Review Article

Ketamine as Adjuvant to Opioids for Cancer Pain. A Qualitative Systematic Review

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Abstract

Ketamine is increasingly being used as an adjuvant to opioids in the treatment of refractory cancer pain. This systematic review examines the available evidence. Randomized, controlled trials, with or without crossover, were included. Studies were identified from MEDLINE, EMBASE, CANCERLIT, the Cochrane Library, handsearched reference lists from review articles and chapters from standard textbooks on pain and palliative care and reference lists from papers retrieved. Four randomized, controlled studies were identified. Two were excluded due to poor quality. Both included studies concluded that ketamine improves morphine treatment in cancer pain. Quantitative meta-analysis was not possible. The available evidence is not sufficient to conclude that ketamine improves the effectiveness of opioid treatment in cancer pain. High quality, randomized, controlled trials with larger numbers of patients and standardized, clinically relevant routes of administration of ketamine are needed. J Pain Symptom Manage 2003;26:867–875. © 2003 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Ketamine, opioids, cancer pain, systematic review, Cochrane

Introduction

Ketamine hydrochloride is commonly given intravenously or intramuscularly for surgical anesthesia. During the last decade, it has become apparent that low, subanesthetic doses of ketamine may improve opioid analgesia.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. There is good evidence from experimental animal models, human volunteer studies and small clinical trials that NMDA receptor antagonists relieve some types of neuropathic pain. However, their use is restricted by unpleasant adverse effects, such as hallucinations. The NMDA receptor also seems to play a role in the development of opioid tolerance. Ketamine in low doses (for example, 1 mg/kg/24 hrs as a subcutaneous infusion) has been suggested to reverse or partially reverse opioid tolerance. Clinical reports indicate that ketamine in low doses as an adjuvant to opioid treatment may improve analgesia with tolerable adverse effects.

Ketamine is now increasingly being used as an adjuvant to opioids in the treatment of refractory cancer pain, that is, cancer pain which
does not respond to opioids alone or opioids in combination with adjuvant analgesic drugs. Such use of ketamine is advocated in several pain/palliative care textbooks. So far, there is little clinical evidence to support this practice.

From published literature, it would appear that ketamine prescribed with opioids for the treatment of cancer pain is used in several countries including the UK, Scandinavia, Italy, Belgium, Japan and Australia. Treatment with low dose ketamine is relatively inexpensive and would be suitable for use in developing countries. This systematic review was performed to determine the effectiveness of ketamine as an adjuvant to opioids in relieving cancer pain.

A more detailed review will be published and updated in the Cochrane Database of Systematic Reviews.

**Methods**

**Criteria for Considering Studies for This Review**

**Studies.** Randomized, controlled trials (RCTs), with or without crossover were included. Trials using placebos or active controls, or both, were included. There was no language restriction. All identified trials, published and unpublished, were considered eligible.

**Participants.** The population addressed by the review included adult patients (over 18 years) with cancer and pain currently treated by an opioid agonist, in any dose and by any route. Patients who were on an established NMDA-receptor antagonist treatment before the study began were excluded. Healthy volunteer studies were not considered.

**Interventions.** The intervention considered by this review was the addition of ketamine, given by any route, in any dose, to pre-existing opioid treatment given by any route and in any dose.

**Search Strategy**

The following electronic data bases were searched:

- MEDLINE on Silver Platter from 1966 onwards
- EMBASE on Silver Platter from 1980 onwards
- CANCERLIT from 1966 onwards
- Cochrane Library Controlled Trials Register and Database of Systematic Reviews (Cochrane Library, Issue 1, 2001)
- Specialized Register of the Cochrane Pain, Palliative and Supportive Care Group

A broad search was performed, combining MeSH terms and a free text search. The following terms were used: “ketamine,” “ketalar,” “dextromethorphan,” “amantadine,” “memantine,” “NMDA receptor antagonist,” “cancer,” “malignant disease,” “neoplasim,” and “palliative” using the Boolean operators “OR” and “AND.”

