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Short Communication

Effect of D-cycloserine on Postoperative Neuropathic Pain after Lumbar Discectomy

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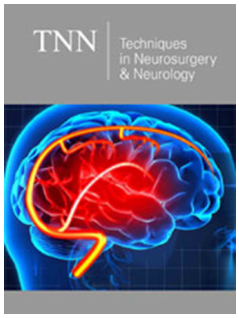
ISSN: 2637-7748



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Submission: January 30, 2021
Published: June 08, 2021

Volume 4 - Issue 2

How to cite this article: Ata Mahdkhah. Effect of D-cycloserine on Postoperative Neuropathic Pain after Lumbar Discectomy. Tech Neurosurg Neurol. 4(2). TNN. 000585. 2021.
DOI: 10.31031/TNN.2021.04.000585

Abstract

Background and Objectives: Neuropathic pain represents a major neurologic complication associated with neuronal injury. It occurs when any injury, disease, or dysfunction nervous system. Nerve root mechanical compression and neuroinflammation are the two main discussed theories for the pathogenesis of neuropathic pain, especially in remained leg pain during lumbar disk herniation [LDH]. D- cycloserine [DCS] is a partial agonist of the NMDA receptors and can prevent neuropathic pain theoretically. In this study, we tested the hypothesis that DCS would reduce the postoperative neuropathic pain during the first 24 hours after single level lumbar discectomy.

Method: In the present study participants were chosen among candidates for a single level lumbar discecyomy, from March 2018 to March 2020. Randomization and data collection patients were randomly allocated into groups A and B using a numerical randomizing computer system. Each patient received an order number and took an identical capsule 2 hours before surgery containing either 250mg D- cycloserin or placebo. Visual analogue scale and morphine consumption were compared at 6 hours intervals up to 24 hours.

Result: Comparing the two groups, the D-cycloserine group showed a significant reduction in remained leg pain during the first 24 hours.

Conclusion: This study suggests that the decision to treat remained neuropathic pain after lumbar discectomies should be taken before the operation. DCS is effective to decrease remaining leg pain by the end of 24 hours in post discectomy patients.

Keywords: D-cycloserine; Discectomy; Leg pain

Introduction

Neuropathic pain represents a major neurologic complication associated with neuronal injury. It occurs when any injury, disease, or dysfunction involves the peripheral or central nervous system. A wide spectrum of mechanisms including mechanical injury, inflammation, focal ischemia, neurotoxicity, viral infection, metabolic abnormalities, and dysfunction of several neurotransmitters has been described as the causative factors. Common clinical examples include pain resulting from diabetic neuropathy, post herpetic neuralgic, neuralgia associated with late -stage cancer, partial nerve injury, multiple sclerosis, amputation and pain due to Lumbar Disc Herniation [LDH]. The occurrence of the latest one, also known as sciatalgia, sciatica, painful radiculopathy, or leg pain, is a common and disabling feature for these patients. Because neuropathic pain is often immutable and maladaptive in nature, it can reduce the patient's ability to work, walk, or sleep, as with other forms of painful disabilities. Nerve root mechanical compression and neuroinflammation are the two main discussed theories for the pathogenesis of neuropathic pain during LDH. Animal studies have also shown that nerve fibers manifested ectopic irritability at or near the injury site. This might be either owing to the abnormal distribution of sodium channels or owing to an abnormal response to endogenous pain evoked by the release of cytokines and inflammatory mediators [1]. Although this sensitization might work as a compensatory mechanism for the functional deficits of the nervous system, the result would be a global sensitization of the

