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The Use of "Burst Ketamin" in Cancer Pain

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Abstract:-

***Background*: Cancer pain is the main focus in the management of cancer patients. It can be developed from tumor invasion, musculoskeletal pain, visceral pain, the effects of radiation treatment, or neuropathy due to chemotherapy. The use of ketamine given primarily by continuous sub-cutaneous infusion (CSCI) has been used in cancer patients with palliative care as an opioid adjuvant with one or more secondary analgesics.**

***Objective*: I reported 3 cases of cancer pain that received intravenous ketamine and the pain improvements were evaluated using Ramsay score.**

***Case*: A 46-year-old woman, presented with complaints of pain in the middle abdomen for 1 year and worsened in 1 week. The pain was dull in nature and felt intermittently throughout the stomach. The patient admitted that pain felt more frequently before she was admitted to the hospital. The patient had a history of morphine treatment for 8 months and had taken morphine 60 mg per day for the last 3 months. The patient received a ketamine dose of 100 mg / 24 hours for 3 days and did not report any complaints of side effects. Pain improvement occurred after 4 days with stable hemodynamics and a Ramsay score score of 0 (zero). The pain reappeared 3 days after the treatment was conducted.**

Male, 70 years old, with Squamous Cell Carcinoma in Right Hemithorax with history of Wide & Deep Excision. Postoperative pain in the right chest was felt for about 2 weeks before hospital admission. The patient had a lump in the chest for 2 years and it get bigger over time. The lump became sore and started to bleed since last year. The patient had a history of morphine treatment for 6 months and had taken morphine 60 mg per day for 2 months. Patients received a ketamine dose of 100 mg / 24 hours for 1 day, a ketamine dose of 300 mg / 24 hours for 3 days, and complained hypersalivation, nausea, and vomiting. Pain improvement occurred after 2 days at a dose of 300 mg / 24 hours and the drug was maintained for 3 days with stable hemodynamics and a Ramsay score of 0 (zero). This patient felt pain persist 2 weeks after the treatment.

52-year-old male was diagnosed with rhabdomiosarcoma on the right femur. Patients experienced right thigh pain for about 2 weeks before admission to the hospital. Initially, the patient complained of a lump on the right thigh since 1 year ago. The lump appeared at the size of a corn kernel and get bigger overtime. History of weight loss was reported. The patient had a history of morphine treatment for approximately 1 year and had taken morphine 60 mg daily for approximately 4 months. Patient received ketamine dose of 100mg / 24 hours in day 1, 300mg / 24 hours in day 2, and 500mg / 24 hours in day 3 to 5 and complained about the side effects, such as nausea, vomiting, hypersalivation, and having nightmares. Pain improvement occurred after 3 days at a dose of 500 mg / 24 hours and the drug was maintained for 3 days with stable hemodynamics and a Ramsay score score of 0 (zero). Another pain attack was felt 4 weeks after the treatment was conducted.

***Discussion*: Ketamine as an opioid adjuvant is generally considered to be effective in good pain control and can reduce opioid dosage. Ketamine provides analgesic, antidepressant, and psychomimetic effects through a variety of routes. The main mechanism is as a noncompetitive antagonist to phencyclidine binding of the N-methyl-D-aspartate (NMDA) receptors located in the central nervous system (CNS), particularly in the prefrontal cortex and hippocampus, which can decrease the frequency of channel opening and the duration of time spent active and open. NMDA receptors are channels with ligand-gated channels that are agonists against major endogens such as glutamate, which is the main excitatory neurotransmitter in the CNS. The results of these case reports are consistent with two other studies which found that ketamine can improve morphine analgesia. In patients with suspected opioid tolerance problems, ketamine may be an alternative.**

***Conclusion*: This report shows that the continuous administration of ketamine provides a good analgetic effect for cancer pain that does not respond to opioids therapy.**

***Keywords*:-** *Cancer Pain, Ketamine, Ramsay Score.*

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I. INTRODUCTION

Cancer is the second leading cause of death in developing countries after heart disease. However, cancer pain is the main focus in the management of cancer patients but only a few cancer patients receive adequate pain treatment. The World Health Organization (WHO) estimates that 70% of patients with terminal stadium of malignancy experience pain. Pain control can be achieved by following WHO analgesic ladder recommendations.(Schug, Zech and Dörr, 1990; World Health Organization, 1990) However, refractory pain may occur in 20% of patients, especially in neuropathic pain due to nerve damage or pain associated with multiple bone metastases.(Chaudhary et al., 2012)

