Randomized Control Trial of Short Infusion of Low Dose Ketamine Vs Intravenous Morphine as Adjunct Analgesia for Acute Long Bone Fracture Pain in Emergency Department

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Abstract

Background

Ketamine is known as an alternative for pain control, but reports of emergency reactions limits its widespread use. We assessed the efficacy of short infusion of low dose ketamine (LDK) compared with intravenous morphine (MOR) as adjunct analgesia for acute long bone fracture pain.

Methods

Patients aged 18-60 years old, with acute long bone fracture and with numerical pain rating scale (NPRS) of 6 or more after 3mg intravenous morphine were eligible for enrolment. Subjects were consented and randomized to either short infusion LDK (0.3mg/kg) over 15 minutes or intravenous morphine (MOR) (0.1mg/kg) over 5 minutes. Evaluations of NPRS score and vital signs occurred at 15, 30, 60, 90 and 120 minutes. The primary outcome from this study was the mean reduction of numerical pain rating scale (NPRS) score from baseline and the mean time to achieve ³ 3 score reductions in NPRS. The secondary outcomes were the incidence of adverse events and mean consumption of rescue analgesia.

Results

Fifty-eight subjects were enrolled (MOR 27, LDK 31). Demographic variables and baseline NPRS scores MOR (8.33) vs LDK (8.84) were similar. The mean reduction of NPRS were significantly different between LDK (Mean= 3.1, SD=2.03) and MOR (Mean =1.8, SD 1.59), p= 0.009 at 30 minutes. Incidence of dizziness was reported higher in Ketamine group 19.4% (p=0.026).

Conclusion

When used as an adjunct, short infusion low-dose ketamine at 0.3mg/kg over 15minutes provides greater analgesic effect in comparison to intravenous morphine alone for acute long bone fracture pain but has higher incidence of dizziness.

Trial Registration

National Medical Research Register: https://www.nmrr.gov.my/ Registered 24 November 2017 ID:NMRR-17-3184-38970

Background

Pain is a common cause of emergency department visits. 80% of patient with musculoskeletal injury has moderate to severe pain. Pain is the common cause of the emergency department visits and 80% of patients with musculoskeletal injury has moderate to severe pain [1].Each year millions of people from all over the world suffer from bone fractures due to incidence of traffic accidents. One of the most important measures in the management of such patients in emergency department is fixation and pain control.

Malaysia is one of the countries that have highest traffic fatality rates in the world with 25 fatalities/100,000 population which is only second to Thailand in South East Asia[2].

Tackling pain control in this group of patients has been a great challenge for many physicians. Currently the standard practice to treat fracture pain is with opioids[3]. Besides opioids, other medications to treat the acute pain are non-steroidal anti-inflammatory drugs, acetaminophen, and regional treatments. However, it is not recommended to administer opioids repeatedly to patient with acute pain, as it may lead to adverse effect such as hypotension and respiratory depression [4]. Additionally, many patients report inadequate pain control in the ED with opioids [5]. A study done in Malaysia in 2007 reported that only 26.5% of 85% patients in moderate and severe pain received analgesia in the emergency department despite the pain score being displayed on patients' case notes. In emergency department in United States, a 0.1mg/kg dose of intravenous morphine was not adequate for controlling severe acute pain in most patients[6]. A post-operative pain study demonstrated that patients needed on average 12mg or a mean weight-based of 0.17mg/kg of morphine to achieve an acceptable level of pain reduction as determined by a 30mm change on a visual analogue scale.[7]

Besides that, an epidemic of opioid misuse in the US has grown extensively to 300% increase in the past decade for opioid drug overdose death and a two-fold increase in emergency departments' visits for opioid misuse and abuse[8]. Despite limited research for opioid overdose in Malaysia, a study showed that there is a higher prevalence of non-fatal overdose of opioids reported[9]. For this reason, alternative or adjunct to opioids therapy is needed.

An alternative medication is ketamine. In Malaysia, intravenous Ketamine is used in Anaesthesiology Department as an analgesic adjuvant to general anaesthesia and patient controlled anaesthesia (PCA) such as major visceral surgery or hip surgery [10]. It is also used for analgesia and sedation for burns and repeated wound dressing especially in paediatric as it preserves the pharyngeal reflexes, cardiovascular stability and less respiratory depression [11]. Ketamine has also been used for pain control but in much lower dose that does not sedate patients. When it is given in sub dissociative doses, it prevents the development of increased pain sensitivity and opioid tolerance in a variety settings outside of ED [12–14]. In the emergency department, Ketamine at a dose of (1 to 1.5mg/kg) has been commonly used for procedural sedation as well as an induction agent for rapid sequence intubation but its use as analgesia has been slower to gain momentum due to reports of emergence reactions (anxiety, nightmares, hallucinations, delirium) [15].

