Journal of Pain & Relief
ISSN: 2167-0846

Naga and Thaher, J Pain Relief 2013, 2:2
DOI: 10.4172/2167-0846.1000117

Review Article Open Access

Ketamine Effectiveness in Cancer Pain Management: Evidence-based Practice

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Abstract

Ketamine is a drug used for the induction and maintenance of general anesthesia. Despite the evidence of epidural ketamine in pain management in the oncology settings, there is still a gap in the clinical setting regarding the effectiveness of using ketamine in the management of cancer related pain. The purpose of this study is to review and analyze the existing research studies on using ketamine in the management of cancer pain, summarize the findings into evidence-based recommendations, and to answer the following PICO question: is of whether or not ketamine is an effective option for the management of cancer pain? A comprehensive literature review was conducted using the electronic database of CINAHL, EBSECO, MEDLINE, COCHRANE, and PubMed, for articles published between 2005 and 2013. The need for more RCTs in different cancer patients to understand the benefits/adverse effects of using ketamine in the management of cancer related pain. Some of the reviewed studies on ketamine show success rate, either due to pain management failure or appearance of adverse effects of opioids, ketamine as an third line analgesic have proven to be of effect in cancer patients with severe pain.

Keywords: Ketamine; Pain management; Cancer pain

Introduction

Ketamine is a drug used for the induction and maintenance of general anesthesia, usually in combination with a sedative. Other uses include sedation in intensive care unit especially in emergency cases [1]. Historically, the effects of intrathecal ketamine in reducing opioids such as morphine in cancer pain were evaluated by Yang et al. [2].

Despite the side effects of opioids, most health care institutions uses opioids for cancer related pain particularly for moderate and severe pain. Thus, looking for the advantage and disadvantage of adding ketamine to pain-killers such as morphine for the control of cancer related pain is needed. Also, Cancer pain management is the most common problem in patients who have malignant tumor and the most feared illness for patients and their families [3].

However, there is an inadequate pain management drug in clinical settings [4]. Ketamine is considered as a third line drug and it provides an option for controlling unrelieved cancer pain and also reduces the side effects of opioids [5].

Despite the evidence of epidural ketamine in pain management in the oncology settings, there is still a gap in the clinical setting with regards to the effectiveness of using ketamine in the management of cancer related pain. This paper in general is aimed at introducing the available data on the role of ketamine in the management of cancer related pain.

The purposes of this paper is to (1) review and analyze the existing research studies on the use of ketamine in the management of cancer pain, (2) summarize the findings into evidence-based recommendations for an effective and safe usage of ketamine in the management of cancer pain, and (3) to answer the following PICO question: of whether or not ketamine is an effective option for the management of cancer pain.

Methodology

A comprehensive literature review was conducted using the electronic databases of CINAHL, EBSECO, MEDLINE, COCHRANE, and PubMed, for articles published between 2007 and 2013. The following key words were used to search the electronic databases: Ketamine, pain management, and cancer pain. Also, out of many articles obtained and reviewed, it was only 17 research articles that achieved the inclusion criteria for the purpose of this study. The inclusion criteria include the following: (1) it is a research-based study; (2) written in the English, language and (3) uses ketamine as intervention to manage cancer pain. The articles included in this paper were quantitative studies randomized control trills (RCTs) which was published in peer reviewed nursing and medical journals. Countries in which the studies for this review were conducted include the United States of America, Australia, Canada, China, India, Greece, and Taiwan. The sample sizes which was randomly assigned in the 17 studies in this review, ranges from 24 to 118 adult cancer patients aged between 20 and 61 years of age.

According to Melnyk's Hierarchy method [6], the evidence will be categorized as the follows: level (I): evidence from a systematic review or meta-analysis of all relevant (RCTs), or evidence-based clinical practice guidelines based on systematic reviews of RCTs. Level (II): evidence from at least one well-designed RCTs. Level (III): evidence from well-designed controlled trials without randomization. Level (IV): evidence from well-designed case-control and cohort studies. Level (V): evidence from systematic reviews of descriptive and qualitative studies. Level (VI): evidence from a single descriptive or qualitative study. Level (VII): evidence from the opinion of authorities and/or reports of expert committees [6] (Table 1).