nervous system [or central sensitization], which is responsible for the chronicity of the pain and hyperalgesia. When no compensatory intervention exists, both central and peripheral mechanisms will be involved. Initially, the injured axon is the pain producing site. Later on, neurons of the dorsal root ganglion, and even post synaptic neurons of the dorsal horn of the spinal cord and higher order neurons up to the cortex will be recruited to emit pain signals [1-3]. As a result, neuropathic pain is believed to be a progressive disease of the nervous system. Such processes contribute to the slow progression of the disease, which is also known as the pain memory. So, the main goal of therapeutic modalities for the neuropathic pain is to hinder the development and the progression of the pain memory with preventive methods. Haman brain imaging studies suggest that neuropathic pain has a strong emotional component that is mediated by medial prefrontal cortex [mPFC] activity; in rodents, the mPFC is involved in emotional and cognitive aspects of behavior, including the extinction of behavior fear conditioning [4]. Together, these findings suggest that the cortex may modulate the memory trace of pain. The efficacy of several drugs on neuropathic pain has been tested in animal studies. These include morphine [5], antidepressants [6-8], clonidine, dexamethason [9], anti convulsants [10], ketoprofern [11], magnesium sulfate [12] and canabinoides [13]. All of them have different side effects in gastrointestinal, cardiovascular, respiratory and electrolytes abnormalities. Based on the accepted spinal mechanisms of pain, glutamate the most prevalent excitatory neurotransmitters, binds to two classes of ionotropic receptors termed NMDA [N-methyl-D-aspartate] and non – NMDA. When the spinal cord is in its normal state in the absence of tissue damage, there is a voltage dependent Mg2+ block of the NMDA receptor ion channel. When nociceptive afferent fibers are excited by a noxious stimulus glutamate is released from the central terminals exciting postsynaptic neurons. D-cyclomerize [DCS] is a partial agonist of the NMDA receptors and can prevent neuropathic pain theoretically. In animal Studies, repeated oral administration of DCS reduced mechanical sensitivity of the injured limb with mPFC changes in a dose-dependent manner. In addition, re-exposure to DCS further enhanced antinociceptive behavior. In this study, we tested the hypothesis that DCS would reduce the postoperative neuropathic pain during the first 24 hours after single level lumbar laminectomy and discectomy.

Remaining leg pain makes the outcome in a group of patients with lumbar discectomy unfavorable. Before the surgery, the pain starts gradually until it become s intolerable and makes the patient seek medical advice. The pain, which is also referred as radiculopathy or sciatica, is mostly considered as a neuropathic pain rather than a nociceptive pain. Neuropathic pain is believed to be a progressive disease of the nervous system [2]. Lumbar discectomy is usually considered for the patients with no response to conservative treatments after a period 6 to 8 weeks, those who develop the symptoms and signs in favor of an emergency situation such as cauda equina or those with a progressive neurological deficit such as foot drop. Although most patients experience complete relief of their symptoms after the surgery, it is estimated that only 70% of patients have significant pain reduction within four weeks postoperatively [14]. Moreover, 10% of these patients might even undergo a repeat operation. As a rule, the surgeon must first exclude the possibility of remaining disk material within the canal. MRI makes this exclusion possible within the first 24 hours after the surgery, when the postoperative changes are still minimal [15]. The chronicity of pain is thought to be one major determinant factor in the development of remaining leg pain after lumbar discectomy by the gradual recruitment of the dorsal root ganglion neurons, postsynaptic neurons of the dorsal horn and higher order neurons [4]. Initially, the pain might be a simple axonal signal caused by the compression of herniated nucleus pulposus on the never root fibers [3]. Later on, other neurons at the dorsal root ganglion, posterior horn of the spinal cord and higher order neurons up to the cortex level might treat as pain producing sites [4]. Animal studies have also shown that nerve fibers manifest exaggerated ectopic irritability at or near the injury site. This might be either due to abnormal distribution of sodium channels or due to an abnormal response to endogenous pain evoked by the release of cytokines and inflammatory mediators. Although this sensitization might work as a compensatory mechanism for the function deficits of the nervous system, the result would be global sensitization of the nervous system [or central sensitization], which is responsible for the chronicity of the pain and hyperalgesia [2]. Initially, the injured axon is the pain-producing site. Later on, neurons of the dorsal root ganglion, and even postsynaptic neurons of the dorsal horn of the spinal cord and higher order neurons up to the cortex will be recruited to emit pain signals [4]. So, the main aim of therapeutic modalities for the treatment of neuropathic pain is to break the processes through which the development and the progression of pain memory occur. Recently, there has been a growing interest to alter this process by the suppression of pain during the acute stage after the surgery. The efficacy of several drugs on neuropathic pain has been tested in animal studies. When the results of a pre-clinical study of a particular drug on animal models are satisfactory, they also need to be evaluated clinically on human volunteers to find their way into clinical practice. This should be done under close scrutiny not violating the patient's right. The evaluated drugs on neuropathic pain include morphine [5], antidepressants [6-8], clonidine, dexamethasone [9], antuconvulsants [10], ketoprofen [11], magnesium sulfate [12] and canabinodes [13]. Preclinical studies D-Cycloserine is effective in the management of neuropathic pain [4]. Human brain imaging studies indicate that the medial prefrontal cortex activity can predict more than 80% of the variance of back pain intensity [4]. Therefore, the investigators have hypothesized that modulation of brain activity at this site should result in analgesia. D-cycloserine has been shown to potentiate conditioned fear extinction. Based on this, the investigators hypothesize that neuropathic pain [back pain with radiculopathy] is partially mediated or potentiated by decreased ability to extinguish the pain memory, which the investigators hypothesize to be mediated through reward/aversion brain circuitry, and specifically through medical prefrontal cortex. They have tested this idea in per-clinical studies [4] and demonstrated that rats with neuropathic pain show analgesia over the long-term when treated with Dcycloserine [4]. Recently

