Age and Ageing 2024; **53:** 1–8
https://doi.org/10.1093/ageing/afad255

CLINICAL TRIAL

A non-inferiority randomized controlled trial comparing nebulized ketamine to intravenous morphine for older adults in the emergency department with acute musculoskeletal pain

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Abstract

Objective: Our study aimed to investigate the analgesic efficacy of nebulized ketamine in managing acute moderate-to-severe musculoskeletal pain in older emergency department (ED) patients compared with intravenous (IV) morphine.
Methods: This was a non-inferiority, double-blind, randomized controlled trial conducted at a single medical centre. The patients aged 65 and older, who presented at the ED musculoskeletal pain within 7 days and had a pain score of 5 or more on an 11-point numeric rating scale (NRS), were included in the study. The outcomes were a comparison of the NRS reduction between nebulized ketamine and IV morphine 30 minutes after treatment, incidence of adverse events and rate of rescue therapy.
Results: The final study included 92 individuals, divided equally into two groups. At 30 minutes, the difference in mean NRS between the nebulized ketamine and IV morphine groups was insignificant (5.2 versus 5.7). The comparative mean difference in the NRS change from baseline between nebulized ketamine and IV morphine [−1.96 (95% confidence interval—CI: −2.45 to −1.46) and −2.15 (95% CI: −2.64 to −1.66) = 0.2 (95% CI: −0.49 to 0.89)] did not exceed the non-inferiority margin of 1.3. The rate of rescue therapy did not differ between the groups. The morphine group had considerably higher incidence of nausea than the control group (zero patients in the ketamine group versus eight patients (17.4%) in the morphine group; $P = 0.006$).
Conclusions: Nebulized ketamine has non-inferior analgesic efficacy compared with IV morphine for acute musculoskeletal pain in older persons, with fewer adverse effects.

Keywords: ketamine, morphine, pain, numeric rating scale, nebulized, older people

Key Points

- Nebulized ketamine is an effective analgesic for treating musculoskeletal pain in emergency department older adults.
- Nebulized ketamine has non-inferior analgesic efficacy compared with intravenous morphine.
- Acute musculoskeletal pain in older adults.

Introduction

The prevalence of persistent pain in older adults rises from 30% in those aged 65–84 to 34% in those aged 85 or more [1]. These painful conditions are associated with various adverse effects, including decreased mobility, functional decline, frailty, dependency, depression and impaired cognitive function [2–4]. Therefore, providing appropriate analgesia for older patients experiencing pain is crucial, as it can lead to pain reduction and improved satisfaction [5–7]. However, it is important to consider age-related physiological changes in older adults, such as declines in renal and hepatic function, decreased muscle mass and increased adiposity, as these factors can affect medication clearance and distribution volume [8].

Opioids have long been used to treat moderate-to-severe pain; however, their administration in older adults can cause haemodynamic instability, nausea, respiratory depression and central nervous system depression. Consequently, older patients often receive lower rates of opioid medication [9–11]. Ketamine, on the other hand, is a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor complex antagonist that provides analgesia by reducing central sensitisation at the spinal cord and central nervous system level [12]. Sub-dissociative doses of ketamine (SDK) have fewer side effects and do not negatively impact the circulatory or respiratory systems, making it a potentially effective and safer option for pain relief in older patients [13–17].

SDK can be administered intravenously, intramuscularly, intranasally or via nebulization. A study by Motov *et al.* [17] found that intravenous SDK has comparable analgesic efficacy to intravenous morphine in older emergency department (ED) patients for short-term pain relief for up to 120 minutes, although it was associated with a higher rate of psychoceptual adverse effects. A non-inferior, randomized controlled trial conducted by Tongbua *et al.* [18] found that intranasal (IN) ketamine is as effective as intravenous (IV) morphine in providing analgesia for older adults with acute moderate-to-severe musculoskeletal pain. The study also observed no significant differences between the two groups regarding adverse effects or the need for rescue therapy. However, the availability of IN ketamine atomiser devices may be limited in many healthcare settings.