Cancer pain can be developed from tumor invasion, musculoskeletal pain, visceral pain, the effects of radiation treatment, or neuropathy due to chemotherapy. Nonetheless, uncontrolled pain can affect every aspect of a patient's quality of life, causing distress, sleep disturbances, reduced physical and social activity, anorexia, and mood disorders.(Wang et al., 1999)

Refractory cancer pain was defined as persistent pain associated with cancer, occured at least 3 months, that did not respond to standard opioid therapy and co-analgesics. (Currow, Spruyt and Hardy, 2012) This type of pain is difficult to control and has been reported to occur in 10-20% of cancer patients.(Hardy et al., 2012) This can occur especially in patients with neuropathic pain due to nerve damage by tumors with multiple bone metastases.(Bruera et al., 1995)

Studies have reported that the N-methyl-D-Aspartate (NMDA) receptor has an important role in refractory pain, with evidence found for NMDA receptors at the level of the substantia gelatinosa of the spinal cord.(Dickenson, 1995) Sustained nociceptive effect ultimately results in activation of the NMDA receptor, which is clinically associated with increased pain, extended pain area, and presented as unresponsive to opioid therapy.(Dickenson, 1995; Woolf, 1995) Therefore, in 1990, Oshima reported the first-ever continuous subcutaneous use of ketamine as a treatment for refractory cancer pain and showed effective results in reducing cancer pain in 13 of the 18 patients studied.(Oshima et al., 1990)

The use of ketamine given primarily by continuous sub-cutaneous infusion (CSCI) has been used in cancer patients with palliative care as an opioid adjuvant with one or more secondary analgesics. Other reports on the role of ketamine in improving refractory cancer pain management have also been widely published in the form of case reports or retrospective series on patients with dominant neuropathic pain.(Bell, 1999; Cherry et al., 1995; Luczak, Dickenson and Kotlinska-Lemieszek, 1995; Mercadante, 1996; Oshima et al., 1990)

According to Lossignol et. al. (1999), 15 patients with refractory cancer pain who were given a combination of ketamine with an initial dose of 1.5 mg / kg / 24 hours and morphine experienced a long-lasting decrease in pain scores. This study reported that 10 patients were discharged from hospital with a continuous infusion of ketamine via a portable syringe pump, while 5 patients continued to undergo treatment for at least 6 months with increasing doses during the progression of the disease.(Lossignol, Obiols and Body, 1999)

The method of administrating ketamine in a way not previously reported, such as subcutaneous or intravenous infusion for 3 to 5 days, depending on the response, then discontinued is called burst ketamine. This method was designed to test the possibility of tapering the dose with the hypothesis if minimal dose was administrated, analgesic effect would achieved and persisted after ketamine administration was stopped.(Ashby et al., 1999; Jackson et al., 1999)

II. CASE REPORT

A 46-year-old woman, presented with complaints of pain in the middle abdomen for 1 year and worsened in 1 week. The pain was dull in nature and felt intermittently throughout the stomach. The patient admitted that pain felt more frequently before she was admitted to the hospital. The patient had a history of morphine treatment for 8 months and had taken morphine 60 mg per day for the last 3 months. The patient received a ketamine dose of 100 mg / 24 hours for 3 days and did not report any complaints of side effects. Pain improvement occurred after 4 days with stable hemodynamics and a Ramsay score score of 0 (zero). The pain reappeared 3 days after the treatment was conducted.

Male, 70 years old, with Squamous Cell Carcinoma in Right Hemithorax with history of Wide & Deep Excision. Postoperative pain in the right chest was felt for about 2 weeks before hospital admission. The patient had a lump in the chest for 2 years and it get bigger over time. The lump became sore and started to bleed since last year. The patient had a history of morphine treatment for 6 months and had taken morphine 60 mg per day for 2 months. Patients received a ketamine dose of 100 mg / 24 hours for 1 day, a ketamine dose of 300 mg / 24 hours for 3 days, and complained hypersalivation, nausea, and vomiting. Pain improvement occurred after 2 days at a dose of 300 mg / 24 hours and the drug was maintained for 3 days with stable hemodynamics and a Ramsay score of 0 (zero). This patient felt pain persist 2 weeks after the treatment.