However, recent studies suggest the use of sub dissociative ketamine doses for acute pain control. Ketamine at sub dissociative dose of (0.1-0.6mg/kg) and particularly at a dose of (0.3mg/kg) gives analgesic effect while maintaining the airway reflexes is comparable with intravenous morphine for acute treatment of pain in ED [16, 17]. However, there is a higher incident of adverse effect such as emergence phenomenon occurred when ketamine is given as intravenous push. A recent study by Motov et al. compared intravenous push of low dose ketamine versus short infusion of low dose ketamine in 15 mins for undifferentiated pain such as abdominal, flank or low back pain in Emergency Department reported

that by giving short infusion of low dose ketamine significantly reduce unreality adverse effect without compromising the analgesic effect [18].

To the best of our knowledge, there are limited studies regarding short infusion low dose ketamine in ED as adjunct analgesia for acute long bone fracture pain. Therefore, we hypothesized that, when use as an adjunct, short infusion low dose ketamine has the analgesic effect comparable with IV morphine in acute long bone fracture in the emergency department. The primary outcome of effectiveness is measured by mean reduction of pain score. The amount and timing of administration rescue opioid analgesia was also be evaluated as outcome. The adverse events of intravenous morphine and short infusion of low dose morphine will be monitored.

Methods

Study Design

This was a single-center, prospective, randomized, single-blinded trial study comparing short infusion low dose ketamine (LDK) versus intravenous morphine as adjunct analgesia for acute long bone fracture pain in ED.

Study Setting and Selection of Participants

This study was conducted in a 620-bed hospital with an annual ED census of more than 160,000 visits. Enrolment occurred from May 2018 until February 2019. Patients were recruited at unplanned intervals during the study period, subject to availability of the investigators and patient consents. Patients were eligible for enrolment after they were assessed by attending emergency medicine residence or emergency physician on duty as having the following: were aged 18 years old to 60 years old, able to give consent, conscious (Glasgow Coma Scale [GCS] score = 15) with long bone fracture (femur, tibia/fibula, humerus and radius/ulna bone) and with numerical pain rating scale (NPRS) score greater or equal to 6 after 3mg of intravenous morphine given by the treating physicians in ED. Exclusion criteria consisted of altered mental status (GCS $\leq$ 14), pregnant, breast feeding patient, allergic to ketamine or morphine, hemodynamically unstable vital signs (systolic blood pressure < 90 or > 180mmHg, pulse rate < 50 or > 150 beats/min, and respiratory rate < 10 or > 30 breaths/min), and medical history of acute head injury or eye injury, seizure, intracranial bleed, renal or hepatic insufficiency, ischemic heart disease, cerebrovascular accident, asthma or chronic lung disease, drug or alcohol abuse, psychiatric illness.

Study Protocol

After written informed consent was obtained, each participant enrolled in the study was randomly assigned according to a predetermined randomization list that was generated using IBM SPSS Statistic 23.0 by the investigator. Participants were randomized to either short infusion LDK (0.3mg/kg) mixed in 100 mls normal saline solution given over 15 minutes or intravenous MOR (0.1mg/kg) in 10 mls normal saline solution over 5 minutes. ED pharmacist on duty who was independent of this study was alerted regarding the patients' body weight for drug randomization and preparation, while the treating nurse who

was briefed and taught on administration of the intervention or control medication prior to intervention, administered the medication to eligible patients. This was a single-blinded protocol study; thus, the investigator, ED pharmacist, treating providers and statisticians were the only ones with the knowledge of the study arm to which patients was randomized. However, to minimize bias, the researcher had appointed one independent individual who was not a part of the study team (trained nurse) to assess vital signs and pain score after administration of medication. This individual was trained to assess vital signs and pain score prior to starting of this study. This independent individual was blinded from the treatment arm and recorded pain score, vital signs and adverse effects at baseline, 15 min, 30 min, 60 min, 90 min and 120 min. For participants reported of NPRS score ≥ 6 and still desiring pain medication 30 min after study drug administration, investigator offered intravenous fentanyl 1-2mcg/kg, maximum 100 mcg, as rescue analgesia. Data collection ended at 120 minute or upon patient admission or whichever came first. This study was approved by Malaysian Research and Ethics Committee (MREC) Malaysia and was registered with the National Medical Research Register (NMRR-17-3184-38970). Written and signed informed consent was obtained in accordance with institutional policy.