Nebulization of analgesics offers advantages such as rapid and adjustable delivery, reduced pain during administration and minimized toxicity and side effects [19]. When ketamine is administered via nebulization, its bioavailability ranges from 20 to 40% compared with the IV route, and higher doses result in increased maximal concentration values [20]. Two randomized trials focusing on postoperative sore throat demonstrated that nebulized ketamine provided substantial pain relief without significant adverse effects [21, 22]. Another randomized, double-blind trial compared three doses of nebulized ketamine (0.75, 1 and 1.5 mg/kg) delivered through a breath-actuated nebuliser in the ED to patients with moderate-to-severe pain. The study found no differences in efficacy among the three doses and concluded that nebulized ketamine effectively reduced significant pain and provided short-term pain relief for up to 120 minutes with no serious adverse effects [23].

There is no existing literature on the analgesic efficacy of nebulized ketamine in managing acute musculoskeletal pain in older patients visiting the ED. Therefore, we conducted a non-inferiority analysis to evaluate the efficacy and safety of nebulized ketamine compared with IV morphine in older adults with acute moderate-to-severe musculoskeletal pain.

Methods

Study design and setting

This non-inferiority, double-blind, randomized controlled study was conducted at a single tertiary medical centre in Bangkok, Thailand. The Thai Clinical Trials Registry (trial number TCTR20220719005) and the hospital's Institutional Committee on Research Involving Human Participants registered and approved this trial.

Selection of participants

Patients aged 65 years and older who presented to the ED between 1st August, 2022 and 31st May, 2023. Participants were recruited if they had a chief complaint of musculoskeletal pain within the past 7 days and a pain score of 5 or more on an 11-point numerical rating scale [0 (no pain) to 10 (most severe pain)].

Patients were excluded if they had haemodynamic instability (defined as systolic blood pressure of <90 or greater than 180 mmHg, heart rate of <50 or greater than 150 beats/minute, respiratory rate of <10 or greater than 30 breaths/minute), comorbidities of coronary artery disease or congestive heart failure, psychological disorder or severe chronic obstructive pulmonary disease, chronic pain (defined as persistent pain more than 12 weeks after treatment), history of traumatic brain injury, eye injury, seizure, intracranial hypertension, history of morphine or ketamine allergy, history of opioid use within 8 hours, history of alcohol or drug abuse, actual body weight <40 kg or greater than 115 kg, creatinine clearance <30 mL/minute, hepatic insufficiency (abnormal liver function with impaired coagulation [INR > 1.5]), patients requiring immediate intervention, patients with communication difficulties, for example, impaired mental status, severe dementia (defined by a 6-item cognitive screening score of 12 or higher) and language barrier.

Recruitment process

The emergency physician (EP) was the first to assess patients who reported acute moderate-to-severe musculoskeletal pain. Patients who met the inclusion and exclusion criteria were approached by a research assistant (RA) to perform the 6-item cognitive screening test, and those who scored 12 or higher (indicating serious

cognitive impairment) were excluded. Patients who met all requirements provided written consent after the drug delivery, prospective outcomes and adverse effects were explained.

Randomization and marking

Web-based, independent randomization was performed. The schedule was produced using a permutated block with a block length of four. The study participants were divided into two groups. The experimental group was the nebulized ketamine group and the control group was IV morphine. To ensure allocation concealment, the type of pain medication for each patient was kept in a non-transparent envelope and in numerical sequence. The investigator opened the envelope 15 minutes before preparing the pain-relief medication.

Medication preparation

Both morphine and ketamine were colourless. Each patient was administered both nebulized and IV. According to the planned randomization list, an investigator prepared 0.75 mg/kg of nebulized ketamine or 0.1 mg/kg of IV morphine and normal saline solution 5 mL for nebulized or normal saline solution 10 mL for IV. The experimental group of patients received ketamine 0.75 mg/kg via nebulized and normal saline solution (10 mL) intravenously. The control group received 5 mL of normal saline solution with nebulized and 0.1 mg/kg of morphine in normal saline solution up to 10 mL via IV.