52-year-old male was diagnosed with rhabdomiosarcoma on the right femur. Patients experienced right thigh pain for about 2 weeks before admission to the hospital. Initially, the patient complained of a lump on the right thigh since 1 year ago. The lump appeared at the size of a corn kernel and get bigger overtime. History of weight loss was reported. The patient had a history of morphine treatment for approximately 1 year and had taken morphine 60 mg daily for approximately 4 months. Patient received ketamine dose of 100mg / 24 hours in day 1, 300mg / 24 hours in day 2, and 500mg / 24 hours in day 3 to 5 and complained about the side effects, such as nausea, vomiting, hypersalivation,

and having nightmares. Pain improvement occurred after 3 days at a dose of 500 mg / 24 hours and the drug was maintained for 3 days with stable hemodynamics and a Ramsay score score of 0 (zero). Another pain attack was felt 4 weeks after the treatment was conducted.

III. DISCUSSION

Ketamine as an opioid adjuvant is generally considered effective in pain control and can reduce opioid dosage. (Subramaniam, Subramaniam and Steinbrook, 2004) Several RCT studies and systematic reviews have reported the effectiveness of ketamine in the management of cancer pain.(Blonk et al., 2010)

Ketamine provides analgesic, antidepressant, and psychomimetic effects through variety of routes. The main mechanism is ketamine acts a noncompetitive antagonist to phencyclidine binding of the N-methyl-D-aspartate (NMDA) receptors located in the central nervous system (CNS), particularly in the prefrontal cortex and hippocampus.(Cohen et al., 2011) It decrease the frequency of channel opening and the duration of time spent active and open.(Orser, Pennefather and MacDonald, 1997) N-methyl-D-aspartate receptors are ligand-gated channels that binds with glutamate, which is the main excitatory neurotransmitter in the CNS. Nervous system activity is decreased when these receptors are inhibited. The activation of NMDA channels plays a major role in consciousness, chronic pain, opioid tolerance, and mood. It is also considered as a major receptor involved in central sensitization and wind up phenomena.(Chang et al., 2015; Cohen et al., 2011; Duman et al., 2012)

The result of this case report is consistent with two other studies that showed that ketamine can improve morphine analgesic effect. Ketamine as an NMDA receptor antagonist is believed to play a role in inhibiting opioid tolerance. Ketamine in a mouse-trial study has shown to prevent fentanyl-induced hyperalgesia and acute morphine tolerance. Opioid tolerance can develop early, but it is not clear how often this can cause clinical problems in cancer patients. In patients with suspected opioid tolerance, ketamine may be an alternative option.(Laulin et al., 2002)

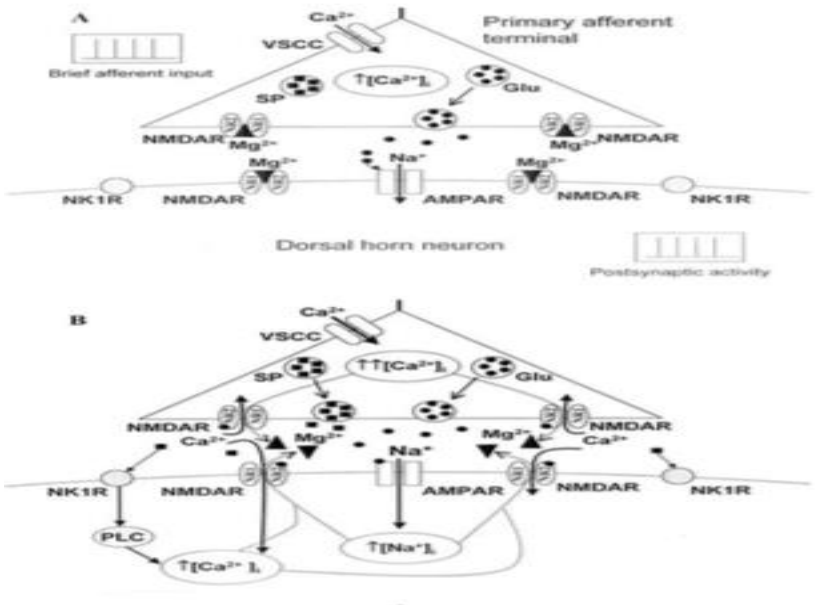

Figure 4. Schematic Illustration of the Role of NMDARs.(Petrenko et al., 2003)

