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The impact of a standardised ketamine step protocol for cancer neuropathic pain

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Context: Ketamine at sub-anesthetic doses is a potent analgesia. Its use in cancer pain remains equivocal with protocols varying in patient selection, starting dose, titration, duration of use and adjustment of co-analgesics.
Objective: To study the impact of a standardised Ketamine Step Protocol on cancer pain in a Palliative Care Unit (PCU).
Methodology: This is a prospective cohort study of a standardised Ketamine Step Protocol which was developed in a PCU for use in cancer pain. The subcutaneous ketamine infusion was standardised at a starting dose of 75 mg over 24 hours with Haloperidol 5 mg as prophylaxis against psycho-mimetic side effects. Incremental doses of ketamine followed the daily stepwise protocol.
Result: Of the 48 patients analysed, 41 (85.4%) had neuropathic cancer pain. The median Palliative Performance Scale score (PPSv2) was 40%. Mean Numerical Rating Score (NRS) improved from 6.74 to 2.61 ($P < 0.0001$) with a mean percentage reduction of 58.05%. The final mean daily ketamine dose needed to achieve stable pain control was 137.50 mg/day (±81.54). 31(62.5%) patients achieved pain control by day 3. The mean Morphine Equivalent Daily Dose (MEDD) reduction was from 130.34 mg to 107.33 mg ($P < 0.002$) with a percentage reduction of 18.85%. More than half of our patients completed the 5 d protocol with mild to moderate side effects not warranting urgent medical intervention nor termination of the ketamine protocol.
Conclusion: Use of a standardised Ketamine Step Protocol showed a statistically significant reduction in pain and MEDD in patients with predominantly neuropathic cancer pain. It also demonstrated a safe and effective method for opioid reduction after commencement of parenteral ketamine.

Key Message:
How can a standardised ketamine protocol impact on cancer pain control?
Our study shows that:
- Parenteral ketamine is a potent analgesic which significantly reduced pain in patients with cancer neuropathic pain.
- This study also demonstrated a safe and effective method for titration of opioids after parenteral ketamine is started.
- Concurrent use of psychotropics also helps to reduce psycho-mimetic side effects, increasing tolerability to ketamine.

Keywords: Ketamine, Cancer pain, Neuropathic, Step protocol

Introduction

Ketamine has been a mainstay of surgical anesthesia at doses of 0.5–4.5 mg/kg for more than four decades.[1] At lower sub-anesthetic doses of 0.1–0.3 mg/kg per hour, ketamine has been shown to have remarkable analgesic effects, with case series and anecdotal reports supporting its potential as a potent analgesia in neuropathic cancer pain management.[2–5]

Neuropathic pain arises from a lesion or disease of the somatosensory system. It may be etiologically heterogeneous but patients share the same characteristics of experiencing prolonged pain, dysesthesias and hyperalgesia.[6] Ketamine has N-methyl-D-aspartate (NMDA) receptor antagonist activity which is an important mechanism in the management of

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Table 1 Ketamine step protocol

Ketamine Step Protocol			
STEPS	**Dose of Ketamine over 24 hours**	**Dose of Haloperidol over 24 hours**	**Dilution**
STEP 1	75 mg	5 mg	Syringe out 75 mg of ketamine (1.5mls) + 5 mg Haloperidol (1 ml) and dilute with normal saline up to 24 mls and run at 1mls per hour over 24 hours. PROCEED TO STEP 2 DILUTION PROTOCOL IF NRS/VAS >3. OTHERWISE, KEEP THE SAME DILUTION for the NEXT 5 days.
STEP 2	175 mg	5 mg	Syringe out 175 mg of ketamine (3.5mls) + 5 mg Haloperidol (1 ml) and dilute with normal saline up to 24 mls and run at 1mls per hour over 24 hours. PROCEED TO STEP 3 DILUTION PROTOCOL IF NRS/VAS >3. OTHERWISE, KEEP THE SAME DILUTION for the NEXT 5 days.
STEP 3	275 mg	5 mg	Syringe out 275 mg of ketamine (5.5mls) + 5 mg Haloperidol (1 ml) and dilute with normal saline up to 24 mls and run at 1mls per hour over 24 hours PROCEED TO STEP 4 DILUTION PROTOCOL IF NRS/VAS >3. OTHERWISE, KEEP THE SAME DILUTION for the NEXT 5 days
STEP 4	375 mg	5 mg	Syringe out 375 mg of ketamine (7.5mls) + 5 mg Haloperidol (1 ml) and dilute with normal saline up to 24 mls and run at 1mls per hour over 24 hours PROCEED TO STEP 5 DILUTION PROTOCOL IF NRS/VAS >3. OTHERWISE, KEEP THE SAME DILUTION for the NEXT 5 days
STEP 5	475 mg	5 mg	Syringe out 475 mg of ketamine (9.5mls) + 5 mg Haloperidol (1 ml) and dilute with normal saline up to 24 mls and run at 1mls per hour over 24 hours MAINTAIN SAME DILUTION PROTOCOL for the NEXT 5 days

