The Effects of Single Dose Ketamine on Pain Symptoms and Functional Mobility in Patients with Lumbar Spinal Stenosis

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Need for the Study

Lumbar spinal stenosis is a condition in which narrowing of the central canal of the spinal column compresses its contents resulting in back pain and referred leg pain. This pain is exacerbated by standing, walking and lumbar extension. The leg pain or neuroclaudication can severely interfere with walking distances required for functional activities, thus impairing quality of life. Spinal stenosis commonly results from arthritic bony overgrowth from the zygoapophyseal joints in older adults. These spondylytic changes may also occur in younger adults as a result of chronic lumbar disc disease or multiple failed back surgeries. Treatments for spinal stenosis include surgery to decompress the spinal canal, pain medication, and physical therapy. Surgical treatment is not conclusively effective for all patients and is not an option for others with surgical risks. Pain medications include non-steroidal anti-inflammatory drugs (NSAIDS), anticonvulsants, antidepressants and opioids. In some patients these medications are either not effective or the side effects are too severe. N-methyl-D-aspartate (NMDA) receptors play an important role in spinal neuropathic pain. Thus, an NMDA receptor antagonist, such as ketamine, may be an effective drug treatment for back and leg pain due to spinal stenosis. If pain is effectively managed, patients' ability to function, and thus quality of life, may also improve.

Objectives of the Study

This pilot study was designed to test the effects of oral ketamine as a treatment for back and leg pain in patients with lumbar spinal stenosis and to provide information needed to design a larger efficacy study. Analysis of data is used to address the following questions:

- Does ketamine affect the severity and distribution of back and leg pain?
- Does ketamine affect patients' ability to perform activities of daily living?
- Based on the effect of ketamine on back/ leg pain severity and distribution and ability to perform selected functional activities, what sample size is needed for a larger efficacy study?
- Is there a relationship between change in pain severity and distribution and ability to perform activities of daily living?

Subjects

Subjects were 10 patients (age 40 years or older) referred by one of the authors (RF) from Temple University's Pain Management Center. All patients had a confirmed clinical diagnosis of lumbar spinal stenosis with a history of low back and leg pain for a minimum of 6 months and onset of neuroclaudication pain on walking one city block or less. All patients had back and leg pain that was unsuccessfully treated with one or more of the following: NSAIDS, steroid injection, antidepressants, or opioids. Patients were not required to stop other medications during the study. Exclusion criteria included: (1) resting HR >100 bpm or resting diastolic BP >100 mmHg, (2) comorbidity of stroke with residual hemiplegia, Parkinson's disease or vascular claudication, and (3) comorbidity of spinal tumor, infection or lumbar radiculopathy due to recent disc herniation.

Demographics

Ten subjects participated in this study, 7 men and 3 women. The subjects ranged from 44-65 years of age (mean = 54.4 ±10.9). The distribution of race is: 3 African Americans, 2 Hispanics, 4 Caucasians and 1 Native American. The mean number of months since the diagnosis of spinal stenosis was made is 21.6 ± 20.46 (range, 6-42 months). All subjects showed a probability of experiencing depression according to scores on the CES-D[1]. Scores on a Folstein Mini-Mental State Exam showed that no subjects had significant cognitive impairments[2]. Scores on the Roland-Morris Back Questionnaire, used to measure the amount of disability due to back pain, ranged from 15-22 (maximum disability = 24; mean = 18.7±2.83)[3]. Thirty percent of the subjects underwent prior back surgery. Six subjects had a course of physical therapy. Five of the subjects who had PT did not have lasting benefit. Ninety percent of the subjects had full PROM in both lower extremities. One subject had limited ROM in one joint (knee extension). Fifty percent of the subjects displayed limited ankle strength. Comorbidities were insignificant.

