The Role Of NMDA Receptors In Neurophysiology Of Pain And Modulation

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Abstract: Background & Objective**:** NMDA is a receptor for the excitatory neurotransmitter glutamate, which is released with noxious peripheral stimuli. The activation of NMDA receptors has been associated with hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors. Hyperalgesia and neuropathic pain are a result of increased spinal neuron sensitization, leading to a heightened level of pain. The reduced function of opioid receptors is caused by a decrease in the opioid receptor's sensitivity. Therefore, NMDA antagonists have a role in these areas of pain management. Ketamine is a strong NMDA antagonist. To study the role of NMDA receptors in pain and modulation by blocking the receptors through antagonist ketamine given pre-emptively and postoperatively via epidural route in patients of lower limb amputation. Methodology: This study was conducted at Civil Hospital Ahmedabad during the year 2012-2015 with the permission of ethical committee of hospital and after written informed consent of 60 adult patients of age group 18- 60 years of either sex and ASA grade 1 or 2 posted for lower limb amputation. Patients were divided into three groups where one was administered epidural opioid and ketamine, the second group was administered epidural opioid only and in the third group epidural saline was administered. Pain scores of all the groups were compared. Results: Requirement of first dose of analgesia in group 1 is after 12.5±1.03hrs, in group 2 after7.6± 0.98 hrs and in group3 after 3.4± 0.8hrs and average duration between consecutive analgesic doses were 11.5hrs in group 1, 7.6hrs in group 2 and 4.5hrs in group 3 respectively. Conclusion: NMDA receptor antagonist is effective in management of acute post-operative pain compared to opioid analgesics alone as the time to first dose of analgesia is much larger in group 1 than 2 and 3. Ketamine has definitive role in opioid sparing effect as supplemental analgesic requirement is decreased. [Lamoria M NJIRM 2015; 7(1):1-6]

Key Words: NMDA receptor, pain, glutamate, opoid receptor.

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Introduction: The skin, muscle and tendon, periosteum and synovium, heart and blood vessels, and the viscera and the connective tissues capsules that encase them are all innervated by somatosensory primary afferent neurons that are specialized to respond to stimuli that cause, or threaten to cause, tissue injury. These pain sensing afferent neurons, called “nociceptors,” come in two general types, one with slowly conducting unmyelinated axons (C-fiber nociceptors) and the other with thinly myelinated axons (A-delta nociceptors). During inflammation, nociceptors become sensitized, discharge spontaneously, and produce ongoing pain. Prolonged firing of C-fiber nociceptors causes release of glutamate. This glutamate can bind to the NMDA receptor and this binding results in opening of the ion channel portion of the receptor. Channel opening allows an influx of calcium ions. This increase in intracellular calcium ions results in a cascade that results in activation of pain signaling proteins. These calcium-induced changes involve both phosphorylation of receptors, including the NMDA receptor, as well as changes in gene expression. Long-lasting enhancement of synaptic strength (long-term potentiation, LTP) is an ubiquitous phenomenon of synaptic plasticity throughout the central nervous system and is believed to play a major role in learning and memory formation. The perceptual consequence of this use-dependent increase in the excitability of central nociceptive neurons is neurogenic hyperalgesia, i.e. an increase in pain sensitivity caused by the nociceptive input to the spinal cord rather than by tissue damage. If this sensitized state persists, it may contribute to chronic pain. These transcriptional and posttranslational changes can persist well beyond the initial peripheral stimulation and are major elements of a series of persistent changes described as central sensitization.

Central sensitization is considered to be a major contributor to injury-induced persistent hypersensitivity pain and secondary hyperalgesia. It is a major contributor to pain states that involve inflammation and/or nerve injury. Mu (μ) opioid receptor activation by morphine can result in signaling changes that remove a magnesium ion block of the NMDA receptor ion channel. The open NMDA channel allows a calcium influx with consequences that promote the development of tolerance.

Intervening at the NMDA receptor with an antagonist could have two desirable effects. First, it could improve pain management by interfering with the hyperalgesic mechanisms (central sensitization) that result from the activation of the NMDA receptor by injury. Second, by blocking or reversing morphine tolerance, an NMDA

receptor antagonist will have an opioids-sparing effect and improve the efficacy of an opioid that is used to control the pain.