Data Analysis

Power analysis determined that a sample size of at least 20 subjects per group would achieve 80% power to detect a 2-point change in NPRS scores between treatment groups, with estimated groups of SDs of 2 for a 2-sided test with a significance level α of 0.05. We used repeated measures linear model with adjustments for treatment group, time and the group by time interactions. All analyses were performed with intention to treat. Data entry and analysis were done using Statistical Package for Social Science (SPSS) version 23.0 software. The statistical analysis included descriptive analysis such as mean, standard deviations, percentage, independent t-test and Chi-Square test. Statistical significance was set at $P < 0.05$ in the analyses.

Results

A total of 58 patients were enrolled in the study from May 2018 to February 2019; 27 in the morphine arm and 31 in the low-dose ketamine arm

Demographic characteristics were similar between 2 groups including median age, sex, baseline vital signs, site of fractures and baseline NPRS scores MOR (8.3) vs LDK (8.9) were similar (Table 1).

Table 1
Baseline Patients Characteristic

Variable	Morphine (n = 27)	Low-dose ketamine (n = 31)	*P* value
Age (years)	25(12) *	27(17) *	0.487
Gender			
Male (n%)	24(46.2)	28(58.3)	0.861
Female (n%)	3 (50.0)	3 (50.0)	
Weight	64.44(12.3) #	66.23(12.7) #	0.593
Mechanism of injury			
Road Traffic injury (n%)	25(47.2)	28(52.8)	≥ 0.995
Fall (n%)	2(50.0)	2(50.0)	
Site of fracture			
Upper extremities (n%)	2 (28.6)	5 (71.4)	0.203
Lower extremities (n%)	26 (50.0)	26 (50.0)	0.90
Baseline NRS pain score	8.3 (1.3) #	8.9 (1.2) #	0.136
Note: *Data not normally distributed presented as Median (IQR) # Data presented as mean (SD)			

The primary outcome was the mean reduction in NPRS score from baseline between 2 groups (Table 2). Both treatment groups showed significant reduction from baseline. At 30 minutes, short infusion LDK group had significantly greater mean reduction in pain from baseline (Mean reduction = 3.1, SD = 2.05) in comparison with morphine (Mean reduction = 1.8, SD = 1.59), t (56) =-2.70, p = 0.009. At 60 minutes, the mean reduction of NPRS score were also significant in low-dose ketamine (Mean reduction = 3.5, SD = 2.17), in comparison with morphine (Mean reduction = 2.4, SD = 1.84), t (56) =-2.09, p = 0. 041.There was no significant difference in mean reduction of pain score found in other interval times.

Table 2
Comparison of mean NPRS between patients treated with IV morphine or Short infusion low-dose ketamine based on time

Study Drug	Time (minutes)	Mean NPRS score (SD)	Estimated marginal mean (95% CI)
Morphine	0	8.3 (1.3)	7.84,8.83
	15	7.1 (0.36)	6.34,7.79
	30	6.6 (0.33)	5.86,7.18
	60	5.9 (0.34)	5.29,6.64
	90	5.4 (0.40)	4.57,6.17
	120	5.1 (0.39)	4.29,5.86
Low-dose Ketamine	0	8.9 (1.2)	8.37,9.34
	15	6.7 (0.35)	5.98,7.38
	30	5.8 (0.32)	5.24,6.54
	60	5.6 (0.33)	4.95,6.27
	90	5.3 (0.40)	4.54,6.11
	120	5.5 (0.39)	4.69,6.24
Repeated Measures ANOVA			
SD = Standard Deviation CI = Confidence Interval			

Figure 2 showed the comparison of pain scores over all time points, which demonstrates the mean pain numeral rating scores in both groups. There was significant difference at 30 min between low-dose ketamine infusion and morphine ($p = 0.009$)

The proportion of patients reporting a 3-point or more reduction in pain numeric rating scale score at 15 min and 30 min between low-dose Ketamine and Morphine were significantly different ($p = 0.042$) and ($p = 0.014$) (Table 3)