1 Center for Epidemiological Studies-Depression symptom scale. Scores of >16/40 are considered elevated and individuals have a high probability for experiencing clinically significant depression.
2 Folstein Mini Mental State exam. Scores ≤ 20 /30 are indicative of significant cognitive impairment.
3 Roland Morris Back Pain Questionnaire. Zero is indicative of no disability and a score of 24 is indicative of the most severe disability.

Methods

This study used a repeated measures cross over design with subjects serving as their own controls. Subjects were tested twice in each of two visits and performed selected activities of daily living at a self selected, usual speed" and "as fast as possible". They were also timed walking on a treadmill at self selected and fixed (1.2 mph) walking speeds to determine onset of, and recovery from, claudication symptoms. After each group of activities, subjects rated the intensity of their back/leg pain using a visual analog scale (VAS) and a completed a body diagram to indicate pain/symptom distribution. After completing all the tests once, subjects were given a juice drink containing either ketamine (35mg/kg) or placebo. All subjects rested for 45 minutes after receiving the ketamine or placebo drink and then repeated all the timed functional activities and walking tests in the same order as during the first session. The second visit occurred 7 to 2 days later. On the second visit, subjects performed the same timed functional and walking tests as on the first visit. However, if the subject received the ketamine drink on the first visit, the placebo drink was given on the second visit. Subjects and investigators were blinded to the sequence of the placebo or ketamine intervention. Activities were performed in four clusters. Specific activities in each cluster are listed in results. A computerized gait mat was used to measure spaciotemporal characteristics of gait.

Results

Activity	VAS Back (mm)	VAS R Leg (mm)	VAS L Leg (mm)	Pain Body Diagram (#blocks)
Initial Session#1(>20)	58.7 ± 16.4	42.5 ± 26.7	48.6 ± 25.2	90.1 ± 87.5
Before Tx (n=20) Cluster 1	79.1 ± 15.5	59.5 ± 25.0	61.8 ± 26.4	90.1 ± 86.6
Cluster 2	74.6 ± 15.2	55.6 ± 23.8	56.0 ± 25.6	79.8 ± 84.9
Cluster 3	74.9 ± 16.0	61.6 ± 22.7	59.4 ± 25.5	79.6 ± 80.4
Treadmill	82.1 ± 14.4	69.9 ± 25.3	71.5 ± 23.7	120.9 ± 115.7
Initial Session#2 (n=10)	59.0 ± 23.0	49.4 ± 30.1	53.5 ± 33.3	81.8 ± 102.1
After Placebo Cluster 1	65.8 ± 26.9	57.2 ± 35.6	57.3 ± 36.2	95.4 ± 130.8
Cluster 2	62.2 ± 24.6	52.4 ± 33.4	56.6 ± 33.3	94.3 ± 116.7
Cluster 3	65.4 ± 27.0	50.6 ± 31.6	54.2 ± 33.6	74.6 ± 79.8
Treadmill	69.5 ± 28.7	64.0 ± 37.9	64.2 ± 32.9	117.6 ± 137.0
Initial Session#2 (n=10)	52.5 ± 29.0	37.9 ± 28.6	52.4 ± 32.5	49.1 ± 42.6
After Ketamine Cluster 1	75.4 ± 16.2	59.5 ± 31.7	70.7 ± 25.3	60.8 ± 49.6
Cluster 2	74.1 ± 16.0	62.5 ± 27.2	61.4 ± 30.4	66.9 ± 50.2
Cluster 3	76.5 ± 23.1	61.0 ± 42.6	75.0 ± 25.2	57.3 ± 8.3
Treadmill	74.4 ± 18.2	62.4 ± 29.8	61.2 ± 26.2	81.5 ± 62.9
Cluster	**Activity**	**Time(s): Pre**	**Time(s): Placebo**	**Time(s):Ketamine**
One	Lie to Sit	6.4 ± 2.5	4.8 ± 1.2	5.4 ± 1.9
	Sit to Lie	5.4 ± 2.0	4.5 ± 1.4	4.9 ± 1.7
	Sit to Stand x 5	22.4 ± 7.0	20.6 ± 7.2	22.4 ± 9.7
Two	Amb Fwd -20'	7.0 ± 1.7	6.3 ± 1.3	6.8 ± 1.5
	Amb Bkwd -10'	9.3 ± 4.9	6.7 ± 2.1	7.8 ± 2.9
	Amb Fig 8	20.2 ± 4.6	17.4 ± 2.8	19.1 ± 4.0
Three	Step over 2"	3.8 ± 1.0	3.5 ± 0.7	3.9 ± 0.9
	Step over 6"	3.8 ± 0.9	3.5 ± 0.6	3.6 ± 0.8
	Ascend 4 steps	4.6 ± 1.4	4.0 ± 1.0	4.3 ± 1.5
	Descend 4 steps	4.1 ± 1.5	3.5 ± 1.0	3.5 ± 0.8
Treadmill	Time to 1st claudic	112.1 ± 67.2	125.1 ± 72.0	113.5 ± 81.4
	Time to Stop	146.7 ± 69.5	148.9 ± 73.2	131.2 ± 76.4
	Time stop to recov	158.5 ± 110.2	112.5 ± 45.2	104.7 ± 60.4
Gait	BOS-L(cm)	11.8 ± 3.3	11.2 ± 3.7	12.1 ± 3.8
	BOS-R	11.8 ± 3.3	10.7 ± 4.1	12.1 ± 3.5
	Step length-L(cm)	55.9 ± 8.6	62.5 ± 14.6	58.7 ± 14.7
		55.9 ± 7.8	62.2 ± 15.8	58.2 ± 13.1
	Step length-R	107.7 ± 26.5	119.4 ± 18.6	112.8 ± 13.9
	Stride length-L(cm)	112.8 ± 15.9	119.3 ± 17.1	112.2 ± 14.7
		102.9 ± 16.2	107.4 ± 13.4	103.7 ± 16.9
	Stride length-R	96.8 ± 23.9	106.6 ± 23.8	97.2 ± 24.3
	Cadence(steps/min)	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
	Velocity(cm/sec) Velocity normal (LL/min)			