At concentrations within the clinical dose range, ketamine is now known to directly affect a wide range of cellular processes – including blockade of NMDA channels, mu(μ)-opioid agonism and opioid potentiation.

Present study is undertaken to evaluate the role of NMDA receptor antagonist in lower limb amputation with following strategies:

Any additive or synergistic role of N methyl D aspartic acid receptor (NMDA) antagonist in analgesia over traditional opioids.

Whether dose of supplemental analgesic requirement following surgery is reduced or not when NMDA antagonist is given.

To study adverse effects of NMDA antagonist given epidurally.

Material and Methods: This study was conducted at CIVIL HOSPITAL AHMEDABAD during the year 2012-2015 with the permission of ethical committee of hospital and after written informed consent of 60 adult patients of age group 18- 60 years of either sex and ASA grade 1and 2. Patients were posted for lower limb amputation. Patients with systemic diseases like diabetes, hypertension, bleeding disorders, heart diseases and anaemia were excluded from study. 60 patients were randomly allocated in 3 groups (n=20). There were 20 patients in each group.

They were named:
GROUP1
GROUP2
GROUP3

Patient and relatives are fully explained about the surgery and anaesthesia and informed consent taken. Epidural catheter is placed in every patient a day before surgery. Epidural catheter was placed by anesthesiologist in L3/4 space and directed 10 cm in caudal direction under full aseptic precaution. Test dose of Inj. Xylocard 2% 3 ml was given.

Preoperative epidural dose timings:
8:00 PM on the day of catheter placement.
8:00 AM on the day of surgery.

Preoperative epidural drugs:
GROUP 1: Inj. ketamine 0.5mg/kg + Inj. buprenorphine 1μg/kg in 10ml saline
GROUP2: Inj. buprenorphine 1μg/kg in 10ml saline
GROUP3: inj. Normal Saline 10ml

Surgery was done under spinal anesthesia in all 60 patients.

Postoperative data:
After completion of surgery and shifting the patient to post operative ward, patient's vitals, pain status, rescue analgesic requirement, adverse effect of drugs and sedation score were monitored and noted.
Pain was assessed by using VAS score.

Visual Analog Scale:
0: no pain
1-4: mild pain
5-7: moderate pain
8-10: severe pain

At VAS 8 and above epidural dose is given according to group in group 1 and 2 and time is noted. Four such doses are given and duration of analgesia is charted. Duration of analgesia is to be compared in both groups. After 4th epidural dose epidural catheter is removed.

In control group i.e. group 3 pain relief is done using NSAIDS: Inj voveran 75 mg. Time, frequency and dose of drug are noted.

Time and number of doses of rescue analgesia are also noted in first 48 hrs.post operatively. Rescue analgesic doses are given to patients between two subsequent epidural analgesic doses at VAS 5 and above.

Sedation score was noted in all patients:
0: Alert
1: Sometimes drowsy/ easily aroused
2: Often drowsy/ easily drowsed
3: Often drowsy/ difficult to arouse
S: Asleep or stir to touch

Patients were monitored for any adverse effects of epidural drugs:
1.Nausea /vomiting
2.Tachycardia/bradycardia

3.Hypertension/hypotension
4.Ventilator depression
5.Psychosomatic reaction

Results: Table 1: Demographic Data: Age, Sex And Weight Distribution

Group	Age Mean± S.D.	Weight Mean ± S.D.	Sex M:F
Group 1	40.8 ± 16.05	50.45 ± 10.18	15:5
Group 2	37.25 ± 14.97	47.95 ± 7.70	16:4
Group 3	36.65 ± 14.60	50.05 ± 9.37	13:7

The table shows demographic data of patients which were almost comparable in three groups. Most of the patients were male in all groups.

Table 2: Incidence Of Pre Operative Pain In Three Groups

Group	Number Of Patients
Group 1	8 (40%)
Group 2	7(35%)
Group 3	7(35%)

The table shows that the incidence of pre- operative pain is comparable in all three groups.

Table 3: Onset Of Block

Group	Sensory Block	Motor Block
Group 1	7.6 ± 0.88	9.65 ± 0.98
Group 2	6.9 ± 0.85	8.8 ± 0.69
Group 3	6.9 ± 0.64	9.1 ± 0.58

The table shows that onset of sensory and motor analgesia is comparable in all three groups.