Following this process, the treating nurse inserted the appropriate medicine dose into a conventional hospital jet nebuliser with a reservoir tube and a continuous oxygen flow at 8 L/minute for 10 minutes. The drug was permitted to be inhaled for 10 minutes via the jet nebuliser with a reservoir tube, while the research investigators supervised. The research investigator was the only person who knew the study arms to which the participants were assigned. The EPs, nurses, research participants and study evaluators (RA) were unaware of the medicine and blinded to the medications received.

The RA, blinded to the type of medication, recorded pain scores, vital signs, adverse effects and rescue therapy at baseline and at 15, 30, 45, 60, 75, 90, 105 and 120 minutes.

At 30 minutes, if the evaluator indicated an unimproved pain score or a requirement for rescue therapy, the nurse provided fentanyl 0.5 mcg/kg IV after reviewing the patients' needs and conferring with the EP. If the evaluator reported unimproved pain 1 hour after the first rescue therapy, a repeat dosage of 0.5 mcg/kg IV fentanyl might be delivered.

If patients reported nausea and vomiting, IV ondansetron 0.15 mg/kg was considered. If patients exhibit morphine toxicity symptoms, such as slow breathing, lower oxygen saturation, decreased mental status or apnoea, oxygen is administered along with IV naloxone 0.4–2.0 mg every 2–3 minutes.

Safety monitoring

If a patient experienced a severe adverse effect related to their medication, such as anaphylaxis, cardiac arrest, intractable hypotension, hypersecretion or laryngospasm, the study would be immediately discontinued. In such cases, treatment follows the standard guidelines for managing anaphylaxis or cardiac arrest.

To assess medication side effects, the Side Effect Rating Scale for Dissociative Anaesthetics (SERSDA) [24] and Richmond Agitation Sedation Scale [25] were used. SERSDA measures the severity of side effects, including fatigue, dizziness, nausea, headache, feelings of unreality, changes in hearing, mood changes, general discomfort and hallucinations. Additionally, the Aldrete Discharge scores were used to evaluate patients before their discharge from the study.

Outcome measurements

The primary outcome was the comparative reduction in pain scores on an 11-point NRS between the nebulized ketamine and IV morphine groups at 30 minutes.

Secondary outcomes were the incidence of adverse effects and the rate of rescue therapy.

Statistical analysis

Based on the mean difference and standard deviation (SD) between the experimental and control groups in the study by Motov *et al.* [17], which was 0.2 ± 4.834. To determine the test power of 80%, we used a conventional statistical value under the normal curve corresponding to the test power. The sample size under the non-inferiority hypothesis with a non-inferiority margin of 1.3, a mean difference in pain score after 2 hours of -1.5, SD of 4.834, an Alpha (α) of 5% and a power of the test ($1-\beta$) of 80%. Variables were entered into the sample size calculation formula. The sample size was calculated to be 37 participants per group. To avoid dropouts or loss of follow-up participants, the research team enrolled 30% extra participants. The total sample size was 48 individuals, each in the experimental and control groups. The total calculated research sample size was 96.

Stata version 15.1 (Stata Corp., College Station, TX, USA) was used to analyse the clinical data. Categorical variables are shown as frequencies and percentages and were compared between groups using the Chi-square or Fisher's exact test. Primary comparisons between the ketamine and morphine groups are expressed as the mean (SD) at each measurement period. We estimated the mean differences for both groups and the mean difference change in pain score for the NB ketamine group compared with the IV morphine group, with associated 95% CIs. A two-sample independent *t*-test was used to compare changes in the mean and mean difference. Non-inferiority was concluded if the upper bound of the 95% CI for the mean change in pain score from baseline did not exceed 1.3. Secondary comparisons of adverse effects or rescue therapy between the