Statistical Analysis

Means and standard deviations were computed for all dependent variables. Means were assessed using analysis of variance. All fixed effects were tested for interaction. The effect of treatments (none, placebo, ketamine) was tested and evaluated for statistical significance ($p<.05$). Power analysis (80% power) was used to evaluate the effect size (of treatment) to determine sample size for a larger efficacy study. The effect sizes of ketamine treatment on sit to stand x5 and treadmill test (time to recovery) were used to predict that a sample size.

Conclusions

1. Distribution of pain (# boxes on body diagram) decreased after ketamine ($p <.04$), but no significant change in VAS rating was found in either back or leg.
2. The time required for pain to return to baseline after treadmill test approached significance ($p = .07$). Subjects had a shorter recovery time after taking ketamine than after taking placebo.
3. The functional activities and spaciotemporal characteristics of gait that were measured were unaffected by ketamine.
4. The effect sizes of ketamine treatment on sit to stand x5 and treadmill test (time to recovery) were used to predict that a sample size of 70 subjects will be required to prevent a type II error in a future efficacy study.

Concerns for Future Studies

1. A Practice effect may have occurred in the timed functional mobility tests. Subjects typically did better in second session of the day, regardless of treatment.
2. Some subjects (3) experienced referred pain asymmetrically (all referred pain in only one leg). In future studies, leg pain intensity (VAS) should be analyzed by "legs with symptoms", rather than by side.
3. Some subjects recorded pain in hands and other parts of the body that could not be attributable to lumbar spinal stenosis. In future studies, pain distributiondata should be analyzed by region, back and legs, rather than entire body.
4. Measurements of time to perform common functional activities was not affected. IFuture single dose studies should include only the treadmill test, as it was the only functional measurement that showed a trend toward response to intervention.
5. The speed of performing functional activities are affected by many factors, including habit. In future studies, intervention should include multiple doses over a longer time (one or more weeks) and might include functional training as well.