Table 3
Comparing mean reduction of NPRS score from baseline within patient treated between morphine and short infusion low-dose ketamine

Time	Morphine Mean (SD)	Ketamine Mean (SD)	Mean difference (95% CI)	*P* value
T15*	1(2)	2(4)		0.113[a]
T30	1.8(1.59)	3.1(2.05)	-1.3 (-2.29, -0.34)	0.009[b]
T60	2.4(1.84)	3.5(2.17)	-1.1(-2.27, -0.08)	0.041[b]
T90	3.0(2.03)	3.5 (2.63)	-0.6 (-1.85, 0.70)	0.371[b]
T120	3.3(2.23)	3.4 (2.47)	-0.1 (-1.41, 1.14)	0.834[b]

Note:

*Data not normally distributed presented as median (IQR)

a Mann-Whitney test b Independent t test; SD=Standard Deviation;

CI= Confidence Interval;

The median amount of fentanyl as rescue analgesia administered to both groups was not significantly different (morphine: 50mcg [IQR = 8] vs ketamine: 50 [IQR = 6]; p = 0.921). The proportion of rescue analgesia between both groups were not significantly different ($p = 0.336$) (Table 4).

Table 4
Rates of rescue analgesia over time

Time of rescue analgesia	Morphine n = 27 n (%)	Ketamine n = 31 n (%)	*P* value [a]
30 min [c]	1 (3.7%) [b]	2 (6.4%) [b]	≥ 0.995
60 min	4 (14.8%)	3 (9.7%)	0.694
90 min	2 (7.4%)	5 (17.9%)	0.432
120 min	2 (7.4%)	2 (7.10%)	≥ 0.995
Total	9 (33.3%)	10 (32.3%)	0.366
[a] Fisher's exact test [b] Frequency (percent)			
[c] No rescue analgesia given before 30 min			

No serious adverse events occurred in either drug group; these includes, respiratory distress, seizures, cardiac arrest or allergic reaction (Table 5). The prevalence of patient reported dizziness was statistically significantly observed in low-dose ketamine in comparison with morphine ($p = 0.026$). Fatigue and headache were also reported in low-dose ketamine. One patient in low-dose ketamine was reported to have hallucination but no intervention was required.

Table 5
Adverse effects encountered in each group at any point throughout the study period

Adverse effects	Morphine n = 27 n (%)	Ketamine n = 31 n (%)	*P* value [b]
Fatigue	0	3(9.7%) [a]	0.24
Dizziness	0	6(19.4%)	0.026
Headache	2(7.4%) [a]	2(7.1%)	≥ 0.995
Hallucinations	0	1(3.6%)	≥ 0.995
[a] Frequency (percent) [b] Fisher's exact test			

Discussion

Our study has found that short infusion low-dose ketamine as an adjunct analgesia to intravenous morphine for patients with acute long bone fractures reduces the numerical pain rating scale (NPRS) score and the mean time to achieve ≥ 3 reductions in NPRS.

Short infusion low-dose ketamine whether as adjunct to opioids or as single agent for analgesia is a promising alternative for acute long bone fracture pain management in ED. Its unique mechanism of actions that blocks non-competitive antagonist of the *N*-methyl-*D*-aspartic acid (NMDA) receptor and glutamate receptor antagonist that decreases sensitization at CNS and spinal cord level gives the effects of analgesia, hypnotic and amnestic[19] but adverse effects of emergence reactions limits its usage as analgesia in ED. Several studies have been published regarding ketamine as analgesia in ED setting. An out of hospital setting by Johansson et al [20] demonstrated a significant reduction of pain score in morphine-ketamine combination group by 5.4 points in comparison to 3.1 points of morphine alone. Jennings et al [14] demonstrated that morphine and ketamine combination group is superior than morphine group alone with mean pains score change of -5.6 (CI -6.2 to 5.0) and 3.2(CI -3.7 to -2.7) respectively. Beaudoin et al[21] demonstrated that IV morphine 0.1 mg/kg with IV ketamine at 0.3mg/kg had higher pain relief than ketamine at 0.15 mg/kg. Miller et al [22] compared low-dose ketamine with IV

morphine in ED but concluded that ketamine at 0.3 mg/kg was not superior to morphine in maximum reduction of pain score. In addition, the author concluded that analgesic effect in low dose ketamine was significant within 5 minutes and provide moderate reduction in pain for 2 hours. Motov et al [18] demonstrated that short infusion low dose ketamine is associated with lower rates of unreality with no significant difference in analgesic efficacy ($p < 0.001$).