Glutamate is released from afferent neurons in response to acute and persistent noxious stimulation. The rapid activation of AMPA receptors is responsible for the initial stimulation of noxious and tactile stimulation at the spinal dorsal horn level. However, if the stimulation of C-fibers is repeated with high frequency, the neurons at dorsal horn level will show enhanced and extended responses to the next stimulation, which is called *wind-up* effect.(Dickenson and Sullivan, 1987) This enhanced activity resulted from NMDA receptor activity. Acute and noxious stimulation of the spinal cord cannot activate the NMDA receptor. Physiologically, the receptor ion channels are blocked by magnesium ion (Mg2 +) present in the nervous tissue. This unique blockage of Mg2 + channels requires continuous membrane depolarization to be released and allows NMDA receptor channels to be activated and opened. The co-release of peptidergic transmitters, such as substances P and CGRP, which are found in C-fibers along with glutamate, are responsible for the prolonged slow depolarization of neurons and NMDA.(Seagrove, Suzuki and Dickenson, 2004; Stanfa and Dickenson, 1999) The activation of NMDA receptor has been shown to play a key role in hyperalgesia and increased pain signaling in persistent pain conditions, including inflammatory and neuropathic pain.(Price et al., 1994; Sindrup and Jensen, 1999)

According to research conducted by Jakson on 39 refractory cancer pain patients who were given burst ketamine, the method (3-5 days) had a significant effect on refractory cancer pain; 24 out of 29 patients had good pain control in 8 weeks and 5 out of 29 patients experienced

recurrent pain within 24 hours. Meanwhile 12 patients was reported having psychomimetic side effects and these complaints got worse when the dose was increased.(Jackson et al., 2001)

The number of randomized controlled studies using ketamine for cancer pain has been published in the literature. Most of the studies are small studies or in the form of case reports. Several studies have shown the benefits of using oral or parenteral ketamine for chronic cancer pain. In contrast, some of these studies have failed to demonstrate a benefit from using ketamine in these conditions. Other randomized controlled studies are needed to evaluate all types of cancer, as well as the benefits and side effects of ketamine in the management of chronic neoplacic pain. Dose-dependent analgesic effect of ketamine may be resulted from different mechanism of actions. The oral dose given varies significantly from one patient to another.(Rana et al., 2011)

Ketamine is an effective drug to treat patients with severe pain that no longer respond to conventional treatment or untreated pain, excluding patients with chronic cancer pain. Ketamine should be used with caution if other treatment options are not effective. Thus, clinicians are prompted to weigh the potential risks and benefits of ketamine administration to the patient. (Zgaia et al., 2015)

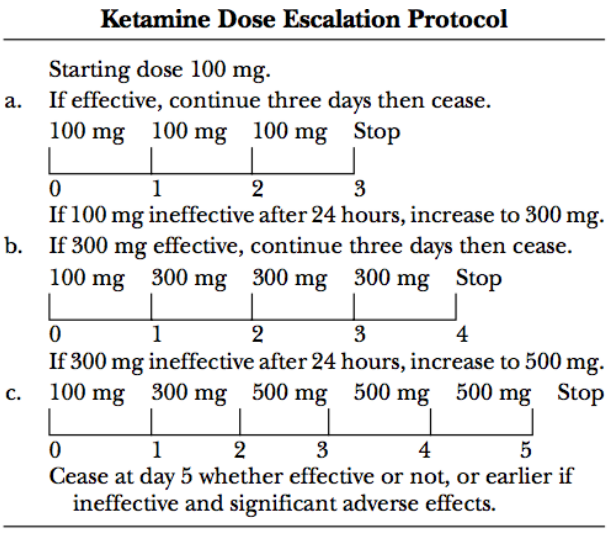

Figure 5. Ketamine doosis protocol in ketamine burst

The most commonly reported side effect of ketamine is psychotomimetics (hallucinations, agitation, anxiety, dysphoria, and euphoria). Ketamine administration can also cause dizziness, nausea, sedation, and tachycardia. Ketamine side effects are dose dependent. At low doses, ketamine acts as an NMDA receptor antagonist, providing an analgesic effect. However, at higher doses, ketamine acts on other receptors and channels including dopamine D2 receptors, monoaminergic receptors, and opioid receptors. Ketamine inhibits monoamine transporter, and is thought to be one of the mechanisms behind psychotomimetic side effects. Chronic ketamine abuse is also associated with a variety of side effects (Figure 6).(Bell and Kalso, 2018)

Adverse effects of ketamine, other than psychotomimetic, reported in cancer/palliative care pain management.

