CASE SERIES

Ketamine as an adjuvant to opioids for cancer pain management

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ABSTRACT

The management of cancer patient's pain with ketamine as an adjuvant to opioids is presented in case reports of three patients with cancer-related neuropathic pain, in which pain proved untreatable with the usual conventional pain therapies. Ketamine was administered either by intrathecal or oral route, in addition to morphine and the pain was controlled successfully in these patients. No untoward side-effects were noted except drowsiness which responded to a reduction in the opioids dose.

Key Words: Oncology; Neuropathic pain; WHO analgesic ladder; NMDA receptor; Psychotomimetic side effects; Adenocarcinoma; Palliative care

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INTRODUCTION

Cancer is the second leading cause of death in developing countries after heart diseases and cancer pain relief is the leading concern for the patients suffering from cancer and their physicians[1].The incidence of cancer worldwide is 6–7 million patients per year, with half or more occurring in developing countries. Statistics show that approximately 4.5 million patients die from cancer each year, and 3.5 million suffer from cancer pain daily. Despite of the fact, only a limited number of cancer patients are receiving adequate pain treatment[2].

The prevalence of pain in early disease is 50%, in advanced disease 75% and in cancer survivors is around 33%. Cancer pain can develop from tumor invasion, musculoskeletal pain, visceral pain, radiation treatment effects, or neuropathy from chemotherapy[2]. No matter its source, uncontrolled pain can affect every aspect of a patient's quality of life, causing suffering, sleep disturbances, reduced physical and social activity, anorexia and mood disorder[3]. The deaths due to cancer and associated pain are alarmingly at 28%, despite the availability of oncologists, pain management and palliative care teams[4].

Studies have shown that approximately 30–50% of all cancer patients experience pain, and out of them, 75–90% experience substantial life-altering cancer-induced pain[1]. Although cancer patients are surviving for significantly longer periods than in the past due to advancement in detection and treatment of cancer, however, the quality of life of these patients is frequently diminished and pain associated with cancer plays a main role in this decline of life quality[3]. While physicians and oncologists are responsible for prolonging survival and nurses and counselors for optimizing comfort, the pain specialists have a major role to play in improving quality of cancer patients by relieving pain[5].

Although cancer pain can be relieved in 80 to 90% of patients with WHO analgesic ladder approach, however in some pain syndromes there is an unfavorable response to conventional therapy[6]. Pain that is not readily responsive to opioids is often problematic and a challenge for physicians[4]. Therefore, a comprehensive treatment plan is essential to control the pain especially in case of resistant pain. Sometimes

invasive pain therapy is needed to manage cancer pain. The N-methyl-D-aspartate (NMDA)-receptor system has been shown to play an important role in these conditions[7]. According to the developing theory of neuroplasticity, "Agents that block the activity of NMDA receptors may provide new tools for the treatment of opioid poorly responsive pain syndromes, particularly neuropathic ones".

Ketamine is a NMDA (N-methyl-D-aspartate) receptor antagonist that modifies nociceptive pain pathways by acting in the medial thalamic nuclei and dorsal horn of the spinal cord. Hyperactivity and over-stimulation of NMDA receptors contribute to neuropathic pain, tolerance to opioids, hyperalgesia and allodynia[8].

Ketamine is licensed to be used as a general anaesthetic; however it is used beyond licence for the treatment of neuropathic pain and hyperalgesia[7]. It is often used with the aim of reversing the state of tolerance and/or hyperalgesia associated with prolonged use of opioids rather than as a direct analgesic. According to several studies, opioid dosage can be reduced significantly while maintaining the same level of analgesia by using ketamine as an adjuvant to therapy[8].

CASE REPORT 1

61 years old male presented to Pain Clinic for the relief of pain associated with urethral carcinoma and metastasis. His pain was not controlled despite numerous drug regimens including standard opioids. Patient complained of intense episodes of lancinating and burning pain in right leg. This patient was on opioids for 3months with some benefits and reported constipation, itching and sedation therefore, alternative analgesic options were warranted. We administered initially ketamine at 7.5mg/day which resulted in Immediate and dramatic reduction in pain. Lancinating pain was completely abolished within hours, however patient still complained of low level continuous burning pain. A Pump for IT infusion was inserted and pain relief remained satisfactory over 10 weeks. We administered a constant IT dose of S-ketamine at 22.5mg/day in combination with morphine. There were no Psychotomimetic drug related side-effects observed during the course of therapy. This patient received 3 months IT S-ketamine before death.