Table 4: Time Of First Postoperative Analgesic Requirement

Group	First Dose Requirement (Hrs)
Group 1	12.5±1.03
Group 2	7.6± 0.98
Group 3	3.4±0.8

This table shows requirement of first dose of analgesia and duration of analgesia is maximum in group 1= 12.5±1.03hrs, moderate in group 2= 7.6± 0.98 hrs and minimum in group3= 3.4± 0.8hrs.

Table 5: Duration Of Analgesia Between 4 Epidural Doses In Three Groups

Group	1-2 Dose Hrs	2-3 Dose Hrs	3-4 Dose Hrs	Average Duration (Hrs)
Group 1	12.5±1.6	11.1±1.5	11.5±.7	11.5 HRS
Group 2	7.6±0.9	7.8±0.8	7.4±0.8	7.6 HRS
Group 3	3.9±0.6	4.7±0.6	5±0.6	4.5 HRS

This table shows that duration of analgesia between subsequent analgesia is maximal in group 1, moderate in group2 and minimum in group 3.

Table 6: Average Number Of Rescue Analgesic Doses In 48 Hrs

Group	Average Rescue Analgesic Doses
Group1	0.4 ± 0.68
Group2	1.05 ± 0.75
Group3	5.35 ± 0.93

In this table we can see that average analgesic dose requirement is minimum in group1 and maximum in group 3.

Table 7: Complications Of Epidural Drugs

Group	Nausea/ Vomiting	↓ BP	↑ BP	↑ HR	↓ HR	↓ RR	Psy. React.
Group1	6 (30%)	2(10%)	-	-	-	-	2(10%)
Group2	4 (20%)	4(20%)	-	-	-	-	-
Group3	-	-	-	-	-	-	-

This table shows that incidence of nausea and vomiting and hypotension are comparable in group1 and group2. Psychosomatic reactions are seen only in group1. And no side effects are seen in group3.

Discussion: In normal tissue nociceptors are silent in the absence of tissue injury; when injury occurs, their rate of discharge increases as a function of the amount of tissue damage, i.e., nociceptors signal the occurrence of pain and encode its intensity. In the presence of inflammation, nociceptors acquire new characteristics and are said to be sensitized: (1) They begin to discharge spontaneously. (2) Their threshold for activation is decreased such that normally innocuous stimuli now cause pain (e.g., the pain felt when lightly touching a burn; a phenomenon called allodynia). (3) Their stimulus–response curves are shifted to the left, such that a noxious stimulus causes more pain than normal, a condition called hyperalgesia (e.g., the pain of being slapped on a sunburnt back). The decrease in threshold and the leftward shift of the stimulus–response function underlie the tenderness of an injured region and its immediate surround. Sensitized nociceptors also acquire an excitatory response to norepinephrine; thus, there is a link between pain and sympathetic nervous system discharge. In the case of neuropathic pain, nociceptors also change their characteristics. If their axon has been interrupted, the regenerating sprout may discharge spontaneously and become extremely sensitive to

mechanical, thermal, and ionic stimulation. Unmyelinated (C-fiber) nociceptors release glutamate as their neurotransmitter. The spinal cord neurons that receive input from C-nociceptors express three subtypes of glutaminergic receptor: the N-methyl-D-aspartate (NMDA) subtype, the kainate/AMPA (l-amino- 3-hydroxy-5-methylsoxasole-propionic acid) subtype, and the metabotropic subtype. Glutamate released from C-nociceptors and acting at NMDA receptors evokes a change in the sensitivity of the postsynaptic cell such that it responds more strongly to all of its inputs, an effect called central sensitization. Very recent data suggest that something similar may also be happening via glutamate activation of kainate/AMPA channels, but most of the data in hand implicates the NMDA receptor. Activation of the NMDA receptor causes the spinal cord neuron to become more responsive to all of its inputs, including input from damaged or sensitized nociceptors and input from low-threshold mechanoreceptors ("touch" fibers). The allodynia and hyperalgesia can be reversed by NMDA-receptor blockade.