Adverse effect	Authors	Comment
Neurotoxicity (subpial vacuolar myelopathy)	Karpinski et al., 1997[20]	Intrathecal ketamine with preservative (benzethonium chloride) 5 mg/d
Neurotoxicity (focal lymphocytic vasculitis in medullary tissue, nerves, and leptomeninges of the thoracic and lumbar spinal cord)	Stotz et al., 1999[48]	Intrathecal ketamine with preservative (benzethonium chloride), mean dose 67.2 mg/d
Neurotoxicity (severe histological abnormalities: central chromatolysis, nerve cell shrinkage, neuronophagia, microglial upregulation, and gliosis)	Vranken et al., 2005[54]	Intrathecal preservative-free S(+) ketamine 20–50 mg/d
Generalized hyperalgesia and allodynia	Mitchell, 1999[34]	After abrupt cessation of 3-wk subcutaneous infusion 200 mg/24 h.
Urotoxicity	Storr et al., 2009[47]	Oral administration 50–170 mg × 4. 3 cases
Needle site irritation	Mitchell, 1999[34]; and Oshima et al., 1990[40]	Subcutaneous infusion 60–360 mg/24 hrs; and subcutaneous infusion 200 mg/24 h
Angina	Ward et al., 2003[56]	Subcutaneous infusion of ketamine 150 mg/24 h

Figure 6. Studies reporting ketamine side effects in cancer pain management

IV. CONCLUSION

This report shows that the continuous administration of ketamine provides a good analgetic effect for cancer pain that does not respond to opioids therapy. However, side effects were found in the form of nausea, vomiting, hypersalivation, and nightmares after continuous ketamine administration during the follow-up period and depending on the dose given. Other side effects such as hallucinations, hypertension, heart problems, increased ICP, seizures, visual disturbances, and altered mental status were not found in this case.