Table 1. Baseline characteristics

	Nebulized Ketamine, (N = 46)	IV Morphine, (N = 46)
Age (year), median (IQR)	73.5 (71–79)	73.5 (67–81)
Gender, n(%)		
Male	12 (26.1)	14 (30.4)
Female	34 (73.9)	32 (69.6)
*Emergency Severity Index (ESI)[26], n(%)		
ESI 2	16 (34.8)	9 (19.6)
ESI 3	30 (65.2)	37 (80.4)
Weight (kg), median (IQR)	60 (47–68)	57 (50–68)
Comorbidity, n(%)		
Hypertension	29 (63)	29 (63)
Dyslipidemia	26 (56.5)	22 (47.8)
Cerebrovascular disease	5 (10.9)	4 (8.7)
Chronic kidney disease (CrCl >30 mL/min)	4 (8.7)	4 (8.7)
Diagnosis, n(%)		
Superficial injury (contusion, muscle strain, abrasion, laceration)	26 (56.6)	25(54.3)
Upper extremity fracture	10(21.7)	13(28.3)
Lower extremity fracture	10(21.7)	8(17.4)
Pain score, mean ± SD	7.2 ± 1.8	7.8 ± 1.5
Systolic blood pressure (mmHg), mean ± SD	142.5 ± 17.9	145.3 ± 21.5
Diastolic blood pressure (mmHg), mean ± SD	76 ± 9.8	77.2 ± 12.4
Heart rate, mean ± SD	77.2 ± 14.4	73.8 ± 11.4
Respiratory rate, mean ± SD	19.4 ± 1.1	19.3 ± 1.1
Oxygen saturation, mean ± SD	98.7 ± 1.4	98.7 ± 1.4

*P-value <0.05

two groups were performed using Fisher's exact test, and comparisons of vital sign differences were performed using the Wilcoxon rank-sum test.

Results

Over a period of 10 months, 261 patients aged 65 years and older presented to the ED with a musculoskeletal pain score of 5 or higher. Among these patients, 169 were excluded from the study for various reasons. The final analysis included 92 patients, as there were no dropouts or transfers between the groups. Therefore, all the participants were able to complete the study. (Figure 1).

Baseline characteristics

Mean age, comorbidities and vital signs did not differ significantly between the groups that received nebulized ketamine and IV morphine. Both groups had similar baseline pain scores upon presentation as measured using an 11-point NRS. However, the ketamine group had a slightly lower baseline pain score (7.2 ± 1.8) than the morphine group (7.8 ± 1.5). Notably, there was a discrepancy in the distribution of patients with different emergency severity index (ESI) [26] levels between the two groups. Specifically, the ketamine group had more patients classified as having ESI 2 than the IV morphine group (Table 1).

The pain scores were significantly lower in both the nebulized ketamine and IV morphine groups after 30 minutes. The mean pain scores (SD) at 30 minutes in the ketamine group were 5.2 ± 1.9, *P*-value < 0.001 and 5.7 ± 2.3, *P*-value < 0.001 in the morphine group (Table 2).

Primary outcome

The mean reduction in pain scores on an NRS at 30 minutes was −1.96 (95% CI: −2.45 to −1.46) in the nebulized ketamine group and − 2.15 (95% CI: −2.64 to −1.66) in the IV morphine group. The comparative mean difference in the NRS change from baseline between nebulized ketamine and IV morphine [−1.96 (95% CI: −2.45 to −1.46) and −2.15 (95% CI: −2.64 to −1.66) = 0.2 (95% CI: −0.49 to 0.89)] did not exceed the non-inferiority upper limit margin of 1.3 (Figure 2). Similar results were observed at subsequent time points, indicating that nebulized ketamine is non-inferior to IV morphine in reducing pain scores at 15, 30, 45, 60, 75, 90, 105 and 120 minutes (Table 3).

Furthermore, all patients reported acceptable pain reduction (more than three points) at 60 minutes, with a mean reduction of −3.41 (95% CI: −3.99 to −2.84) in the nebulized ketamine group and −3.2 (95% CI: −3.71 to −2.68) in the IV morphine group. The mean group difference in pain score reduction did not exceed the lower limit of the non-inferior margin.

Secondary outcome

The rate of rescue therapy did not differ significantly between the nebulized ketamine and IV morphine groups [5 patients (10.9%) in the nebulized ketamine group versus 11 patients (23.9%) in the morphine group, *P* = 0.1]. Adverse effects, such as nausea and dizziness, were substantially more common in the morphine group (*P* = 0.006 for nausea and 0.02 for dizziness) In the morphine group, two patients experienced generalized discomfort (Supplementary 1).