As this search resulted in a large number of irrelevant trials a more refined search was performed using the terms “ketamine,” “ketalar,” and “cancer” using the Boolean operators “OR,” and “AND.”

Reference lists from review articles and chapters from standard textbooks on pain and palliative care, and reference lists from papers retrieved through electronic searching were handsearched.

A letter was sent to the manufacturers of ketamine (Ketalar®), Pfizer, requesting access to relevant research material and unpublished studies. Because these searches revealed several clinical studies from Japan, an attempt was made to access appropriate Japanese journals not indexed in Medline and Embase. An enquiry was made to the Australasian Cochrane Centre and to the Bodleian Library. Napp Pharmaceuticals in the UK were also contacted regarding an unpublished study.

The last electronic search was performed in February 2002.

**Data Collection**

All identified records from each of the databases were examined. The titles and abstracts of studies were assessed independently by two reviewers (RFB, EK) and potentially relevant studies, including review articles, were selected for assessment for inclusion in the review. Each trial report that appeared to meet the criteria was independently assessed for inclusion by three reviewers (RFB, CE, EK).

A data extraction form was designed, and the following data were collected independently by the three reviewers:

1. Publication details.
2. Patient population, number of patients, age, condition.
3. Description of intervention.
4. Quality (randomization/allocation concealment, details of blinding measures, withdrawals and dropouts, overall quality score).

Studies to be included in the review were evaluated using the Oxford Quality Scale.13

5. Validity was assessed using the Oxford Pain Validity Scale (OPVS).14

Studies were classified as double-blind if they were described as such in the text.

Results

The broad search in EMBASE gave 531,163 items identified, 294 possible items and then, with abstracts read, 3 randomized controlled trials. The Medline search gave 223,723 items identified, 120 possible items after the refined search, 4 randomized controlled trials after reading the abstracts. A refined search on Cancerlit gave 50 possible items, including 2 randomized, controlled trials, while the PARDLARS (Pfizer) search gave 90, including 4 randomized, controlled trials. A final search on Medline in February 2002 gave 3 additional reports, but no new RCT’s. Details of the Napp study were, in July 2002, not yet available.

A total of 4 randomized, controlled trials with a total of 57 patients were identified. Hand-searching of reference lists in review articles and textbooks gave no added trials. A search of the Cochrane Library gave one review article, but no new trials. Enquiries regarding the Japanese literature did not result in the identification of additional trials.

Three independent reviewers assessed the quality of the four identified trials using a standard data extraction sheet and Oxford scales for quality and validity. Two trials15,16 were included in the review (Table 1) and two were excluded due to poor methodological quality.

The total number of patients in the included trials was 30. Both studies were positive with regard to the effect of ketamine. Ketamine was found to reduce morphine requirements in cancer patients and to significantly reduce pain intensity in cancer pain with a neuropathic component. Ketamine did not cause serious adverse effects. Adverse effects in the chronic setting were generally milder than in the control group; this was considered to be due to ketamine’s morphine-sparing effect and subsequent reduction of opioid-related adverse effects. Ketamine caused hallucinations in 4 patients in the acute study,16 whereas morphine caused hallucinations in one patient in the chronic study.15

In the acute study, ketamine added to morphine gave significant increases in drowsiness; this effect was dose-related with the higher dose (0.5 mg/kg) causing more drowsiness.

It was not possible to perform a quantitative meta-analysis due to the small number of trials, small number of patients and the heterogeneity of the data. Only two studies could be included, but all four studies will be discussed for the methodological implications. Conclusions regarding effectiveness are based on the two included studies.

Description of Studies

Four randomized, controlled studies were identified.15–18 The studies were published between 1996 and 2000. All were published in English. Two studies were undertaken in Brazil, one in Taiwan and one in Italy.

Populations. All studies were conducted with adults aged from 21 to 74 years. The populations were defined as patients with “cancer pain unrelieved by systemic opioid or NSAID therapy;” “terminal cancer pain” and “cancer pain unrelieved by morphine, Karnofsky 50 or more.” Two studies were carried out in an outpatient setting17,18 and one study15 was with hospitalized patients. The fourth study16 did not describe whether the patients were hospitalized or ambulant.