REFERENCES

[1]. Ashby, M., Jackson, K., Martin, P. and White, M. (1999) 'The incidence of adverse effects with the use of "burst" ketamine: a prospective audit.', 9th World Congress on Pain. Vienna.
[2]. Bell, RF (1999) 'Low-dose subcutaneous ketamine infusion and morphine tolerance', Pain, 83 (1) Pain, pp. 101–103. Available at: 10.1016 / S0304-3959 (99) 00096-2 (Accessed: 22 December 2020).
[3]. Bell, RF and Kalso, EA (2018) 'Ketamine for pain management' Available at: 10.1097 / PR9.0000000000000674 (Accessed: 23 December 2020).
[4]. Blonk, MI, Koder, BG, Bemt, PMLA va. den and Huygen, FJPM (2010) 'Use of oral ketamine in chronic pain management: A review', European Journal of Pain, 14, pp. 466–472.
[5]. Bruera, E., Schoeller, T., Wenk, R., MacEachern, T., Marcelino, S., Hanson, J. and Suarez-Almazor, M. (1995) 'A prospective multicenter assessment of the Edmonton staging system for cancer pain ', Journal of Pain and Symptom Management, 10 (5) J Pain Symptom Manage, pp. 348–355. Available at: 10.1016 / 0885-3924 (95) 00052-Z (Accessed: 22 December 2020).
[6]. Chang, CH, Hsiao, YH, Chen, YW, Yu, YJ and Gean, PW (2015) 'Social isolation-induced increase in NMDA receptors in the hippocampus exacerbates emotional dysregulation in mice', Hippocampus, 25 (4) John Wiley and Sons Inc., pp. 474–485. Available at: 10.1002 / hipo.22384 (Accessed: 23 December 2020).
[7]. Chaudhary, W., Kennett, J., Bano, I. and William, D. (2012) 'Ketamine as an adjuvant to opioids for cancer pain management', Anaesth Pain & Intensive Care, 16 (1), pp. 174–8.
[8]. Cherry, DA, Plummer, JL, Gourlay, GK, Coates, KR and Odgers, CL (1995) 'Ketamine as an adjunct to morphine in the treatment of pain', Pain, 62 (1) Pain, pp. 119–121. Available at: 10.1016 / 0304-3959 (95) 00010-P (Accessed: 22 December 2020).
[9]. Cohen, SP, Liao, W., Gupta, A. and Plunkett, A. (2011) 'Ketamine in pain management', Advances in Psychosomatic Medicine, 30 Adv Psychosom Med, pp. 139–161. Available at: 10.1159 / 000324071 (Accessed: 23 December 2020).
[10]. Currow, DC, Spruyt, O. and Hardy, J. (2012) Defining refractory pain in cancer for clinicians and researchers Journal of Palliative Medicine. J Palliat Med, Available at: 10.1089 / jpm.2011.0326 (Accessed: 22 December 2020).
[11]. Dickenson, AH (1995) 'Spinal cord pharmacology of pain', British Journal of Anesthesia, 75 (2) Oxford University Press, pp. 193–200. Available at: 10.1093 / bja / 75.2.193 (Accessed: 22 December 2020).
[12]. Dickenson, AH and Sullivan, AF (1987) 'Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following c fiber stimulation.', Neuropharmacology, 26 (8) Neuropharmacology, pp. 1235–1238. Available at: 10.1016 / 0028-3908 (87) 90275-9 (Accessed: 23 December 2020).
[13]. Duman, RS, Li, N., Liu, RJ, Duric, V. and Aghajanian, G. (2012) 'Signaling pathways underlying the rapid antidepressant actions of ketamine', Neuropharmacology. Neuropharmacology, Vol. 62, pp. 35–41. Available at: 10.1016 / j.neuropharm.2011.08.044 (Accessed: 23 December 2020).
[14]. Hardy, J., Quinn, S., Fazekas, B., Plummer, J., Eckermann, S., Agar, M., Spruyt, O., Rowett, D. and Currow, DC (2012) 'Randomized, double -blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain ', Journal of Clinical Oncology, 30 (29) J Clin Oncol, pp. 3611–3617. Available at: 10.1200 / JCO.2012.42.1081 (Accessed: 22 December 2020).
[15]. Jackson, K., Ashby, M., Martin, P., Pisasale, M., Brumley, D. and Hayes, B. (2001) 'Burst' ketamine for refractory cancer pain: An open-label audit of 39 patients ', Journal of Pain and Symptom Management, 22 (4) J Pain Symptom Manage, pp. 834–842. Available at: 10.1016 / S0885-3924 (01) 00340-2 (Accessed: 23 December 2020).
[16]. Jackson, L., Ashby, M., Martin, P. and White, M. (1999) 'Can "burst" ketamine wind down wind-up ?: A prospective audit', 9th World Congress on Pain. Vienna.
[17]. Laulin, JP, Maurette, P., Corcuff, JB, Rivat, C., Chauvin, M. and Simonnet, G. (2002) 'The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance', Anesthesia and Analgesia, 94 (5) Lippincott Williams and Wilkins, pp. 1263–1269. Available at: 10.1097 / 00000539-200205000-00040 (Accessed: 23 December 2020).
[18]. Lossignol, D., Obiols, M. and Body, J. (1999) 'Ketamine and morphine in cancer pain [abstract]', 9th World Congress on Pain. Vienna: International Association for the Study of Pain.
[19]. Luczak, J., Dickenson, AH and Kotlinska-Lemieszek, A. (1995) 'The Role of Ketamine, an NMDA Receptor Antagonist, in the Management of Pain', Progress in Palliative Care, 3 (4) Informa UK Limited, pp. . 127–134. Available at: 10.1080 / 09699260.1995.11746707 (Accessed: 22 December 2020).
[20]. Mercadante, S. (1996) 'Ketamine in cancer pain: An update', Palliative Medicine, 10 (3) Palliat Med, pp. 225–230. Available at: https://pubmed.ncbi.nlm.nih.gov/8817593/ (Accessed: 22 December 2020).
[21]. Orser, BA, Pennefather, PS and MacDonald, JF (1997) 'Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors', Anesthesiology, 86 (4) Anesthesiology, pp. 903–917. Available at: 10.1097 / 00000542-199704000-00021 (Accessed: 23 December 2020).
[22]. Oshima, E., Tei, K., Kayazawa, H. and Urabe, N. (1990) Continuous subcutaneous injection of ketamine for cancer pain Canadian Journal of Anesthesia. Can J Anaesth, Available at: 10.1007 / BF03005598