Dr JA Wilson et al had studied the effect of pre-emptive analgesia with epidural ketamine in lower limb amputation patients in 53 patients. So I selected 60 patients randomly for my study and divided them into 3 groups of 20 patients each. I also chose epidural route for pre-emptive analgesia like their study. I chose buprenorphine for the study due to its long duration of action and high analgesic potency. The dose selected was 1 microgram/kg as recommended dose for epidural analgesia is 1-3 microgram/kg for epidural dose. Dr Takekazu Terai et al[25] (1994) in their study of effect of Lumbar epidural buprenorphine for post-operative pain relief following hepatectomy used buprenorphine in the dose of 0.06mg to 0.12 mg. The dose in this study is comparable to doses used by Dr Takekazu Terai et al[25] (1994) in their study and Dr Veena R Shah et al in their study. As early as 1985 Islas et al. injected a low dose (4 mg diluted in 10 ml 5% dextrose in water) of ketamine epidurally when the effect of lidocaine or bupivacaine had worn off and observed potent postoperative analgesia without respiratory depression or other side effects. However, they were not aware of the concept of pre-emptive analgesia and NMDA receptors at that time. They assumed that the analgesic effect of epidural ketamine was due to lamina specific inhibition of dorsal horn activity, as suggested by Kitahara ET al and interaction as an agonist with opiate receptors as suggested by Kinck and Ngaiet al. In contrast to the above result, a low dose of epidural ketamine, i.e., 4-6 mg did not produce significant analgesic effects in adult patients. Adequate analgesia was obtained in 54% of the patients for 24 hours after a single epidural injection by increasing the dose of ketamine to 30 mg. Although the ability of NMDA receptor antagonists to suppress post injury hyperalgesia associated with peripheral inflammation or nerve damage was known to occur in experimental animals, it was not until 1993 that ketamine was used clinically as a pre-emptive analgesia. Since then several studies have shown pre-emptive analgesic action of ketamine with opioid either given intravenously or epidurally in different dosages.

Dr Veena R Shah et al[19] in their study used ketamine 1mg/kg. Dr C S Wong et al[20] in their study used ketamine 30 mg. Dr Y Y Chia et al[24] used 0.4 mg/kg ketamine, Dr Mohamed Naquib et al studied epidural ketamine for post-operative analgesia 30 mg ketamine. Dr M E Abdel Ghaffar et al[11], studied analgesic effect of epidural ketamine on post – operative pain & epidural PCA consumption after total abdominal hysterectomy with 30 mg ketamine. Dr Xie et al[23] studied, the analgesic effects & pharmacokinetics of a low dose ketamine preoperatively administered epidurally or intravenously with 0.5 mg/kg ketamine. In this study dose of ketamine was selected as 0.5mg/kg. So dose in this study is comparable to all the above studies.

Analgesic dose interval in my study in Group1 11.5hrs, Group2: 7.6hrs and in Group3: 4.5hrs respectively is comparable to study of Dr Veena R Shah et al[19] where duration of analgesia was 13.06hrs with inj. Buprenorphine + ketamine 30 min before skin incision and duration of analgesia in group 2 is comparable to study of Dr Takekazu Terai et al[25] where epidural buprenorphine alone produces 8 hrs analgesia. Time to first dose of analgesia was significantly prolonged in Group 1 compared to Group 2 and Group 3. And time to first dose of analgesia was significantly prolonged in Group 2 compared to Group 3. It shows the positive and additive role of ketamine in prolonging analgesia.

Nausea/ vomiting were noted in both group 1: 6 (30%) and group 2: 4 (20%). Incidence was similar to study of Dr Veena R Shah et al[19] i.e. 20% in patients receiving buprenorphine and ketamine. Psychosomatic reactions were noted only in group 1: 2 (10%). It shows that ketamine is responsible for psychosomatic reactions as proved in the study of Dr Y Y Chia et al[24]. For nausea and vomiting inj. Ondansetron was given and for psychosomatic reactions inj. Midazolam was given.

Hypotension was also noted in both group 1: 2 (10%) and group 2: 4 (20%).

Conclusion: The resistance of certain kinds of pain to opiate analgesia, or tolerance, was generally thought to involve simple receptor downregulation. We now know that the mechanisms of tolerance interact directly with pain sensitivity. Understanding these mechanisms, which include glutamate-mediated activation of NMDA receptors, points to the possibility of improving opiate analgesic therapy with the co-administration of an NMDA-receptor antagonist.