Note: NRS: Numerical Rating Score; VAS: Visual Analogue Scale.

neuropathic cancer pain and sensitisation. Central sensitisation resulting from repeated C-fiber stimulation activates the NMDA receptors in the dorsal horn, inciting allodynia, hyperalgesia and a state of prolonged pain response which is non-responsive to increasing doses of opioids. Prolonged stimulation also results in neuroplasticity and a tolerance to opioids which ketamine was shown to be effective in mitigating.[7,8]

Despite its potential pharmacokinetic benefit in analgesia, a Cochrane review revealed insufficient evidence for its use as an adjuvant to opioids for the relief of cancer pain.[9] In a randomised controlled trial, ketamine did not show net clinical benefit when used as an adjunct to opioids and standard co-analgesics in cancer pain.[10] Limitations of the study included a heterogeneous patient population with participants suffering refractory chronic pain from cancer or the treatment itself. Ketamine was also prematurely discontinued in patients before the completion of the five-day trial due to unacceptable toxicities which were not clearly defined.[11]

Several regimens have been published for ketamine use in patients with cancer pain.[12–14] They are highly varied in the selection of patients, ketamine commencement dose, titration, duration of use, adjustment of co-analgesics and use of neuroleptic agents for psycho-mimetic side effects.

For almost a decade, ketamine has been used in our tertiary hospital based PCU but its use was predicated on physicians' experiences and the selection of patients was varied. To determine the prescription practice of ketamine in our institution, a retrospective review of the experiences and challenges in the use of ketamine for cancer pain was undertaken involving patients in our PCU who suffered from non-curative advanced metastatic cancer. The mean starting dose was 64.3 mg/day (± 25.9) and the most common titration method was increase in ketamine volume by 100 mg every 24 hours for increasing intensity of pain. In the review, the safety of the subcutaneous route was demonstrated for the administration of ketamine, and the number of patients with severe pain reduced from 21 (51.2%) to 1 (2.4%).[15] The profile of patients selected and the varying volumes of ketamine used showed gaps in our clinical practice which included (a) the need to use a cancer pain classification tool to refine patient selection and (b) the lack of a standardised protocol to guide physicians on the initiation and titration of ketamine in patients being treated with existing opioids. Based on these findings, the Ketamine Step Protocol was developed to address shortcomings in practice.

Therefore, the aim of this study is to understand the impact of a standardised Ketamine Step Protocol on complex cancer pain in a Palliative Care Unit (PCU).

Methods

This is a prospective study conducted in the PCU of a tertiary university teaching hospital in Singapore using a standardised Ketamine Step Protocol.

Patients were consecutively enrolled between July 2015 to July 2018. Included were patients with (a) opioid neurotoxicity, (b) opioid induced hyperalgesia or allodynia and (c) sub-optimal pain management, defined as pain score of more than 3 on the Edmonton Symptom Assessment Scale [ESAS] despite optimal opioids used. Excluded from the study were patients with (a) inability to assess response due to significant confusion (b) significant tachycardia (heart rate of >100 beats per minute) or hypertension (blood pressure >140/90 mmHg), (c) raised intra-cranial pressure, (d) severe cardiac disease, (e) history of hemorrhagic stroke, (f) raised intra-ocular pressure and (g) uncontrolled seizures.