(Accessed: 22 December 2020).
[23]. Petrenko, AB, Yamakura, T., Baba, H. and Shimoji, K. (2003) 'The Role of N-Methyl-d-Aspartate (NMDA) Receptors in Pain: A Review', Anesthesia & Analgesia, 97 (4) Lippincott Williams and Wilkins, pp. 1108–1116. Available at: 10.1213 / 01.ANE.0000081061.12235.55 (Accessed: 23 December 2020).
[24]. Price, DD, Mao, J., Frenk, H. and Mayer, DJ (1994) 'The N-methyl-d-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man', Pain, 59 (2) Pain , pp. 165–174. Available at: 10.1016 / 0304-3959 (94) 90069-8 (Accessed: 23 December 2020).
[25]. Rana, SPS, Ahmed, A., Kumar, V., Chaudhary, PK, Khurana, D. and Mishra, S. (2011) 'Successful management of a difficult cancer pain patient by appropriate adjuvant and morphine titration', Indian Journal of Palliative Care, 17 (2) Wolters Kluwer - Medknow Publications, pp. 162–165. Available at: 10.4103 / 0973-1075.84541 (Accessed: 23 December 2020).
[26]. Schug, SA, Zech, D. and Dörr, U. (1990) 'Cancer pain management according to WHO analgesic guidelines', Journal of Pain and Symptom Management, 5 (1) J Pain Symptom Manage, pp. 27–32. Available at: 10.1016 / S0885-3924 (05) 80006-5 (Accessed: 22 December 2020).
[27]. Seagrove, LC, Suzuki, R. and Dickenson, AH (2004) 'Electrophysiological characterisations of rat lamina I dorsal horn neurones and the involvement of excitatory amino acid receptors', Pain, 108 (1–2) Elsevier, pp. 76–87.
[28]. Sindrup, SH and Jensen, TS (1999) Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to the mechanism of drug action Pain. Pain, Available at: 10.1016 / S0304-3959 (99) 00154-2 (Accessed: 23 December 2020).
[29]. Stanfa, LC and Dickenson, AH (1999) 'The role of non-N-methyl-D-aspartate ionotropic glutamate receptors in the spinal transmission of nociception in normal animals and animals with carrageenan inflammation', Neuroscience, 93 (4) Pergamon, pp. 1391–1398.
[30]. Subramaniam, K., Subramaniam, B. and Steinbrook, RA (2004) 'Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review', Anesthesia & Analgesia, 99 (2) Lippincott Williams and Wilkins, pp. 482–495. Available at: 10.1213 / 01.ANE.0000118109.12855.07 (Accessed: 23 December 2020).
[31]. Wang, XS, Cleeland, CS, Mendoza, TR, Engstrom, MC, Liu, S., Xu, G., Hao, X., Wang, Y. and Ren, XS (1999) 'The effects of pain severity on health -related quality of life ', Cancer, 86 (9) John Wiley & Sons, Ltd, pp. 1848–1855. Available at: 10.1002 / (SICI) 1097-0142 (19991101) 86: 9 <1848 :: AID-CNCR29> 3.0.CO; 2-M (Accessed: 22 December 2020).
[32]. Woolf, CJ (1995) 'Somatic pain: Pathogenesis and prevention', British Journal of Anesthesia, 75 (2) Oxford University Press, pp. 169–176. Available at: 10.1093 / bja / 75.2.169 (Accessed: 22 December 2020).
[33]. World Health Organization (1990) 'Cancer pain relief and palliative care: report of a WHO expert committee', Geneva: WHO.
[34]. Zgaia, AO, Irimie, A., Sandesc, D., Vlad, C., Lisencu, C., Rogobete, A. and Achimas-Cadariu, P. (2015) The role of Ketamine in the treatment of chronic cancer pain Clujul Medical. Universitatea de Medicina si Farmacie Iuliu Hatieganu, Available at: 10.15386 / cjmed-500 (Accessed: 23 December 2020).