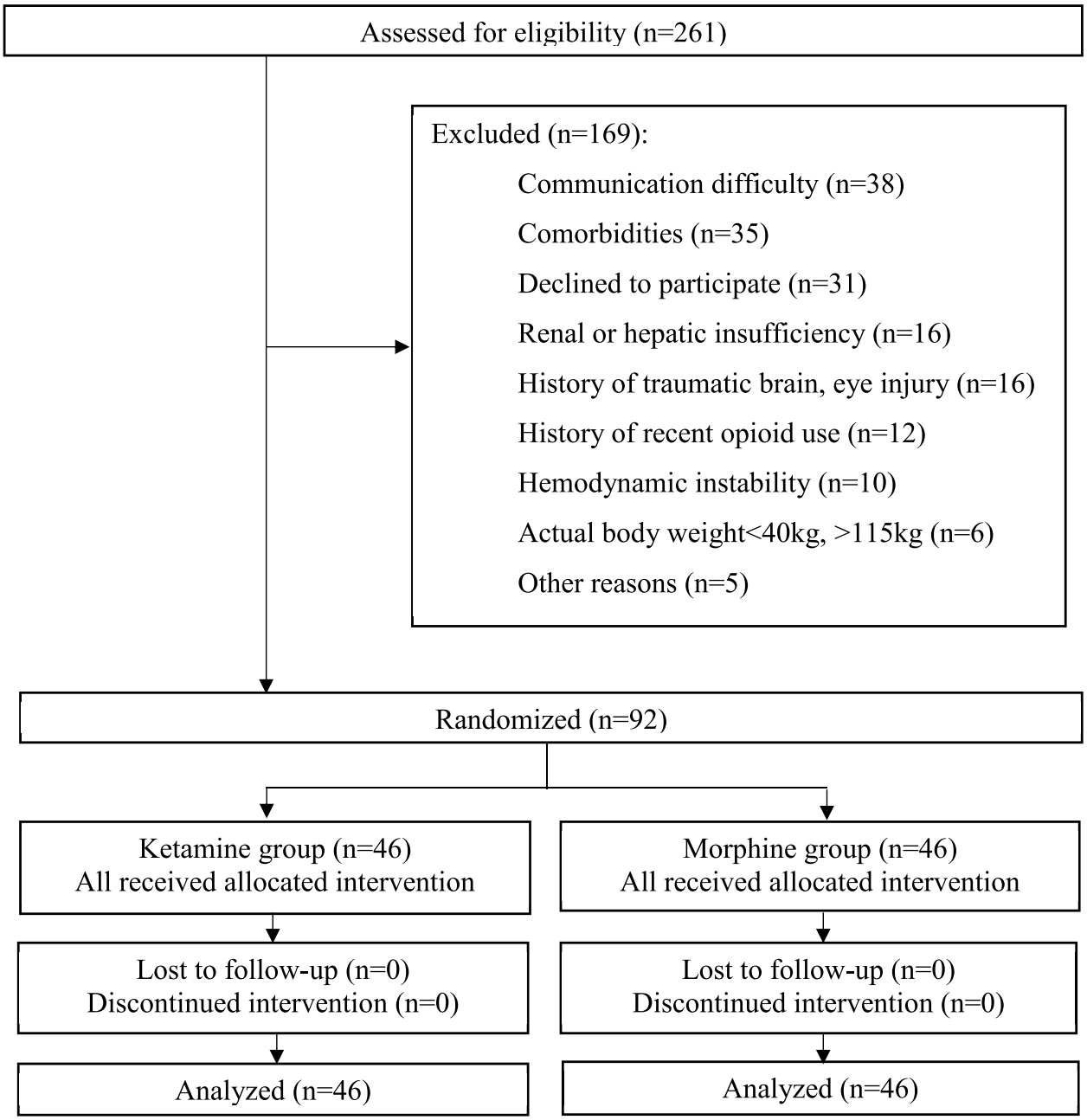

Figure 1. Recruitment of subjects.

There was no statistically significant difference between nebulized ketamine and IV morphine in the recorded vital signs (Supplementary 2–4).