CASE REPORT 2

A 64 year old male with metastatic squamous cell carcinoma presented to the pain clinic for uncontrolled severe pain despite various conventional pain therapies including standard opioids. His pain scores were 7-8/10 on the Numerical Rating Scale and he was not using morphine effectively as he was feeling very nauseous and had significant pruritis overnight. Test dose of ketamine 15mg was given SC after evaluation that showed temporary improvement in pain scale. This patient then admitted to the ward and administered CSCI Ketamine (40-400mg) over 24 hours that demonstrated good pain control. Ketamine was given in combination with hydromorphone and midazolam. Later on shortage of IV ketamine necessitated oral administration (50mg TDS) i.e. ~37.5% stable parentral dose. The dose was increased as necessary to maximum (75mg TDS PO) that resulted in good pain relief. We continued ketamine (75mg TDS PO) until the patient was no longer able to tolerate oral medication. Oral ketamine was then switched to CSCI (300mg) over 24 hours until patients' death.

CASE REPORT 3

A 57 year old female in A&E with severe pain due to adenocarcinoma of the colon and bone metastasis was evaluated by Pain Management Team. She was on sustained-release morphine, the dose of which was eventually increased to 1,200 mg total per day (over a 3-month period). The sustained-release morphine was supplemented with immediate-release morphine solution (600 mg) up to four times per day for breakthrough pain. Approximately 3 weeks before, she was gradually switched to fentanyl patches (Duragesic patch) with continued use of oral morphine solution for breakthrough pain. The decision by her local care team to switch to fentanyl was presumably due to inadequate analgesia combined with increasing opioid side effects, especially constipation, itching and sedation. Over the 3-week period, her pain continued to worsen, despite increasing numbers of fentanyl patches. At our initial evaluation, the patient was using a total of 20 100-μg/h (2,000 μg/h total) fentanyl patches at a time. The patches were being changed every 3 days, and the large number of them required placement over her chest, abdomen, back, and portions of all four extremities. Her pain remained uncontrolled despite escalating doses of opioids, fentanyl patches and other supplemental therapies. After evaluation IV, ketamine infusion at 0.2 mg/kg/hr was started, and then slowly titrated to 0.3-0.4 mg/kg/hr over next 4 hours. Later on ketamine was used in conjunction with morphine by PCA, which gave her a good pain control. On admission to palliative care, IV Ketamine was changed to oral Ketamine at dose of 54 mg over 24 hours and her pain was controlled with a reduction in use of breakthrough medications. Over next month Ketamine was titrated to 30mg TDS PO till her death.

DISCUSSION

As an adjunct to opioids, ketamine is generally thought to be effective with good pain control and often enabling a reduction in opioid doses. Dose of concomitant opioids can often be reduced and in some studies a dose reduction is advised as ketamine is initiated.[7] Several RCTs and systematic reviews have been identified looking at the efficacy of ketamine in cancer pain. The number of published studies, specifically RCTs and clinical audits has risen steadily over the past few years. Some trials reported improvement in analgesia using ketamine as an adjuvant to opioids, whereas others failed to find any significant outcome. Cochrane Systematic Reviews from 2003 to 2011 suggested that ketamine as adjuvant to opioids for cancer pain is effective with good pain control and often enabling a reduction in opioid doses.[8]

The bioavailability of ketamine varies with the route of administration. Following oral administration, the bioavailability of ketamine is only ~ 15-20% due to high first pass metabolism and which may lead to the assumption that oral ketamine does not have the analgesic potency of parenteral ketamine[9]. However, following oral administration, ketamine is metabolised largely to an active metabolite norketamine which has a suggested analgesic potency ~1/3rd that of ketamine. Norketamine levels after oral ketamine are 2-3x greater than those after parenteral ketamine. The peak analgesic effect of oral ketamine corresponds with the peak serum levels of norketamine not ketamine and suggests that norketamine contributes significantly to the analgesic effect of oral ketamine[10]. This has led some authors to suggest that for patients stabilised on parenteral ketamine (with stable serum levels of ketamine and norketamine) starting with an oral dose of ketamine 1/3rd of the parenteral dose should maintain existing serum norketamine levels and be an effective dose[9]. Other studies have reported however, that if this practice is followed, upward quite rapid titration of the oral dose is required to maintain effective analgesia. Some authors suggest an effective oral dose to be ~5x the parenteral dose (based on oral bioavailability of ~20%).