there has been a growing interest to use pre-operative antibiotics in patients with remaining leg pain after lumbar discectomies and the potential of these drugs to decrease central sensitization and resultant pain seems promising. D-cycloserine is an antibiotic. It is also a partial agonist of the NMDA receptor and can enhance learning and potentiate the extinction of acquired fear and pain [16]. There are some studies relating the effects of D-cycloserine on pain in the literature. One of the oldest papers in 1996 is the post injury administration of D-cycloserine following experimental brain injury based on changes of cognitive performance [17]. The results of this study showed that it could enhance cognition performance after traumatic brain injury. In 2008, a meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy by Norberg and others concluded the dramatic effects of this drug on animal models and patients with anxiety disorders [18]. Another double-blind, randomized, parallel group escalating dose study comparing D-cycloserine with placebo in patients with neuropathic back pain in Northwestern university of USA is an going [19]. Finally, in Denmark, a new study has been completed about the antibiotic treatment to patients with low back pain [20]. The results of this study have not been published. Now, we want to evaluate the effects of this drug on postoperative neuropathic pain after lumbar discectomy for the first time.

Material and Method

Study design

The present study was approved as a randomized, double-blind, placebo-controlled clinical trial by the review board of neurosurgery research team and ethics committee of Umia University of Medical Sciences. All patients were asked to sign an informed consent if they were willing to enter the trial. The patients, surgeons and the statician remained blinded to the study groups to the end of trial and statistical analysis. The research protocol was approved by the research vice chancellor of Urmia University of Medical Sciences and the ethics committee. The trial has been registered at www.irct.ir [registered number: N2IRCT2013071413947].

Patients

Participants were chosen among candidates for a single level lumbar discectomy, from March 2018 to March 2020. Inclusion criteria were: 1. Age range of 18 to 70 years, 2. Weight range of 60 to 80Kg, 3. Informed consent, 4. Concordant clinical and imaging characteristics necessitating the need for discectomy in one single lumbar level. Primary exclusion criteria included : 1. Pervious neurosurgical intervention, 2. Past history of alcohol or drug addiction, 3. Pregnancy , 4. Side effects of morphine during study, 5. Lactation, 6. Psychiatric disorders such as depression, 7. Neurological disorders such as epilepsy, 8. Intra-operative instability making a fusion technique necessary, 9. Analgesic consumption during the last 24 hours, 10. Complete relief of postoperative neuropathic pain, 11. Known co morbidities such as diabetes, malignancies or cardiovascular disorders, 12. Refusal to provide informed conformed consent or other conditions such as aphasia, visual abnormalities or lack of ability to read and sign.

Randomization and data collection

Patients were randomly allocated into groups A and B using a numerical randomizing computer system. At last, there were 40 cases and 40 controls. The night before the surgery a junior resident [blinded to study] trained the patient how to report their pain according to the visual analogue scale [VAS]. The patients were asked to classify their pain based on VAS. The purpose was to give the crude post-operative VAS score a real measure for comparing the pain intensity. In other words, a VAS score of 6 would be interpreted as maximum pain in one patient, average in another or minimum in the last. A comparative analysis was then feasible at the time of statistical analysis to determine any difference in achieving minimum or less than minimum preoperative pain levels between two groups. Each patient received an order number and took an identical capsule 2 hours before surgery containing either 250mg D-cycloserine or placebo. No other drug was given to the patient until the patient underwent surgery.

