Mean STD				**P-value**
	Epidural placebo with oral gabapentin group		**Epidural Ketamine group**		
Baseline	6	0	6.3	0.733	0.075
After 30 mins	6	0	4.9	1.651	0.005
After 1 hour	6	0	3.5	1.821	<0.001
After 2 hours	6	0	2.6	1.142	<0.001
After 3 days	6	0	2.4	0.821	<0.001
After 7 days	5.7	0.733	2.4	0.821	<0.001
After 14 days	5.4	0.94	2.5	0.889	<0.001
After 21 days	5.3	0.979	2.5	0.889	<0.001
After 28 days	5.3	0.979	2.6	0.94	<0.001
After 42 days	5.3	0.979	2.7	0.979	<0.001
After 60 days	5.3	0.979	2.9	1.21	<0.001

In both the groups, the baseline mean VAS score before epidural injection was 6 and 6.3cm, respectively, and showed no significant difference.

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In the Epidural placebo group, who were given oral gabapentin 300 mg TDS throughout the study period, the pain score decreased to a mean VAS of 5.7 at around seven days of taking oral gabapentin daily. The pain decreased to a mean VAS of 5.3 at 21 days and remained at 5.3 throughout the remaining study period.
In the EPI-Ketamine group, the pain was reduced after half an hour of the epidural injection. A reaching a minimum level of VAS of 2.4 three days after the epidural injection. The analgesia lasted throughout the study with a mean VAS of 2.9 at 60 days. This significantly reduced VAS compared to the oral gabapentin group [Table 3].

Table 4: Comparison of adverse effects between groups

Adverse effects during the period	Epidural-Placebo Oral Gabapentin Group	Epidural Ketamine Group	P-value
Giddiness	17 (85%)	0	<0.001
Visual disturbances	1 (5%)	0	
Nausea	0	2 (10%)	
Other adverse effects	0	0	
Nil	2 (10%)	18 (90%)	

In the epi-placebo group receiving oral gabapentin, 85% of the patients complained of episodes of giddiness, and 5% complained of visual disturbances. In the epi-ketamine group, 10% of the patients complained of nausea. There is a significant difference in adverse effects between groups ($p<0.001$) [Table 4].

DISCUSSION

In the present study, the analgesia caused by epidural ketamine was significantly better and sustained for one month after the injection than those who received an epidural placebo with oral gabapentin. Further, the vitals measured during and immediately after the procedure showed no significant variations from the baseline in the epidural ketamine and epidural placebo with the oral gabapentin group. This suggests that the procedure is acceptably safe.[5]
The quick onset of analgesia and pain relief in the epidural ketamine group is explained by a significant concentration of (N-methyl-D-aspartate) NMDA receptors in the spinal neurons, causing noticeable pain relief. NMDA receptor antagonists prevent hyperalgesia brought on by tissue and nerve damage, inflammation, and pain. The prolonged duration was hypothesized to be due to the inhibition of the wind-up of dynamic wide neurons in the dorsal horn by NMDA receptor antagonists.[6]
Comparing the pre- and post-injection VAS scores, the group receiving epidural ketamine showed a minimum mean VAS score of 2.4, lasting around 60 days. The mean onset of maximum analgesia was at three days and stayed throughout the study period with the group that had received epidural ketamine. The onset of analgesia was also considerably quicker, with the subject noticing improvement in analgesia and better pain relief within a mean duration of half an hour after the administration of epidural ketamine. The group that received an epidural placebo injection with oral gabapentin showed a modest reduction in pain with a mean VAS score of 5.3 from a baseline of 6 during the study period. The onset of analgesia in the epidural placebo group was after a mean duration of 21 days which was longer than the epidural ketamine group.
Another important observation was the incidence of significant adverse effects like giddiness and visual disturbances in 90% of the patients in the group that had received oral gabapentin. This brings challenges to patient compliance with therapy. However, in the epidural ketamine group with oral placebo, only one subject had an episode of nausea during the epidural injection. Yasser Mohamed Amr conducted a study in 2010 that investigated the effects of adding a multi-day low-dose ketamine intravenous infusion to oral gabapentin for treating chronic post-spinal cord injury pain. The author found the drug was safe and effective at reducing pain, but the analgesic effect vanished two weeks after infusion termination.[7] An additional study by Amr YM et al,[3] observed a longer potency (one-month post-injection) for epidural ketamine. The analgesia resulting from the addition of epidural ketamine to gabapentin in the same research was superior and maintained for a whole month after injection compared to that in the group receiving gabapentin alone. The explanation for the lengthy potency was that NMDA receptor antagonists prevented the dorsal horn's wind-up.[8]
Interestingly, a study using epidural catheter insertion in patients with low back pain and 0.1 mg/kg ketamine followed by 30 mg lidocaine 1% applied three times daily (8-h intervals) for three weeks concluded that epidural ketamine was more effective than clonidine for controlling refractory chronic low back pain. In that trial, the VAS was maintained between 0 and 3 cm during the administration of epidural ketamine. No side effects of the drug were noted for two to five weeks after removing the epidural catheter.[9]
It was noted that intrathecal ketamine was an effective treatment for non-malignant pain.[10] Another study revealed that ketamine is effective in cases where other standard analgesic treatments have failed, despite the moderate to weak evidence supporting its use in treating chronic pain.[11] The possibility of undesirable psychotomimetic and hemodynamic effects from NMDA receptor blockade constrains the use of high doses.[8] Single,

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low-dose injections had minimal and well-tolerated adverse effects. Similarly, in the present study, we have also reported mild and manageable side effects like nausea (in 10% of subjects) attributed to ketamine.

The primary limitation of this study is that only one epidural injection was administered. It would have been possible to assess the feasibility and effectiveness of intermittent or continuous epidural ketamine to provide prolonged pain relief. When administered by a qualified doctor, epidural steroid injections are a safe and effective treatment for back, neck, and arm discomfort caused by various illnesses. It is critical to understand that epidural steroid injections are not necessarily intended to treat neck or back pain; instead, they're meant to offer short-term respite so that the patient can resume regular activities or keep up with their physical therapy schedule. Patients may need a single injection or a series of injections to experience the greatest pain relief with epidural steroid injections, which may take anywhere from one week to a year.[12]

CONCLUSION

Compared to oral gabapentin, epidural ketamine has significantly fewer side effects and offers noticeably greater analgesia in chronic pain related to spinal injury. However, epidural steroid injections are frequently performed. It is crucial to inform the patient that not everyone has pain relief from these medications, nor is the reaction always instantaneous. Therefore, the patient should be educated about lifestyle changes like regular exercise, quitting smoking, maintaining a healthy weight, and avoiding a sedentary lifestyle by the primary care physician, nurse practitioner, and orthopaedic nurse.

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