Finding

There is a debate around the effectiveness of ketamine in the management of cancer related pain, thus, this paper will investigate and discuss the available literature studies on the effectiveness of using ketamine in the control of cancer related pain to implement evidence

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Received March 28, 2013; **Accepted** May 27, 2013; **Published** May 29, 2013

Citation: Badr Naga BSH, Thaher MM (2013) Ketamine Effectiveness in Cancer Pain Management: Evidence-based Practice. J Pain Relief 2: 117. doi:10.4172/2167-0846.1000117

References	Number of Study	Level of Evidence
(Palliative Care Guidelines – Ketamine, 2010) [10] (Bell et al.) [7] (Bell et al.) [18]	3	I
(Huge et al.) [11]; (Jackson et al.) [13]; (Hardy et al.) [19]; (Salas et al.) [20] ; (Schwartzman et al.) [8]	7	II
(Chung and Pharo) [12]; (Carter et al.) [16]; (Benitez-Rosario et al.) [15]; Ugur et al. [14]; (Chaudhary et al.) [9]	6	IV
(Prommer) [17]	1	V

Table 1: Research articles which use ketamine as an intervention in cancer pain management and level of evidence.

based practice in order to improve the quality of life and to reduce pain among patients suffering from malignancy tumor.

To determine the effectiveness of ketamine as an adjuvant to opioids in the treatment of cancer pain, systematic reviews of RCTs was conducted by Bell et al. [7] with evidence level (I). The researchers found that ketamine improves the effectiveness of morphine used in the treatment of cancer pain, reduces the dependence of morphine, and recommend the use of diazepam to control hallucination which results from ketamine usage. Also, Robert Schwartzman et al. [8] used randomized double-blind placebo controlled trial with evidence level (II) to investigate the usage of ketamine in cancer patients with pain syndrome, and all the participants were infused intravenously with normal saline with or without ketamine for 4 h (25 ml/h) daily for 10 days, and found out that the use of Intravenous ketamine reduces pain score, while the control group (placebo group) demonstrated no treatment effect in any pain parameter. Moreover, Chaudhary et al. [9] conducted a case report with evidence level (IV) and found that ketamine can reduce cancer pain if used as an adjuvant analgesic, and Ketamine should be used as an alternative modalities if opioids therapy is not effective with recommendation to use oral ketamine because it produces fewer side effects more than Intravenous or subcutaneous route.

Similarly, Palliative Care Guidelines for Ketamine, [10] with evidence level (I) have recommended the following: (1) Ketamine can be used for pain management (neuropathic pain) in palliative care with supervision (2) Ketamine can be used to manage very complex neuropathic or vascular pain that has not responded to opioids (3) Opioids and oral adjuvant analgesics should be tried first before adding ketamine as a therapeutic regimen (4) Patients with high intracranial pressure, uncontrolled hypertension, delirium or recent seizures, and history of psychosis are contraindicated to use ketamine.

In another study by Huge et al. [11] who reported that neuropathic pain can be managed by low dose intranasal S-ketamine which produce adequate plasma concentrations of S-ketamine and sustained concentrations of S-norketamine that leads to prolong pain reduction.

Also, Chung and Pharo [12] used ketamine infusion with small doses varying between 0.2 mg/kg/hour and 0.65 mg/kg/hour; these doses were effective in controlling pain without inducing significant side effects and reduction in opioid dosage, and found that IV ketamine used for 30 days enables the control of cancer pain at home.

Moreover Jackson et al. [13] conducted a study with evidence level (II) to ascertain the effectiveness of SC ketamine. The researchers used an intervention of three-to-five day's continuous subcutaneous (SC) infusion of ketamine which escalated from 100 to 300 to 500 mg/24 hours according to the need of patients. The response rate was 22/44 (50%), with 4 (9%) becoming free of pain. Pain relief lasting for two or more weeks was documented in 50 percent of responders. The researchers concluded that ketamine SC is effective for pain management in palliative care unit.

The effect of oral ketamine in the management of cancer pain was studied by Ugur et al. [14] who reported that oral ketamine may decline cancer pain score, reduced patient's daily morphine need and oral ketamine help patients to overlap side effects of opioids; and they found out that no clinical side effects occurred when using oral ketamine. Similarly, Benítez et al. [15] found out that oral ketamine successfully controlled cancer pain with a median dose of 300mg/day. And also no side effect was noted with the use of oral ketamine.

Ugur et al. [14] found that low doses of ketamine intravenously (IV) may be useful in managing pediatric cancer pain at the end of life, decrease other opioid dosage and a decrease in opioid-related side-effects with the ketamine infusions initiated at 0.05-0.1 mg/kg/hour and increasing up to 4.1 mg/kg/hour. Ketamine can prevent the development of opioid tolerance and provides additional analgesia without any increase in sedating effects and help patients in restored interaction or communication with families.

Similarly, Carter et al. [16] reported that ketamine can be used for palliative sedation because of its fast onset of action which produces a state of dissociative anesthesia before full sedation is achieved, while its action as a central and peripheral catecholamine reuptake inhibitor precludes the cardio-respiratory depression associated with barbiturates and propofol.