Pain. The primary site of the lesion that lead to pain was described in all studies and included: oropharynx, stomach, liver, colon, pancreas, kidney, lung, cervix, uterus and prostate. Only one study16 described the possible mechanisms of pain. In this study the pain was classified as being “neuropathic” or having a “neuropathic component.”

Interventions. The opioid in all studies was morphine. The morphine route differed between studies: oral, epidural, intrathecal, and in the most recent study,16 oral, subcutaneous and intravenous routes. Morphine doses varied
<table>
<thead>
<tr>
<th>Study</th>
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<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Mercadante 2000</td>
<td>Randomized but procedure not described</td>
<td>Cancer patients with neuropathic pain unrelieved by morphine</td>
<td>Treatment 1: saline (IV)</td>
<td>Pain intensity</td>
<td>Acute treatment. Washout period (&quot;at least 2 days&quot;) Rescue medication: none</td>
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<td>Treatment 2: KET bolus 0.25 mg/kg (IV)</td>
<td>Adverse effects</td>
<td>Withdrawal: not described Adverse effects: ketamine gave central adverse effects (hallucinations, drowsiness, confusion) in 4 of 10 subjects</td>
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<td>Treatment 3: KET bolus 0.5 mg/kg (IV)</td>
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<td>Quality/validity: OPVS score: 12 Jadad score: 3</td>
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<tr>
<td>Yang 1996</td>
<td>Randomized but procedure not described</td>
<td>Hospitalized patients with terminal cancer pain</td>
<td>Treatment 1: Mo (IT)</td>
<td>Pain intensity</td>
<td>Chronic treatment. Rescue medication: &quot;Mo 5 mg IM as needed&quot;</td>
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<td>Treatment 2: KET 1.0 mg (IT) bid + Mo (IT)</td>
<td>Pain frequency</td>
<td>Withdrawals/dropouts: not described</td>
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<td>Total titrated Mo</td>
<td>Adverse effects: Side effects including pruritus, constipation, urinary retention, nausea, vomiting and hallucination were not serious. The frequency of side effects did not show differences between phase M and phase M+K</td>
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<td>dose (IT)</td>
<td>Quality/validity: OPVS score: 13 Jadad score: 3</td>
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<td>Frequency of IT titration</td>
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<td>Results:</td>
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<td>Co-administration of low-dose KET reduces the amount of IT Mo required to control cancer pain</td>
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KET = ketamine; Mo = morphine; IT = intrathecal; IM = intramuscular; SC = subcutaneous; IV = intravenous.
between patients and between studies. The ketamine route differed between studies. Ketamine was administered by oral, epidural, intrathecal and intravenous routes. The ketamine doses also differed between studies and ranged from 0.5 mg/kg oral × 2 to 0.5 mg/kg IV bolus. It is assumed that racemic ketamine was used in all reports. Rescue medication was morphine in three studies, and the fourth study did not involve rescue medication. The rescue medication route differed in the three studies and included oral and intramuscular routes. One study may have included epidural morphine as rescue medication; however, this was not clearly described.

Outcomes. A variety of outcomes were reported. All studies reported adverse effects. All studies registered pain intensity either using a Visual Analogue Scale (VAS) or a numerical rating scale (NRS). Other outcomes differed between studies and included daily morphine consumption, time to VAS 4 after study drug, pain frequency, group morphine dose, total titrated intrathecal morphine, total rescue medication, frequency of intrathecal titration, life interference and sleep deprivation.

Study Duration. Duration differed between studies and ranged from 30 minutes to 30 days. In one study, it was not possible to elucidate study duration.