Anesthesia

All patients received total intravenous anesthesia during general anesthesia. The induction was accomplished by propofol [2mg/kg], fentanyl [1.5mg/kg], midazolam [0.05 to 0.1mg/kg] and atracorium [0.15mg/kg] Remifentanyl [1mg/kg/, in] and propofol [50 to 150mg/kg/min] were used to maintain anesthesia.

Operative procedure

Patients were positioned on a Wilson frame after the induction of general anesthesia. A 2-inch midline incision was made over the involved spinal level using fluoroscopy. After opening the fascia and subperiosteal dissection, a standard discectomy was done under surgical microscope. For each case, foraminotomy and release of the involved nerve root was also accomplished. No gel foam or surgical was applied over the thecal sac and neural foramen and the surgical wound was repaired in 4 layers after satisfactory homeostasis.

Postoperative management

At the end of operation, the anesthesiologist reversed muscle relaxants using neostigmine [40µg/kg] and atropine [0.02µg/kg]. The patient was then transferred to post anesthesia care unit [PACU] after successful extubation and ventilation. Each patient received the first dose of morphine [0.1mg/kg] and then was transferred to the ward to be under close observation for the next 24 hours. A similar approach was performed for all participants. Only patients who were complaining of residual leg pain, but with lesser degree than pre-operative scores remained in the study. Those with postoperative exclusion criteria were also excluded. No other analgesic was prescribed for the patients during the first 24 hours after the surgery. A senior resident [blinded to the study] recorded VAS score and morphine consumption at 6- hour intervals [6,12,18 &24h], postoperatively.

Outcome assessment

The primary outcome measure was to find any significant decrease in pain intensity between the groups according to 24h VAS scores. The secondary outcome measure was to assess the

possible synergism between D-cycloserine and morphine in terms of significant decrease in total 24h morphine consumption in comparison with the placebo group. Subsequent pain evaluation and morphine consumption was also performed at 6,12,18&24 hours postoperatively. Plus, the patients were asked before the operation to classify their pain into maximum, average and minimum scores to evaluate which level of intensity a given postoperative VAS would correspond to.

Statistical Analysis

A stactician who was blinded to the study performed the statistical analysis. Sample size was calculated with a power of 80%. To detect a 15mm difference in mean VAS scores at a two –sided standard error of 50% with a dropout rate of 75% an estimated primary patient population of 150, a minimum of 30 patients were needed in each group. Comparing with the placebo group, an expected 30% reduction in mean VAS scores and morphine consumption was set to be observed. Chi-Square test was used to analyze categorical demographic date and independent sample t-test was applied for numerical demographic date to determine weather there was a statistically significant difference between the groups, which might have affected the results as a bias. To verify any significant difference in VAS scores and morphine consumption at the designated time intervals [6,12,18&24h], independent samples t-test was used. Statistically significant was defined as $P<0.05$. All the statistical analyses were performed using statistical package for the social sciences [SPSS] 13.0 for windows, SPSS Inc, Chicago, Illinois. The groups were reveled after the statistical analysis.

Result

D-cycloserine Vs. Placebo 104 patients were initially assessed for the eligibility in our study, from which 100 patients were enrolled in each group. 62 and 61 patients were also excluded postoperatively due to different reasons from group A and B, respectively. Finally, the data of 40 patients in the Dcycloserine [A] group [18 males [45%] and 22 females [55%]], and 40 patients in the placebo [B] group [24 males [60%] and 16 females [49%]] were analyzed. The demographic data was not significantly different in the two study arms. The operation time was 110.53±10.12 in group A and 109.44±13.23 min in group B. Discectomy was done on L3/4, L4/5 and L5/S1 intervertebral space in both groups. By the end of 24 hours, the pain decreased in each group, significantly [P value<0.001]. Comparing the two groups, the D-cycloserine group showed a significant reduction in pain after 24 hours [P value=0.044]. While 78% of patients in the D-cycloserine group achieved their minimum or less than minimum preoperative VAS by the end of 24 hours, only 68% of the placebo group achieved this level of pain reduction. In addition, 22% of patients in the D-cycloserine group and 7.5% in the placebo group achieved complete pain relief [VAS=0] at the mentioned time; however, this was not to be statistically different in our study. The mean morphine consumption was 20mg and 21mg in the D-cycloserine and placebo group, respectively, which was not to be a statistically significant difference. Also, the mean morphine consumption at each time interval was not statistically different between the two groups, however in both groups, morphine consumption decreased significantly over time [P-value<0.001]. There was not any significant difference between two groups in the rate of low back pain [the 2nd objective of our study] after surgical intervention [P-value: 0.976]. Moreover, there was not any significant difference between the studied groups in the number of sensory abnormalities [the 3rd objective of our study] after lumbar discectomy [P-value: 0.867]. On the other hand, it means that two items of our hypothesis were not confirmed based on our results.