Data collected included patient demographics (age, gender, race and marital status), functional status using the Palliative Performance Scale (PPSv2),[16] cancer diagnosis, presence of metastasis and treatments received in the preceding 6 months. Profile of pain was characterised using the Edmonton Classification System for Cancer Pain (ECS-CP).[17] The presence of anxiety and depression on the Edmonton Symptom Assessment Scale (ESASr),[18] baseline NRS of pain, daily MEDD and concomitant adjuvants used were also documented.

All patients who satisfied the inclusion criteria were started on the standardised ketamine protocol (Table 1) starting with SC ketamine infusion of 75 mg with haloperidol 5 mg over 24 hours (STEP 1). Concurrent opioids were dose reduced by 30% because of NMDA antagonism which increases opioid sensitivity. Pain intensity was rated using the NRS at the initiation of the protocol with twice daily reviews for response to analgesia. The MEDD was calculated based on the total volume of baseline and breakthrough opioid doses daily. A 'responder' was defined as one with a minimally clinical important difference (MCID) in pain score of ≥1 or ≤3 on the NRS for 3 consecutive reviews. For patients with persistent pain after 24 hours ('non-responder'), the infusion was escalated to the next step with ketamine of 175 mg and haloperidol 5 mg over the next 24 hours (STEP 2). Escalation of ketamine volume subsequently was by increments of 100 mg daily if pain control did not meet the criteria for a responder. This was continued until either optimal pain control was achieved or when the maximum dose of 475 mg over 24 hours was reached. The ketamine infusion was continued for 5 days at the lowest effective dose needed to achieve analgesia. It was thereafter either discontinued or converted to oral ketamine using a 1: 1 ratio based on the physician's discretion.[19] For patients who did not achieve effective analgesic relief, ketamine was still continued at the maximal tolerated dose for a full trial of 5 days. The MEDDs were calculated and compared at the first and final day of the study and evaluated against ketamine. The doses of adjuvants used were recorded on a daily basis. Retrospectively, based on the data gathered, severity of side effects were graded using the Common Terminology Criteria for Adverse Events version 5.0.[20]

The conduct of this study was approved by the institutional review board (IRB 2020/00116).

Statistical analysis

Descriptive statistics and frequency distributions were calculated for demographics and clinical characteristics of patients. Continuous variables were presented as means with standard deviation. Paired T- test was used for assessment of the intervention with Pearson's correlation coefficient used to evaluate the association between continuous variables. Analysis of results was performed using the software Statistical Package for the Social Sciences (SPSS V 22) version 22.

Results

Baseline demographics (Table 2): 48 patients were included in the study. 27 (56.3%) were male and 30 patients (62.5%) were married. All patients had metastatic cancer. 36 (75.0%) patients were still receiving disease modifying treatments and 31 (64.5%) were on adjuvant analgesics. Gabapentin (13 [40.6%]) was the most commonly prescribed adjuvant at a mean dose of 175 mg/day (SD ± 317.77). The predominant nature of pain experienced was neuropathic in 41 (85.4%) of patients with 36 (75.0%) of them experiencing incident pain. 23 patients (47.9%) were psychologically distressed i.e. anxious, depressed, scared, worried and 5 (10.5%) were assessed to be cognitively impaired.

Pain score and MEDD at the initiation and final day of ketamine use (Table 3): There was a mean pain reduction of 58.05% (SD ±40.98) after parenteral ketamine was started, with the NRS decreasing from 6.74 (SD ±2.41) to 2.61 (SD ±2.45) [$P < 0.000$]. Similarly, the MEDD decreased from 130.34 mg (SD ±68.51) to 107.33 mg (SD ±71.42) [$P < 0.002$] with concurrent use of ketamine. The final mean ketamine dose used to optimise pain was 137.50 mg /day (SD ±81.54).