Methodological Quality of Studies

Two studies had a crossover design. Only one study used a placebo control, and one study used an active control (morphine). Two studies claimed to use a “placebo-controlled design” but in fact used an active control (morphine). The first of these studies was not blinded and was considered to be methodologically flawed (using morphine as control and morphine consumption as outcome measure). This trial scored 1 on the OPVS scale and was excluded from the review. The second study, which scored 7 of 16 possible points on the OPVS, used the same kind of control, a fixed baseline dose of morphine and fixed daily dose of rescue medication. This study was also considered to be methodologically flawed and was excluded from the review.

The remaining trials scored 13 and 12 respectively on the OPVS scale and 3 on the Oxford Quality Scale. Both were randomized, but the process of randomization was not described. Both studies were convincingly blinded. Neither study described withdrawals and dropouts. Both studies reported the statistical analysis used. In general, the most important methodological problems were: inadequate description of the pain to be treated and absent or inadequate description of rescue medication policy. One study examined the effect of chronic administration of ketamine while the other was an acute study examining the effect of bolus administration.

Thus, only two studies were included in the final analysis of efficacy. Both included studies were positive with regard to the effect of ketamine. Ketamine was found to reduce morphine requirements in cancer patients and to significantly reduce pain intensity in cancer pain with a neuropathic component. Ketamine gave no serious adverse effects. Adverse effects in the chronic setting were generally milder than in the control group; this was considered to be due to ketamine’s morphine-sparing effect and subsequent reduction of opioid-related adverse effects. Ketamine presumably caused hallucinations in 4 out of 10 patients in the acute study, but was not associated with hallucinations in the chronic study. In the acute study, ketamine added to morphine gave significant increases in drowsiness; this effect was dose-related with the higher dose (0.5 mg/kg) causing more drowsiness.

Discussion

This systematic review examined the effect of ketamine as an adjuvant to opioids in cancer pain. With regard to search strategy, the PARD-LARS search gave an excellent gain, compared to the other searches. Of the 90 possible titles, 41 were relevant for the review. This would suggest that collaboration with the pharmaceutical companies is important to enable maximum retrieval of information when preparing systematic reviews involving drug treatment.

In preparing this review, we addressed the difficulty of conducting scientific trials in a terminally ill, cancer patient population. The importance of study design needs to be emphasized. For example, the use of placebo control
may potentially expose the cancer patient to unnecessary pain and the study design must address this problem. Conducting scientifically sound trials in this patient population is a considerable challenge, reflected perhaps by the small number of published trials. It is difficult to recruit large numbers of patients from this population. A crossover design, as used by the two included studies may be a useful solution. It also may be difficult to resist the temptation to address several different outcomes in one study. Both excluded studies investigated several interventions at the same time, giving a complicated design and small numbers of patients in each group.

It would seem wise to restrict the study outcome as much as possible. Outcomes should be clearly defined and the studies should provide clinically useful information, such as which route of administration/dose is effective and cost of treatment in terms of adverse events. There is a lack of consensus across the four identified trials as to the primary outcomes. Should the standard outcome be relief of neuropathic pain, reduction of tolerance or reduction of morphine consumption? In one study, the type of pain was defined and the patients were on moderate doses of morphine. In the three other studies, the type of pain was not described and the patients were on low doses of morphine. Insufficient information is given to judge the appropriateness of the intervention with these patients.

The main adverse effect of ketamine was hallucination and seemed to be dose-related. Recently S-ketamine has been introduced. Studies using S-ketamine would be of interest as it may have a safer adverse effect profile. If ketamine is used spinally, issues of neurotoxicity should be considered.

In the two included studies, ketamine was found to improve morphine analgesia. Ketamine is an NMDA receptor antagonist. The NMDA receptor is believed to play a role in the development of opioid tolerance and ketamine has recently been shown in a rat model to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Whether reduction of opioid tolerance is an important factor in the improvement of morphine analgesia remains to be studied. It has been suggested that pharmacological tolerance to opioid may develop early, but it is not clear how often it is a clinical problem in cancer patients. It may be difficult in this patient population to distinguish between tolerance and disease progression, both of which require an increase in opioid dose. In those patients in whom opioid tolerance is suspected to be a problem, ketamine may be a treatment option. It should be noted that morphine was the opioid in both included studies, and that the results may not apply to all opioids.