In this prospective, randomized control trial study, we compared short infusion low dose with single dose morphine as adjunct analgesia for acute long bone fracture pain in ED. All patients were administered with 3 mg of morphine before randomization and enrollment into the study. This was an important component to the protocol because ketamine was not routinely administered as first-line analgesic. It was reserve to patient whose pain was refractory to morphine. Administering ketamine as the initial parental analgesic agent would not reflect the actual practice. Despite Motov et al. reported that mean NPRS from baseline to 30 min between both treatment groups were not statistically significant different [17], interestingly our study demonstrated that low-dose ketamine provides safe and effective adjunct analgesia to acute long bone fracture patient, with mean reduction pain score (Mean = 3.1, SD = 2.05) in compare with morphine (Mean = 1.8, SD = 1.59), $p = 0.009$ was significant observed at 30 min and lasting up to 60 min. It is interesting to note that the proportion number of patients reporting a 3-point or more reduction in pain numeric rating scale score at 15 min and 30 min between LDK and MOR were statistically significant different ($p = 0.042$) and ($p = 0.014$) respectively. Even though these results differ from earlier studies, the authors reported that at 15 min, complete resolution of pain was observed in ketamine group compare to morphine group [17].

This effect maybe due to the synergic effect of morphine and ketamine combination which enhanced the analgesic effect [23]. The mean pain score plotted over time differed between both groups (Fig. 2); ketamine group has steeper slope reflecting the rapid reduction of pain score over time in comparable with the morphine group. However, the analgesic effect of low dose ketamine was unable to sustained after 60 min thus frequency of low-dose ketamine requiring rescue analgesia increased at 90 min. This finding contradicts with that of Beaudoin et al, who reported a greater pain reduction in patient who received ketamine over a 2-hour period [21]. Beaudoin et al. reported the median dose of rescue analgesia was 4.9mg to 6.1mg of intravenous morphine. In addition, the median time in which rescue analgesia was administered ranged between 54–143 minutes which may explained the observed reduction of pain score beyond 2 hours. In contrast with our study, the median dose rescue analgesia administered was 50mcg of intravenous fentanyl while the mean time rescue analgesia was administered ranged between 72–107 minutes. We strongly believed that if ketamine was infused over a longer period or ketamine was administered in repeated doses, perhaps the further decreased of pain score could have been observed over 60 min.

There was no serious adverse event reported during the study but the incident of dizziness was reported more in the low-dose ketamine group ($p = 0.026$) in comparison with morphine. These findings are consistent with a previous study conducted by Ahern et al [24] of which 24 of 30 patients (80%) who received IV combination of hydromorphone 0.5mg and ketamine 15mg experienced dizziness being most

common. Beaudoin et al [21] also reported that 9 of 20 (45%) combination of IV Morphine 0.1mg/kg and IV Ketamine 0.3mg/kg reported dizziness. By reviewing previous studies, there is a strong probability that the incidence of adverse effect reported in low-dose ketamine may be attributed to the rate of initial bolus administration and the dilution for ketamine. We believe that further trials of ketamine dose ranges and duration of infusion, may diminished the adverse effect of neuropsychological without compromising the analgesic effect.

Some limitations need to be acknowledged. First, this was a single blinded study conducted in a single center. The investigators were not blinded from the study and the outcome may be skewed despite an independent individual who is not part of the study (trained staff nurse) who recorded the vital signs and pain score from the participants. Second, patient enrollment was subject to the availability of the investigators and the number of enrolled subjects may not represent the rest of the population of the country.

Conclusion

The evidence from this study points that, when used as an adjunct, short infusion low-dose ketamine at 0.3mg/kg over 15minutes provides greater analgesic effect in comparable with intravenous morphine alone for acute long bone fracture pain but has higher incidence of dizziness. Short infusion low-dose ketamine can be given in emergency department as analgesia on patients with long bone fractures for painful procedures such as applications of splints and wound irrigations. Future studies are highly recommended with a bigger sample-pooled size such as a superiority study design with multiple center sites due to its advantages in mean pain reduction from baseline in compare with intravenous morphine alone.