Moreover, Prommer [17] assures that ketamine is physically stable when mixed with morphine, low dose of dexamethasone, haloperidol and metoclopramide. Undesirable effects of high-dose of ketamine include dysphoria, nightmares, hallucinations, excessive salivation and tachycardia.

As for the use of ketamine for acute postoperative pain, Bell et al. [18] with evidence level (I) conducted a systematic RCTs and found that 28 trials was used by ketamine to reduce analgesic requirements or pain intensity, or either to at least 24 hour post-surgery. Ketamine with morphine when used reduces postoperative nausea or vomiting and the adverse effects of morphine are mild or absent.

On the contrary, many RCTs with evidence level (II) [19-21] reported that there is no clinical benefit of ketamine when used as an adjunct to opioids and standard co analgesics. Also, the researchers did not confirm the efficacy of the ketamine-morphine combination in refractory cancer pain; and also patients receiving ketamine are more likely to experience a more severe grade of adverse effects. The researchers concluded that further studies should be performed to take into account the difficulties of conducting clinical research in the palliative care unit.

Discussion

To answer the PICO question should include four parts that determine the patient problem or population (P), intervention (I), comparison (C) and outcome (O). Sackett et al. [22], thus the pico question is ketamine an effective option for management of cancer pain? ; P=cancer patients; I=administration of ketamine; C=effectiveness vs. ineffectiveness of ketamine in cancer pain management; O=effectiveness of ketamine in management of cancer pain.

The analgesic effect from ketamine at the smaller doses may result from the action of different receptor sites than is caused by larger doses. Also, the wide dose range of oral ketamine reflects the variation in diagnoses among many study groups. Increased sensitivity to cancer

pain, which may be caused by damage to nociceptors or peripheral nerves following the acute administration of fentanyl can be prevented by pre-treatment with ketamine [23].

Eilers [24] reported a cancer case where severe tolerance to fentanyl was reversed by ketamine, they result suggest the early use of small-dose ketamine may be reduce the tolerance of fentanyl.

Ketamine may be used as a co-analgesic for breakthrough pain and for severe pain caused in end stage of cancer disease when invasive techniques are inappropriate or cause severe side effect. Regarding morphine consumption among cancer patients, two RCTs proved that used of ketamine in addition morphine decreased morphine use and reduced neuropathic pain intensity [25].

When pain is not responded to morphine it's considered problematic in cancer pain management; clinical studies have suggested that ketamine, may be effective in improving opioid analgesia in pain syndromes among cancer patients, such as neuropathic pain; and reduced the pain intensity in the most cancer patients.

Hallucinations, an unpleasant sensation such as empty head, and drowsiness were also reported. However, the side effects should be taken into consideration, especially when using as a higher doses [26].

Ultimately we found clinical studies proved used of ketamine as a third line in cancer pain management to improve effectiveness of opioids for management cancer related pain or to reduced some adverse effect of this modality or reduced tolerance of opioids such as fentanyl. In addition usage of ketamine should be given in closed unite to monitoring some adverse effect.

Recommendation

Ketamine as an analgesic has proven to be of some effect in patients with severe pain who have failed to respond to other routinely applied pharmacotherapy. In patients with intractable pain, the use of oral ketamine can be beneficial. From this perspective, oral ketamine may be used with precautions as add-on therapy when other therapeutic options have failed. However, the routine use of ketamine in cancer pain management is still insufficiently studied. After reviewing research which uses ketamine in the management of cancer pain; further RCTs are needed to include all types of cancer to gain more knowledge about the benefits/adverse effects of using ketamine to manage cancer pain. As for recommendation for practice, we recommend the use of Palliative Care Guidelines and to take into consideration the importance of using ketamine and observing any possible side effect that may occur during or after treatment.

Summary and Conclusion

Cancer pain management is the most common problem in patients who have malignant tumor and the most feared illness for patients and their families. Thus, looking for the advantage and disadvantage of adding ketamine to pain-killers such as morphine for the control of cancer related pain is needed. Ketamine is considered as a third line drug and it provides an option for controlling unrelieved cancer pain and also reduces the side effects of opioids.

Despite the evidence of epidural ketamine in pain management in the oncology settings, there is still a gap in the clinical setting with regards to the effectiveness of using ketamine in the management of cancer related pain.

This paper in general is aimed at introducing the available data on the role of ketamine in the management of cancer related pain. The review of studies showed that ketamine could be recommended as a third line in cancer pain management and could help to reduce some adverse effect of this modality or reduced tolerance of opioids such as fentanyl. However, usage of ketamine should be given with precaution to monitor any possible adverse effect.

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This article was originally published in a special issue, **Cancer Pain** handled by Editor(s). Dr. Yan-Qing Wang, Fudan University, China