The majority of titles identified by the electronic searches were case reports, open label audits or open label, uncontrolled trials. A total of 32 such reports was identified. Ketamine was used to treat refractory cancer pain, often described as neuropathic. Twenty-eight reports described improvement of analgesia with ketamine. In the majority of cases, ketamine improved opioid analgesia. The most common opioid was morphine, but in some cases ketamine was given as an adjuvant to fentanyl, hydromorphone or diamorphine, or combinations of these opioids. Ketamine also was used as the sole analgesic. Sixteen publications report dramatic relief of refractory cancer pain with ketamine, including “complete cessation of pain,” “complete relief of pain,” “disappearance of pain,” “no pain,” “pain free,” “mostly pain free,” dramatic reduction in VAS scores including VAS 100 reduced to 0, average VAS score 8.3 reduced to 1, average VAS score reduced from 5.9 ± 2.0 to 0.3 ± 0.8, VAS 7/10 to 1/10, reduction of VAS 7/10 to below 2/10, “remarkable analgesia,” and “excellent analgesia.” Adverse effects were related to higher doses of ketamine. The most commonly reported adverse effects were sedation and hallucination. In general, adverse effects were not reported as severe or requiring cessation of treatment. Two reports describe pain relief with ketamine but discontinuance of treatment due to unacceptable adverse effects in the form of “adverse cognitive effects” and pronounced sedation. Other side effects described included evoked nystagmus under treatment with intravenous ketamine and inflammation of syringe driver sites during subcutaneous treatment. One report described generalized hyperalgesia and allodynia after abrupt termination of subcutaneous ketamine infusion. One postmortem report described subpial vacuolar myelopathy after continuous intrathecal
ketamine infusion,\textsuperscript{19} while another described focal lymphocytic vasculitis close to the intrathecal catheter site.\textsuperscript{37} One report described sedation, which improved on tapering the opioid dose,\textsuperscript{4} while another report describes maintenance of syringe driver sites with topical 0.1% hydrocortisone cream.\textsuperscript{29} The total number of patients treated with ketamine in these case reports was 246. The route of ketamine administration included oral, intramuscular bolus, subcutaneous bolus and infusion, intravenous bolus and infusion, epidural bolus, and intrathecal infusion. Ketamine doses ranged from 1 mg/kg/day subcutaneous infusion to 600 mg/day intravenously and 67.2 mg/day intrathecally. Treatment duration ranged from 4 hours to 1 year. Treatment was in most cases adjuvant to opioids and other drugs.

Despite the treatment being recommended in leading textbooks, there are at present only four randomized, controlled trials. Of these, two have poor methodological quality and could not be included in this review. Both included studies favor ketamine as an adjuvant to morphine in the treatment of cancer pain unrelieved by morphine. However, the total number of patients is small\textsuperscript{30} and the two trials are difficult to compare since one is in a chronic setting, using intrathecal morphine and ketamine, while the other is in an acute setting, using ketamine as an intravenous bolus. The relevance of the acute study to chronic cancer pain may be questioned. However, an open label study describes long-term effects of a single ketamine infusion in cancer pain patients.\textsuperscript{38} A recent randomized, controlled trial, although not in cancer pain, also reports lasting effect of a single ketamine infusion in patients with ischemic pain.\textsuperscript{39}

**Conclusions**

The evidence base for ketamine as an adjuvant to opioids for cancer pain is weak. The available literature allows for only a cautious conclusion that there is promise in the potential efficacy of ketamine as an adjuvant to opioids for cancer pain. The two RCT’s of sufficient quality return broadly positive conclusions. In addition, there is a large number of case reports/open label studies describing improvement of opioid analgesia with ketamine. Higher quality randomized controlled trials are needed with larger numbers of patients and standardized, clinically relevant routes of administration of ketamine. Studies using S-ketamine and other opioids would be of interest.

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