Onset of analgesia varies depending on the route of administration of ketamine. Onset is within minutes when administered by the SC or IV routes, ~10-15 minutes following IM administration and ~30 minutes following oral administration[8].

Administered rectally, peak plasma concentrations of ketamine are reached after ~45 minutes although there is wide variation reported in studies. Plasma concentrations of norketamine are higher than those of ketamine although first pass metabolism appears to be less when compared with oral analgesia.

Oral ketamine has been suggested to have a more favourable side-effect profile than parenteral ketamine because of the high first pass metabolism and reduced maximum serum concentration of ketamine[10]. It is suggested that analgesia from ketamine is associated with a plasma concentration of 150nanogram/ml following parenteral administration but only 40nanogram/ml following oral administration. Norketamine is suggested to exert less psychotomimetic side effects than ketamine. However, significant adverse effects with oral ketamine are reported in some studies particularly at higher doses[11].

Ketamine is often used with the aim of reversing the state of tolerance and/or hyperalgesia associated with prolonged use of opioids rather than as a direct analgesic[12]. Many case reports suggest it is possible to reduce the opioid dose significantly while maintaining the same level of analgesia[11]. Some authors advise routine reduction in the opioid dose at the time of commencing ketamine treatment to minimise adverse effects such as sedation[9].

Ketamine exerts a high incidence of psychotomimetic side effects (e.g. drowsiness, alterations in body image and mood, floating sensations, vivid dreams, hallucinations and delirium)[13]. Consider starting with lower doses of ketamine and increase gradually as tolerated[10]. Consider reduction in concomitant opioid dose. Consider the use of benzodiazepines or haloperidol to minimise these adverse effects. Use of benzodiazepines or haloperidol may only be necessary on a short temporary basis[14].

CSCI of ketamine can cause significant irritation at the injection site. The use of ketamine can cause urinary tract symptoms e.g. frequency, urgency, urge incontinence, dysuria and haematuria. The causal agent has not been determined but direct irritation by ketamine and/or its metabolites is a possibility[15].

ALTERNATIVE MANAGEMENT:

A variety of modalities can be used to treat cancer pain and hence to increase the quality of life of cancer patients. Interventional treatment is warranted, if the pain persists despite escalating dosage of opioids and adjuvant therapy[2]. Interventional approaches do work and many authors propose the addition of interventional strategies as fourth step to the WHO analgesic ladder, which is known as modified WHO analgesic ladder [6].

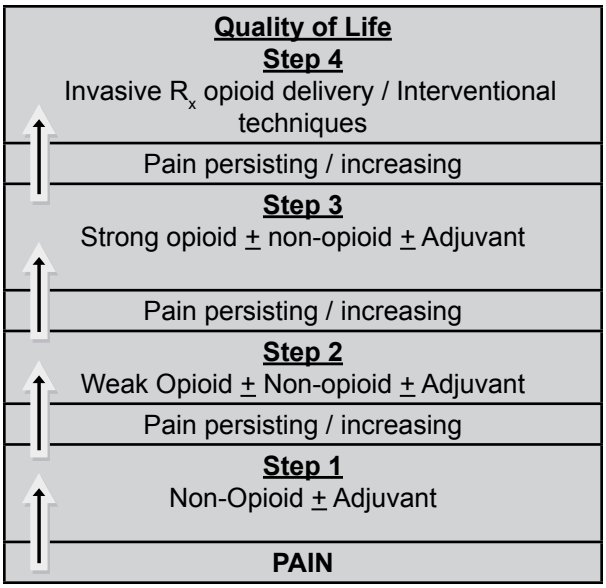

Fig 1: Modified WHO analgesic ladder for cancer pain, including interventional management. Adapted from Miguel.

Neural blockade (Table 1), opioids infusion therapy (Table 2), local anaesthesia with neuro-axial or peripheral nerves are the modalities that can be used for uncontrolled cancer pain treatment and if the tumor is invading bone or soft tissue then radiation therapy is used for decreasing size of tumor[16].