References:

1. Bennett GJ. Neuropathic pain. In: Wall PD, Melzack R, eds. Textbook of pain, 3rd ed. Edinburgh, London: Churchill Livingstone, 1994:201–224.
2. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, eds. Textbook of pain, 3rd ed. Edinburgh, London: Churchill Livingstone, 1994:201–224.
3. Devor M. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R, eds. Textbook of pain, 3rd ed. Edinburgh, London: Churchill Livingstone, 1994:201–224.
4. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–299.
5. LaMotte RH, Shain CN, Simone DA, et al. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66:190– 211.
6. Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK 801 and local nerve anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral mononeuropathy. Brain Res 1992;576:254–262.
7. Chaplan SR, Malmberg AB, Yaksh, TL. Efficacy of spinal NMDA-receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. Pharmacol Exp Therap 1997;280:829–838. 20. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ, Frenk H. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviours in a rat model of peripheral mononeuropathy. Brain Res 1993;605:164–168.
8. Eide PK, Jorum E, Stubhaug A, et al. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994;58:347–354.
9. Max MB, Byas-Smith MG, Gracely RH, et al. Intravenous infusion of the NMDA antagonists, ketamine, in chronic post-traumatic pain and allodynia: a double-blind comparison with alfentanil and placebo. Clin Neuropharmacol 1995;18:360–368.
10. Persson J, Axelsson G, Hallin RG, et al. Beneficial effects of ketamine in a chronic pain state with allodynia, possibly due to central sensitization. Pain 1995;60:217–222. 26. Nelson KA, Park KM, Robinovitz E, et al. Highdose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurol 1997;48:1212–1218. 27. Eisenberg E, Pud D. Can patients with chronic neuropathic pain be cured by acute administration of the NMDA-receptor antagonist amantadine? Pain 1994;74:37–39.
11. Abdel-Ghaffar ME, Abdullatif MA, al Ghamdi A et al. Epidural ketamine reduces postoperative epidural PCA consumption of fentanyl/bupivacaine. Can Anaesth Soc J 1998; 45: 103-09.
12. Eugene S.Fu, Rafael M, John E. Scharf. Pre-emptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997; 84: 1086-90.
13. Islas J-A, Astorga J, Laredo M. Epidural ketamine for control of postoperative pain. Anesth Analg 1985; 64: 1161-62.
14. J. Wilson, A. Nimmo, S. Fleetwood-Walker, L. Colvin. A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain, Volume 135, Issue 1, Pages 108-118
15. Kawana Y, Sato H, Shimada H et al. Epidural ketamine for postoperative pain relief after gynaecological operations: a double-blind study and comparison with epidural morphine. Anesth Analg 1987; 66: 735-38.
16. Kinck AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. Anaesthesiology 1982; 56: 291-97.
17. Kitahara LM, Taub A, Kosaka Y. Lamina-specific suppression of dorsal horn unit activity by ketamine hydrochloride. Anaesthesiology 1973; 38: 4-11.
18. Lanlin JP, Maurette P, Corcuff JB et al. The role of ketamine in preventing fentanyl induced hyperalgesia and subsequent acute morphine tolerance – Anesth Analg 2002; 94: 1263-69

19. Dr.Veena R. Shah, Dr. Raj Rawal, Dr. Manish Pre operative effect of epidural buprenorphine with ketamine on postoperative pain after lower urinary tract surgery Indian, JR. Anaesth 2006;50(4)R:E 271-274
20. Wong CS, Liaw WJ, Tung CS et al. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Regional Anesth. 1996; 21: 534-41.
21. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can Anaesth Soc J 1997; 44: 31-37.
22. Wu CT, Yeh CC, Yu JC, Lee MM, Tao PL, Ho ST, Wong CS. Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. ActaAnaesthesiol Scand. 2000 Jan;44(1):63-8
23. Xie H, Wang X, Liu G, Wang G.Clin J Pain. 2003 Sep-Oct;(5):317-22. Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously.
24. YY Chia, K Liu, YC Liu, HC Chang, and CS Wong Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption Anesth Analg 1998 86: 1245-1249.
25. Takekazu Terai, Hidekazu Yukioka1, Osamu Morimoto1 and Mitsugu Fujimori1. Lumbar epidural buprenorphine for postoperative pain relief following hepatectomy. Journal of Anaesthesia, Springer Japan, Volume 8, Number 4 / December, 1994, 410-414.

Conflict of interest: None
Funding: None
Cite this Article as: Lamoria M, Chaudhuri S, Agarwal G. The Role Of NMDA Receptors In Neurophysiology Of Pain And Modulation. Natl J Integr Res Med 2016; 7(1): 1-6