Discussion

Neuropathic pain represents a major neurologic complication associated with neuronal injury. It is triggered by disease or any dysfunctional status involving central or peripheral nervous system. Neuropathic pain might be felt as a steady, intermittent, sharp or shooting or evoked pain [hyperpathy or allodynia] by the patient. Because it is often immutable and maladaptive in nature, it can reduce the patient's ability to work, walk, or sleep, as with other forms of pain. Indeed, the social and financial impact of pain is tremendous. Leg pain is a common disabling problem in patient with LDH. Although the exact mechanism producing the neuropathic pain in LDH patients is still a matter of debate, it is believed that the central and peripheral mechanisms are involved. Initially, the pain might be an axonal signal caused by the compression of herniated nucleus pulposus on the nerve rot fibers [6]. Later on, other neurons at the dorsal root ganglion [DRG], posterior horn of the spinal cord and higher order neurons up to the cortex level might treat as pain producing sites [7]. Input signals to the spinal cord from the injured nerve fibers are believed to be responsible for the chronicity of the neuropathic pain. This hypothesis is supported by studies on rats showing the effect of rhizotomy to block inputs from injured axons and discontinuance of behaviors associated with the neuropathic pain. Human studied have also shown that local anesthetics are capable to decrease neuropathic pain [19,20]. The brainstem rostral ventral medulla [RVM] exerts both inhibitory and excitatory influences on dorsal horn neurons [21]. Inhibitory bulbospinal pathways have long analgesic effects of opioids with regard to transient pain, and a nerve injury–induced antagonism of this pathway could theoretically contribute to neuropathic pain. However, recent evidence suggests that it is an enhancement of the facilitatory pathways that contributes to neuropathic pain [18]. For example, inactivation of the RVM with lidocaine attenuate the tactile allodynia and thermal hyperalgesia that accompanies spinal nerve injury [20]. The persistent noxious input associated with inflammatory pain causes long–term changes in the activity of RVM region [21] and further RVM microinjection studies indicate that both glutamate and neuropeptide cholecystokinin may drive this tonic descending facilitation to maintain neuropathic pain. This raises an important consideration: such a mechanism may limit the usefulness of intracranial stimulation for the relief of neuropathic pain. Nociceptive signals are sent to the thalamus and cortex for higher levels of processing. Although data are limited, nerve injury may increase the excitability of and recognize the connections of neurons in these supraspinal centers [15]. For example, patients with neuropathic pain demonstrate a dramatic recognization of