Table 1: Examples of Neurolytic Blocks for Cancer Pain

Neurolytic Blocks for Cancer Pain
• Celiac plexus
• Superior hypogastric plexus
• Ganglion impar
• Lumbar sympathetic chain
• Stellate ganglion
• Subarachnoid or epidural neurolysis
• Intercostals nerve
• Peripheral nerves

Interventional techniques for cancer pain management are regarded as part of a multimodal approach to pain relief and not as a stand-alone therapy [2]. Interventional pain management for patients with cancer generally falls into one of two management categories: Surgical or anesthetic. The use, indications, efficacy, and timing of appropriate surgical management of cancer pain have been well reported by Hassenbusch[17].

There are sufficient RCTs that indicate the efficacy of Neurolytic celiac plexus block (NCPB) for pain relief in pancreatic and other visceral cancers[18]. It is evident from these RCTs that Neurolytic celiac plexus blocks not only decrease pain scores but also produce a prolonged dose-sparing effect on analgesic drug requirement.

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The literature on analgesic effects of various chemotherapy and hormonal therapy regimens on pain found to be heterogeneous with respect to inclusion criteria, therapeutic regimens, and methods employed to assess analgesic efficacy. Although, in some studies the use of chemo and hormonal therapy is reported, however, these studies fail measure any significant difference in pain-related outcome between treatment arms, except in only one chemotherapy trial.

External radiotherapy to relieve pain from bony metastases in 14 trials, involving a total of 3,859 patients suggests that external radiation as a modality is effective in decreasing pain. However, no trial found more than a transient, unsustained difference in pain between fractionation schedules due to heterogeneity of dosing schedules, outcomes assessed, variability in the anatomic sites and fields treated.

In the context of acute procedure-related pain and oral mucositis pain after bone marrow transplant,

Table 2: Infusion therapy of opioids and/or local anaesthesia

Neuro-axial analgesia and/or anaesthesia	Regional anaesthesia
• Simple epidural infusion	• Brachial plexus (auxiliary, interscalene, supraclavicular, or infraclavicular infusion)
• Tunnelled epidural infusion	• Lumbar plexus infusion
• Intrathecal programmable infusion	• Selective nerve infusion (sciatic / femoral nerve infusion)
• Implanted intrathecal programmable pumps	• Intrapleural catheter infusion
	• Paravertebral catheter infusion (thoracic or lumbar)

only a few RCTs are found that examine hypnosis in conjunction with cognitive behavioural therapy in the paediatric and adult age groups. Hypnosis and Cognitive behavioural therapy seem to be helpful with both procedural and mucositis-related pain. However, more research work is needed, with larger numbers of patients and with control groups.

Only a few RCTs described relative efficacy of the spinal versus systemic routes of drug administration. Whereas, a large number of supplemental reports and case series suggest that the spinally administered opioids and other agents are beneficial in treating pain. Similarly, cordotomy, rhizotomy and the efficacy of ablative neurosurgical interventions is addressed only in case series. No included trials addressed the efficacy of acupuncture.

CONCLUSION

In above mentioned patients with terminal illness we followed the Ketamine protocol. These patients had moderate to severe pain not controlled by conventional pain therapies, had presumed neuropathic pain and had pain management compromised by opioids toxicity. In these patients Ketamine was given as an adjuvant analgesic that resulted in good pain control.

Preliminary evidence from case reports suggests that oral Ketamine may produce fewer adverse effects[7]. In addition, Ketamine by the oral route may be more potent than by the SC route. The observation that oral administration is associated with higher serum concentrations of the main metabolite of Ketamine (Norketamine), compared to other routes of administration has led to the suggestion that norketamine contributes to the analgesic effects of Ketamine[8]. Researches comment that it is not possible to predict confidently which patients will or will not benefit from 'burst' Ketamine, and it is hard to know the dose to which they will respond[9]. Therefore, it is recommended to escalate dosage to the effective or maximal tolerated dose for 3 days before designating success or failure.

Based on the above discussion and literature review, ketamine can be used as adjuvant analgesic for cancer pain treatment[7]. If conventional pain therapies either fail or are intolerable by the patient, alternative modalities should be considered[6]. There is a need for research to determine clear indication and benefit from adjuvant pain management therapy in cancer pain patients.

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