Abbreviations

BP
Blood pressure
CRC
Clinical Research Centre
ED
Emergency department
IBM
International Business Machine
MOR
Morphine
NPRS
Numerical Pain Rating Scale
GCS
Glasgow Coma Scale

LDK
Low-dose ketamine
IV
Intravenous
MREC
Medical Research and Ethics Committee
NMDA
N-methyl-*D*-aspartic acid
NMRR
National Medical Research Register
PCA
Patient control analgesia
PSA
Procedural sedation analgesia
SPSS
Statistical Package for the Social Sciences

Declarations

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Authors' Contributions

All the authors made substantial contributions to the concept or design of the work; acquisition, analysis, or interpretation of data; drafted the article or revised it critically for important intellectual content; and approved the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Availability of data and materials

Data are available on request to the corresponding author.

Ethics approval and consent to participate

This study was approved by Medical Research and Ethics Committee (MREC) and registered with the National Medical Research Register (NMRR-17-3184-38970) on 24 November 2017. Written informed consent was obtained from patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Consent for publication

Not applicable

Competing interests

The authors declare that there is no conflict of interest

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Figures

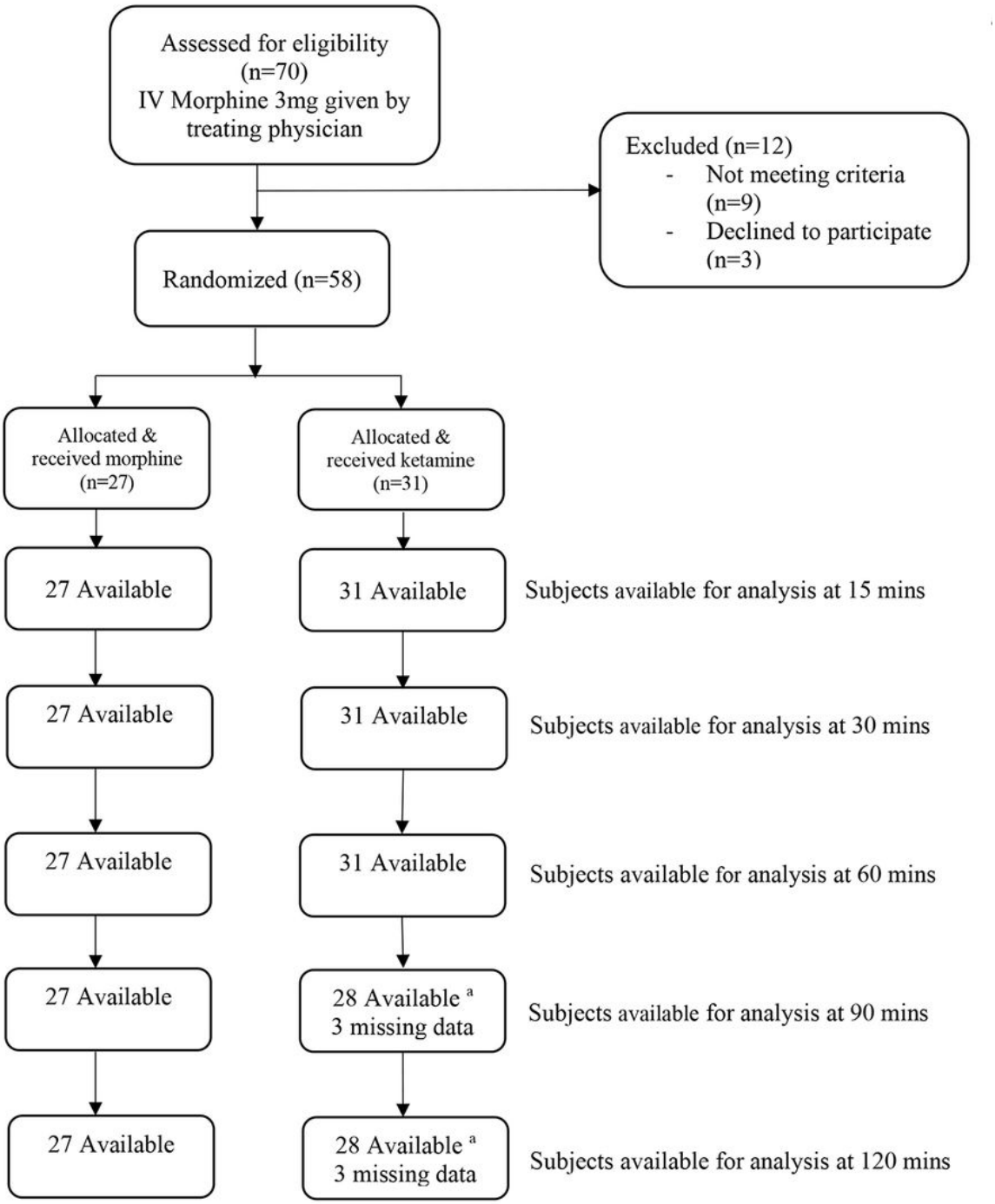

Figure 1

Study flow for consented subjects. a Subjects were missing data because of transfer from the ED to ward.