Correlation between final ketamine dose and final MEDD as well as pain score (Table 4).

There was no correlation between the final ketamine dose with the final MEDD and the pain score.

Number of days before achieving pain control (Table 5): The median time taken to achieve stable pain control was 3 days [30(62.5%)] after the initiation of the Ketamine Step Protocol. Only 4 patients needed to be escalated to STEP 3 (275 mg/24 hours) and 2 patients to STEP 4 (375 mg/24 hours) suggesting a

lower ketamine dose needed to achieve optimal pain control. 27 (56.25%) patients continued and completed 5 days of ketamine as per protocol after pain control was achieved. Reasons for early discontinuation included adequate pain control (35.41%), death due to disease progression (29.16%) and transfer to inpatient hospice (6.25%).

Side effects (Table 6): 35 out of 48 patients developed side effects while using ketamine. The most common side effects experienced were depressed level of consciousness [15 (31.25%)], delirium [10 (20.83%)] and confusion [5(10.42%)]. These CTCAE Grade 1–2 neuropsychiatric disorders with mild to moderate symptoms were not life threatening nor disabling and did not require urgent medical intervention. 2 (4.17%) patients developed CTCAE Grade 1 skin induration over their injection sites and 2 (4.17%) patients experienced CTCAE Grade 1–2 cardiovascular disorders: tachycardia and hypertension. 1 (2.08%) patient was noted with CTCAE Grade 1 transient tongue dyskinesia. None of the patients discontinued ketamine because of the side effects. These adverse events by frequency were consistent to prospective ketamine trials done previously.[21]

Table 2 Baseline demographic data

Variables	Number (N=48)	Percentage (%)
Gender		
Male	28	58.3
Female	20	41.7
Marital Status		
Single	11	22.9
Married	31	64.6
Divorced / Widowed	6	12.5
Metastatic Cancer		
Yes	48	100
No	0	0
Treatment received over the last 6 months		
Radiotherapy (RT) only	11	22.9
Chemotherapy only	5	10.4
Intervention +/- Surgery	5	10.4
Chemotherapy + RT	8	16.7
Chemotherapy + RT + intervention/ Surgery	4	8.4
Chemotherapy/RT + intervention	5	10.4
No treatment received	10	20.8
Adjuvants used		
Gabapentin	18	37.5
Pregabalin	4	8.3
Lignocaine patch	7	14.6
Duloxetine	2	4.2
None	17	35.4
(Edmonton Classification of Cancer Pain [ESC-CP])		
Mechanism of pain		
Neuropathic	41	85.4
Nociceptive	7	14.6
Incident pain		
Yes	36	75.0
No	12	25.0
Psychological distress		
Yes	23	47.9
No	25	52.1
Addictive behaviour		
Insufficient information	2	4.2
No	46	95.8
Cognitive Impairment		
No	44	91.6
Partial	2	4.2
Complete	2	4.2

Discussion

Our study demonstrates that parenteral ketamine administered through a standardised step protocol is effective and well tolerated by patients with predominantly neuropathic cancer pain and this may be due to the following reasons:

Patient selection using a standardised tool to recognise mechanism of pain

Only about half of a study population of cancer patients with neuropathic or somatic pain due to bone metastasis and chemo/radiotherapy-induced mucositis responded in an open label study of a burst ketamine protocol using doses at 100, 300 and 500 mg/24 hours for 3 days.[22] Similarly, a 5-day titration of subcutaneous ketamine versus placebo did not show clinical benefit despite ongoing treatment with opioids and other co analgesics.[10] The lack of response in this study may be due to the patients recruited. They may be representative of the patient population commonly referred to a palliative care service with chronic refractory pain but they may not represent those who will respond to ketamine based on its pharmacokinetics. It may also suggest that ketamine does not show clinical benefit when used as an adjuvant.[23] In contrast, with careful selection of patients, our study utilised ketamine as a

Table 3 Pain score and MEDD at the initiation and final day of ketamine use

Variable	Start of Ketamine	End of Ketamine	Statistical Significance
Average pain score (Mean, SD*)	6.74(±2.41)	2.61 (±2.45)	$P < 0.001$
Average pain reduction (Mean %, SD)	58.05(±40.98)		
MEDD (Mean, SD)	130.34 (±68.51)	107.33 (±57.39)	$P < 0.002$
Final Ketamine Dose (mg) (Mean)		137.50 (±81.54)	

*Standard Deviation.