sensory modalities in the thalamus [16]. Also, the phantom limb pain following arm amputation is associated with a spatial reorganization of somatosensory cortex mapping. In rats, sciatic ligation increased the responsiveness of thalamic and S1 neurons to tactile and cold thermal stimulation of the paw, and S1 displayed a reorganization of somatic input [17]. Thus, like the spinal cord dorsal horn, plasticity in supraspinal centers may contribute to the severity and quality of neuropathic pain. This may underlie reports that posterior thalamus lesions significantly reduce pain in patients with peripheral nervous system lesions. Most neurologic surgeons deal with pain on a regular basis, be it the reason for referral or as a postoperative phenomenon. Pain assessments are now considered standard of care. There are a number of different classes of medicines that provide analgesia. Some simple principles have been laid out in study. The surgeon should become facile with a typical medicine in each class. Familiarity with and practical application of the array of medications that have analgesic potential is essential to provide competent, effective, compassionate pain care. Part of the survival value of pain is its intimate association with learning. Pain induces single event learning, the memory of which can persist for a lifetime. As such, Pavlovian paradigms of learning often utilize painful stimuli to study learning and memory processes, especially in fear conditioning where the more painful the unconditioned stimulus the fewer trials are required to establish an aversive negative emotional association with a conditioning stimulus [18]. The ability to extinguish aversive associations of fearful or painful events after repeated exposure to the conditioned stimulus is also important for normal behavior [19]. Neuropathic pain, and even postoperative leg or low back pain, is a state of continuous learning, in which aversive emotional associations are made with incidental events simply as a consequence of unpredictable fluctuations in persistent pain [19]. Moreover, pain does not allow for extinction to take place, and instead may further reinforce associations, as extinction required repeated exposure to the conditioned stimuli in the absence of the unconditioned stimuli. This hypothesis is based on observations that pain in humans activates medial prefrontal cortex [mPFC], is associated with atrophy in dorsolateral prefrontal cortex [DLPFC], and that such patients show deficits in emotional decision making [20]. D-cycloserine enhances cognitive processes, improves attention and memory and facilitates fear and pain extinction through de novo memory trace formation involving N–methyl-D-aspartic acid [NMDA] plasticity [18]. It can enhance the extinction of pain-related memories and, thus, exhibit antinociceptive properties for neuropathic pain. In rodents the ventral mPFC [Prelimbic and infralimbic cortices] modulates emotional and cognitive aspects of goal directed behavior and is critical in the extinction of gear and pain. In our study, morphine consumption was not statistically different between the two groups at each 6h interval and by the end of 24 hours. This is in contrary to our hypothesis that D-cycloserine would decrease morphine consumption. The main reason for this might be the fact that patients in both groups asked to reduce their low back pain and leg pain with morphine injection. The better response of nociceptive pain to opioids than the neuropathic pain prevents us to draw any conclusion and clarify the possible role of our drug to reduce morphine consumption. This should be considered as a limitation in our study and probably in any other study in which nociceptive and neuropathic pain coexist. Opioids have not long–lasting effect on neuropathic pain and their effect subsides over time. Animal studies have shown decreased level of β-endorphin within the brain and spine after traumatic injury of sciatic nerve is associated with the incidence of autonomy behaviors [19]. Also, spinal opioid receptors have decreased after dorsal rhizotomy in rats [20]. These studies are in support of decreased efficacy of opioids on neuropathic pain over time. Remaining leg pain and numbness is not an unusual complication after lumbar discectomy. Even, genetic susceptibility to poor pain outcome after discectomy have been suggested [21]. Although the true prevalence of retained leg pain is unknown, our experience is that even with optimal surgery and satisfying postoperative MRI, leg pain and numbness may persist for weeks and months after the operation. We believe neuroinflammation has a significant role, especially during the first 24h; however, this needs to be assessed in a scientific manner. In a group of patients, this could be expected by intraoperative visualization of swollen and red-colored nerve roots within the foramen. In addition, surgical insult to the tissues might flare up the inflammatory process by the release of cytokines from inflammatory cells in the vicinity of the nerve root. The other explaining mechanism might be the excessive manipulation of the nerve root a find the fragmented disk material or to release the root within the foramen. This might lead to neuron excitation and hyperalgesia, which is responsible for the persistence of pain, postoperatively. In a study by Almetafy, it was demonstrated that post discectomy somatosensory evoked potential [SSEP] showed no difference during the acute phase after the operation and in 17% of cases, postoperative SSEP was worse than preoperative SSEP. Although SSEP is not a suitable outcome measure foe the discectomy patients, it may show operation induced neurophysiological changes and the possibility of postoperative exacerbation of pain. The preoperative classification of the neuropathic pain of patients into the minimum, average and maximum levels according to the VAS, enabled us to have a better inter-pretation of the pain status after the operation. VAS at a given number, for instance VAS=4 might be interpreted as the minimum by one patient and as the average or maximum by the other ones. Although in our study the percentage of patient who by the end of 24 hours after the operation reached to their minimum or less than minimum between the two groups, [78% in the D-cycloserine and 68% in the placebo group], this difference was not statistically significant. Moreover, the percentage of patients with complete postoperative pain relief by the end of 24 hours as 22% and 4.5% in the case and control group. Factors such as total discectomy and complete nerve root release, less inflammatory responses in some patient, individual and genetic varieties in pain level, lesser manipulation of nerve roots in some patients and complete bed rest might explain this level of analgesia in our patients. While the current study demonstrates the efficacy of pre-emptive D-cycloserine to reduce postoperative neuropathic pain, its limitations should also be considered. Our limitation in this study is that the selection of patients was only based on subjective sensation of neuropathic pain in accordance with the clinical and