Discussion

The study discovered that nebulized ketamine was not inferior to the standard treatment of IV morphine in terms of pain reduction on an 11-point NRS at 30 minutes in patients aged 65 years and older who presented with acute moderate-to-severe musculoskeletal pain. To our knowledge, this is the first study to compare the analgesic effect of nebulized ketamine with that of IV morphine in older patients in the ED. The non-inferior result is consistent with a study by Azizkhani *et al.* [23], which suggests that nebulized ketamine has a comparable effect to IV morphine in adult patients with limb trauma in a pre-hospital setting. The difference between our study and previous studies was that those studies utilized nebulized ketamine 1.6 mg/kg and measured the pain scale at 0, 5 and 15 minutes after arrival at the ED. The study calculated the mean pain score at each time point, but there were no results for mean differences from baseline; therefore, we could not compare their results to ours.

Effect of both nebulized ketamine dose 0.75 mg/kg and IV morphine exhibited significant analgesic effects at 60 minutes, lasting up to 120 minutes. These findings

Table 2. Compare the pain score before and after using nebulized ketamine or IV morphine

Time (minutes)	Nebulized Ketamine, (N = 46)		IV Morphine, (N = 46)	
	Mean ± SD	P-value	Mean ± SD	P-value
0	7.2 ± 1.8	Reference	7.8 ± 1.5	Reference
15	6 ± 1.9	<0.001	6.6 ± 2.2	<0.001
30	5.2 ± 1.9	<0.001	5.7 ± 2.3	<0.001
45	4.3 ± 2.1	<0.001	5.2 ± 2.3	<0.001
60	3.7 ± 2.1	<0.001	4.6 ± 2.3	<0.001
75	3.1 ± 2	<0.001	4.1 ± 2.2	<0.001
90	2.7 ± 2	<0.001	3.7 ± 2.3	<0.001
105	2.5 ± 1.7	<0.001	3.4 ± 2.1	<0.001
120	2.2 ± 1.7	<0.001	3.3 ± 2	<0.001

Table 3. Change in pain score (NRS) from baseline after 15, 30, 45, 60, 75, 90,105, and 120 minutes of nebulized ketamine and IV morphine administration

Time (minutes)	Nebulized Ketamine, (N = 46) Mean different in change of NRS from baseline (95%CI)	IV Morphine, (N = 46) Mean different in change of NRS from baseline (95%CI)	Mean difference in different (95%CI)
15	−1.11 (−1.52 to −0.7)	−1.2 (−1.67 to −0.72)	0.09 (−0.54 to 0.71)
30	−1.96 (−2.45 to −1.46)	−2.15 (−2.64 to −1.66)	0.2 (−0.49 to 0.89)
45	−2.87 (−3.42 to −2.31)	−2.61 (−3.14 to −2.08)	−0.26 (−1.02 to 0.5)
60	−3.41 (−3.99 to −2.84)	−3.2 (−3.71 to −2.68)	−0.22 (−0.98 to 0.54)
75	−4.07 (−4.66 to −3.47)	−3.72 (−4.24 to −3.19)	−0.35 (−1.13 to 0.44)
90	−4.41 (−5 to −3.82)	−4.07 (−4.61 to −3.53)	−0.35 (−1.14 to 0.44)
105	−4.67 (−5.24 to −4.11)	−4.37 (−4.89 to −3.85)	−0.3 (−1.06 to 0.45)
120	−4.96 (−5.51 to −4.4)	−4.52 (−5.04 to −4)	−0.43 (−1.19 to 0.32)