Table 4 Correlation between final ketamine dose and MEDD and pain score using Pearson's correlation analysis

Variable	MEDD Start	Ketamine End Volume
Average pain score		
Sig (2-tailed)	0.94	0.705

potent NMDA receptor antagonist involved in the desensitisation of the wind-up phenomenon responsible for most neuropathic pain syndromes. This is also supported by recent review on cancer pain affirming that ketamine is best selected for patients demonstrating central sensitisation.[24–26] Furthermore, initiating ketamine early in the treatment process led to better outcomes with minimal side effects with a final mean dose of ketamine that was lower in our study compared with previous studies.[10,12]

The correct classification of cancer pain is a critical component of a comprehensive pain assessment and can help in making therapeutic decisions in relation to the choice of analgesia targeting a specific mechanism of pain. The positive response to ketamine in our study may be due to a well-defined selection of patients with cancer-related complex pain using ECS-CP. The ECS-CP encompasses those dimensions or domains that have been shown to have a significant relationship with pain management outcomes, particularly the achievement of stable pain control. These domains identify the mechanism and presence of incident pain, psychological distress, addictive behaviour and cognitive impairment. The ECS-CP was previously validated in a diverse international sample of advanced cancer patients and was shown to predict pain complexity in a range of practice settings. Patients who were correctly identified based on pain mechanisms receiving individualised treatment resulted in improved pain control.[17]

A step protocol to standardise titration of ketamine, duration of treatment and minimisation of side effects

Potential treatment failure with ketamine in cancer pain management may be related to its premature termination due to unacceptable side effects, with Grade 3 and 4 toxicities occurring in patients receiving more than 300 mg/day of Ketamine.[22] Protocols involving ketamine at dose levels of 100, 300 and 500 mg had a higher rate of adverse events and thus, early withdrawal of treatment. A ketamine protocol using 'burst' or 'pulse' courses at these dose levels reported higher incidence of adverse events with increased dose.[11] In our study, the lowest starting dose of ketamine was 75 mg which was titrated gradually by 100 mg after 24 hours in a stepwise manner until either optimal pain control was achieved or when the maximum dose of 475 mg over 24 hours was reached. The final mean ketamine dose for our patients to achieve stable pain control in this study was relatively low at less than 150 mg/day, which may have led to our patients' tolerance of ketamine with no serious adverse effects. More than half of our patients were able to continue and complete 5 days of ketamine at the lowest effective dose with pain adequately controlled. Side effects were prophylactically managed with the concurrent use of haloperidol.

Table 5 Number of days of ketamine use before optimal pain is achieved

Number of days to achieve optimal pain control	Numbers of patients	Percentage (%)
1	5	10.4
2	17	35.4
3	8	16.7
>3	18	37.5

Table 6 Side effects of ketamine

CTCAE Term	CTCAE Grade	Number of Patients	Percentage (%)
Depressed Level of Consciousness	1–2	15	31.25
Delirium (to include agitation and hallucination)	1–2	10	20.83
Confusion	1–2	5	10.42
Skin Induration	1	2	4.17
Sinus tachycardia	2	1	2.08
Hypertension	1	1	2.08
Extrapyramidal Disorder (tongue dyskinesia)	1	1	2.08
NONE		13	27.09