MRI findings. Although the necessity to perform electrophysiological studies was seldom felt in our patients, these studies help to a better classification of the severity of axonal degeneration, demyelinization or neuropathy. For this reason, we feel electrophysiological studies should have also been considered for the optimal matching of patients between the two study arms. Confounding factors such as personality social support, genetic variations, gender and bio-psychosocial nature of the pain also affect the threshold of pain in patient, which inevitably influence the results of our study, as well. Also, different senior surgeons performed the operations. Although the standard discectomy procedure was performed in all patient, we cannot totally exclude the surgeon's influence on the outcome. The role of the factors on the post discectomy pain has been stressed on, recently. The expression of GCH1 halo-type [frequency: 15.4% in population] has been found to be associated with lesser post discectomy pain. If proven in other researches, it should also be considered as an unchangeable confounding variable in pain studies. It means that, genetic factors may be another limitation of our study! Several factors have been suggested to predict the possible development of chronic postsurgical pain. These include the preoperative severity of pain, acute postoperative pain, the degree of anxiety, irritable bowel syndrome, migraine, fibromyalgia and Reynaud's disease [14]. Of these, acute postoperative pain seems to be the most changeable factor, which has an important role to decrease the possibility of chronic postsurgical pain. Ignored postoperative pain and inadequate pain suppression not only ruins the patient-surgeon relationship but might also increase the possibility of chronic postsurgical pain, which leads to the failed back surgery syndrome [FBSS]. Pre-emptive treatment with single or multimodal therapy has been suggested to decrease postoperative pain. Although opioids are widely used to treat postoperative pain, they are more effective on spontaneous pain and show less efficiency on motion evoked pain and their role in neuronal plasticity and reversing central sensitization process is minimal. In comparison, some other drugs such as NMDA antagonists, tricyclic antidepressants, local anesthetics and COX2 inhibitors have shown promise to control motion evoked pain and to prevent central sensitization [17]. The strength of this study lies in its randomized, double-blind, parallel group and placebo-controlled design. The randomization allowed the groups to be matched in their demographic data and preoperative VAS scores. Therefore, we expected minimal bias in patient selection and the statistical analysis. Although we may have ignored some confounding variables, it is likely that the effect of these variables has been lessened by the randomized nature of the trial. The other strength of the trial was the exclusion of patients during intra-operative and post-operative stages, which helped to maintain the uniformity of two studied groups. The lack of a negative cohort group without any pre-emptive drug prescription is another limitation of our study. The presence of such a group helps to define the role of placebo in such trials. Without this control group, we cannot completely exclude the role of psychological impact of placebo to decrease post-operative VAS scores in an equal manner with a potentially effective drug, such as DCS.

Conclusion

This study suggests that the decision to treat remained neuropathic pain after lumbar discectomies should be taken before the operation. All patients should be warned of the possibility of ongoing pain after the surgery and the need to use analgesics. Drugs such as DCS might help to reduce postoperative remaining leg pain by interrupting central sensitization phenomenon. This may be necessary to break the reverse cycle leading to the development of chronic postsurgical pain, which adversely affects the outcome. DCS is effective to decrease remaining leg pain by the end of 24 hours in post discectomy patients.

Suggestion

We propose the single dose pre-emptive DCS as an approach to reduce post-operative remaining leg pain in patients with single level lumbar discectomy. Future directions would be to compare DCS with other drugs in these patients. Moreover, the studies with functional MRI are needed to exactly evaluate the cerebral changes during the usage of DCS in post discectomy patients in the future years. Finally, patients who receive drugs which are effective on postoperative leg pain during the acute stages after lumbar discectomy, should be evaluated and compared with regard to their long-term outcome.

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