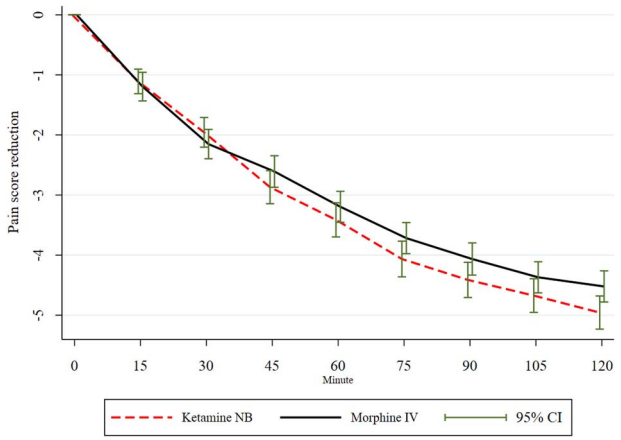

Figure 2. Pain score reduction from baseline after 15, 30, 45, 60, 75, 90, 105 and 120 minutes of nebulized ketamine and IV morphine administration.

conform with Dove *et al.*'s study [22], which performed an randomized controlled trial (RCT) on adults aged 18 and older who presented to the ED with acute moderate-to-severe pain or exacerbation of chronic pain and reported that nebulized ketamine can reduce significant pain and provide short-term pain relief for up to 120 minutes. However, the study reported an average 4-point change in the pain score after 30 minutes, whereas the average change in the pain score at 30 minutes in our study was 1.96 for nebulized ketamine and 2.15 for IV morphine, which was lower than those. This is most likely due to the physiological changes in older persons in terms of drug absorption and excretion, which are delayed and take longer than those in younger adults.

Compared with other methods of drugs administration

According to the study by Tongbua *et al.* [18], which compared IN ketamine to IV morphine, the IN ketamine group had a mean change in pain score from baseline of −2.14 (95% CI: −2.79 to −1.48) at 30 minutes, while the IV morphine group had a mean change in pain score from baseline of −1.81 (95% CI: −2.36 to −1.26). IN ketamine resulted in lower non-inferior pain scores than morphine in older patients. Similarly, our study found that at 30 minutes, ketamine provided a non-inferior reduction in pain score compared with IV morphine. However, there were fewer reports of adverse effects in our study than in other studies.

When compared with IV ketamine administration, Motov *et al.* [17] reported that there was no difference in the change in pain score at 30 minutes between IV ketamine and IV morphine at 30 minutes, while IV ketamine had

more psychoceptive adverse effects than IV morphine which is different from our study.

Adverse effects

In our study, the frequency of morphine-induced, generalized discomfort was higher than that induced by ketamine; however, this difference was not statistically significant. However, morphine significantly induced nausea and dizziness as adverse effects compared with ketamine. These findings align with the results of the study by Azizkhani *et al.* [23], which found that nebulized ketamine is associated with a lower rate of adverse effects. There were no significant changes in vital signs, consistent with the findings of Azizkhani *et al.*

Limitations

A significant number of older adults face challenges related to dementia and cognitive impairment. However, it is important to note that this study specifically excluded individuals with communication difficulties, impaired mental status, severe cognitive impairment and language barriers. Therefore, the present study's findings may not directly apply to this population. We recognize that the exclusion criteria may have influenced its pragmatic use in real-world settings. A large-scale effectiveness trial, ideally multicenter that is pragmatic, inclusive can be accommodated in the future. Another potential concern is the presence of selection bias in the study methodology. The researchers relied on convenience sampling, meaning that the availability of RAs and principal investigators played a role in participant selection.

Additionally, the administration of nebulized medication in this study took place in an isolation room. Given the current prevalence of infectious diseases such as Covid-19, there may be concerns about the potential spread of droplets or airborne pathogens during this procedure. Alternative routes for ketamine and ketamine derivatives delivery are possible such as IN esketamine [27]. Appropriate precautions, including the use of personal protective equipment, should be taken to minimize the risk of transmission during nebulization. Lastly, the adverse events and long-term results following drug administration were not included in our study.

Conclusion

Nebulized ketamine has non-inferior analgesic efficacy compared with IV morphine for acute moderate-to-severe musculoskeletal pain in older persons, with fewer adverse effects.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Acknowledgements: We also acknowledge the employees in the emergency department at Vajira Hospital. We appreciate ENAGO's editing of the English language and Mr Danaiphat Lerdruttanasoontorn's grammar check.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: The Navamindradhiraj University Research Fund provided support for this study, for which the authors are grateful.

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Received 7 September 2023; editorial decision 21 November 2023