Use of psychotropic medications to reduce psycho-mimetic effects

Administration of ketamine, an NMDA receptor antagonist may lead to a number of side effects. Confusion, delirium, vivid dreams, hallucinations and feelings of detachment from the body are associated with ketamine use and are particularly prominent.[27] In clinical practice, ketamine exposure is limited because of these side effects. In our ketamine step protocol, the side effects were not as pronounced due to the gradual stepwise increase in ketamine compared to the burst technique and the concurrent use of haloperidol 5 mg as a psychotropic agent. Cohen et al concluded that there was limited direct evidence supporting the prophylactic use of benzodiazepines, alpha-2 agonists, antidepressants, antihistamines, or anticholinergics prior to the initiation of sub-

anesthetic ketamine for chronic pain treatment (grade C recommendation, low level of certainty). Nevertheless, it is noteworthy that most studies reviewed involved much higher doses of ketamine and benzodiazepines were the most common premedication. Haloperidol is still recommended as the first line agent in delirium management and the mean dose reported by Campbell et al in their systematic review was 6.5 mg over 24 hours.[11,28,29] In our study, depressed consciousness, delirium and confusion were still observed even with the addition of parenteral haloperidol but not to the extent that patients needed to discontinue ketamine. We note a safe margin of tolerability evidenced by the low severity based on CTCAE grading for the documented side effects. More studies are needed to assess the effectiveness of psychotropics and benzodiazepines as premedications for ketamine in cancer pain.

Reduction in opioids used concurrently with ketamine

Presently, there are no clear recommendations for the escalation of ketamine and the reduction of opioids when used concurrently.[11–13] In our study, the concurrent opioid dose was reduced by 30% with each dose escalation of ketamine with no compromise in pain control. A systematic review revealed that ketamine reduced opioid requirements, improving pain control by inhibiting activity of NMDA receptors thought to be essential for increased pain sensitivity (wind up) caused by repeated nociceptive stimulation.[21] This reduction of opioid consumption was explained by the effect of ketamine on pain-induced central sensitisation. An alternative reason for this could be based on the ability of NMDA receptor antagonists to inhibit acute tolerance to the analgesic effect of opioids.[30] Two small studies also reported reduction in pain intensity and morphine requirements demonstrating the combined analgesic effect of ketamine and morphine.[31] The method of MEDD reduction by one third is not novel. In the Edmonton 3-day rotation of opioids to oral methadone which is also an NMDA receptor antagonist, there is a daily reduction by one third of the original opioid until the target dose of methadone is reached on the third day whereupon the original opioid is discontinued.[32] Our study demonstrated that opioid reduction after ketamine initiation justifies correct patient selection and supports the pharmacodynamics of ketamine where opioid sensitivity is increased with NMDA antagonism.

Limitations

Our study has several limitations. This study lacks a comparison placebo-controlled group for comparative effectiveness and only involved a single centre PCU in a tertiary hospital. Our patients' pain profile was described based on the ECS-CP. Our study lacks a validated tool like the Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) pain scale where neuropathic pain can be further identified based on analysis of both sensory description and bedside examination of sensory dysfunction which include allodynia and altered pinprick.[33] In our study, pain was classified as predominantly neuropathic when patients described unpleasant sensations in their skin, when pain occurred for no apparent reason intermittently, and when skin in the area affected was abnormally sensitive to touch. Although side effects were carefully monitored and documented on a daily basis, we failed to grade the severity of these events at the same time. CTCAE severity grading was only done retrospectively after all data were gathered. Our study was also limited by a small sample size due to recruitment from a single centre which will limit generalisability. As such, the results of this study should be interpreted with caution**.** The Ketamine Step Protocol needs to be further studied across different palliative care settings in patients with central sensitisation.

Conclusions

Our study showed that a standardised ketamine protocol where ketamine is titrated at a gentle gradation can achieve optimal analgesia in patients identified with neuropathic cancer pain. It also demonstrated a safe and effective method for opioid reduction after commencement of parenteral ketamine, potentially reducing side effects related to opioid toxicity which may also contribute to premature termination of ketamine use. The incorporation of parenteral haloperidol mitigated the side effects of ketamine, ensuring that patients tolerate the ketamine regime. Overall, the step protocol minimised the ambiguity in the administration of ketamine and standardised the monitoring of patients. However, more trials are needed to evaluate the ketamine step protocol and its role in the management of neuropathic cancer pain.

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