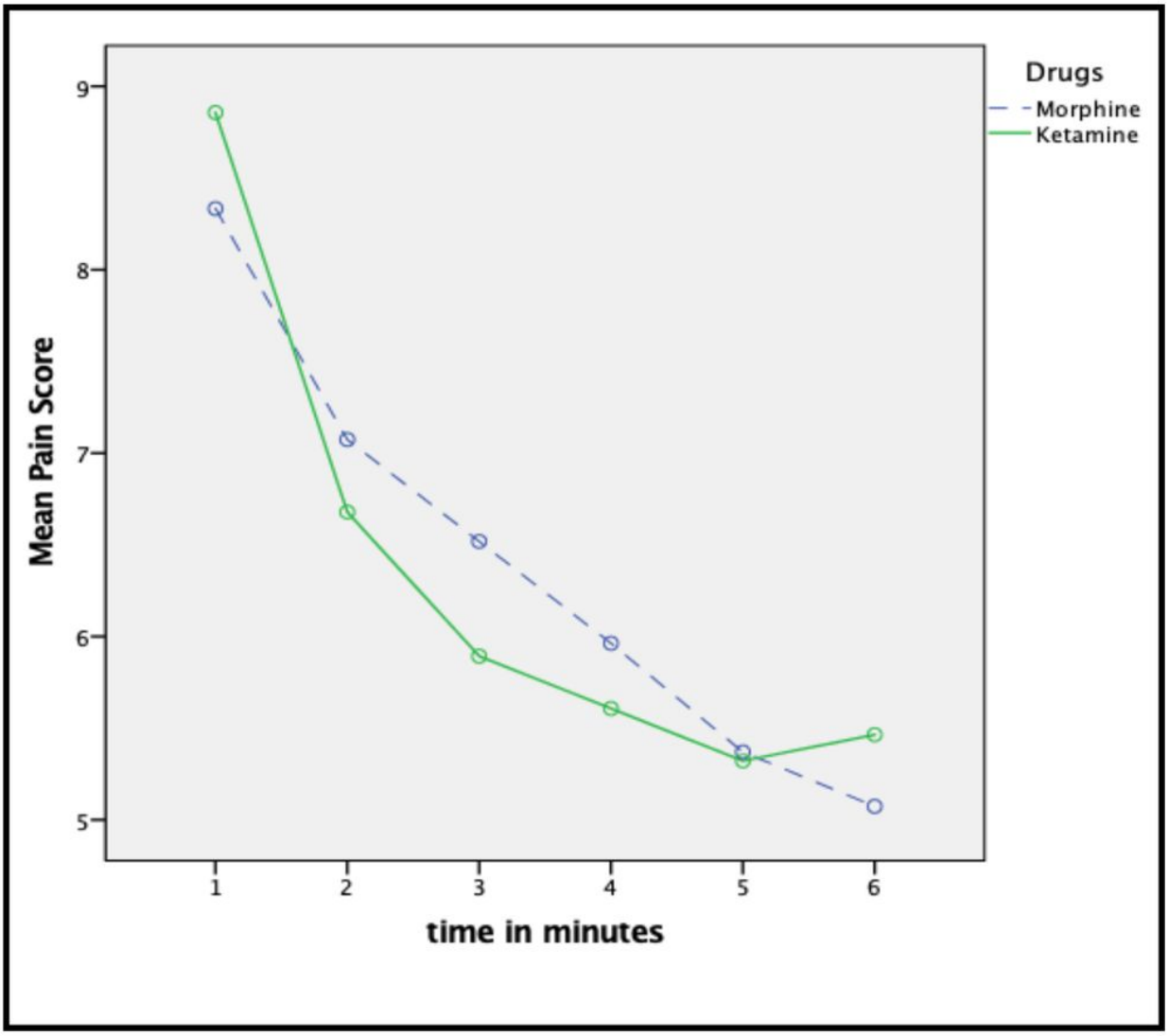

Figure 2

Mean pain score over time.