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Original Article

# Comparative safety and efficacy of low dose ketamine and opioids for acute pain management at the emergency department

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## Abstract

**Background:** Pain is a complex phenomenon for which many pharmacological agents have been discovered and utilized for pain relief. Ketamine is a more preferred pain reliever over opioids in the emergency department (ED). The aim of this study was to compare the safety and efficacy of low dose ketamine (LDK) with morphine (opioid) for pain relief among patients presenting to the ED.

**Methodology:** A prospective, cohort study was conducted over a sample of 280 patients presented with acute pain to the ED, Ziauddin University Hospital, Karachi. These patients were then divided into two groups via simple random sampling with randomization being assured using an online randomizer software tool. The 1st group (n=140) was given 0.2 mg/kg of LDK while 0.1 mg/kg of intravenous morphine (opioid) was given to the 2nd group (n=140). The pain intensity was measured using the Visual Analogue Scale (VAS) from admission to 60 mins, the records were taken after every 15 mins. The adverse events (AE's) were also recorded for both groups. The data was then analyzed using SPSS Version 21 & Microsoft Excel 2016.

**Results:** Out of 280 patients enrolled in the study, there was male majority i.e. 76.07% while the remaining were females with the mean age of 29±7 years. Within 15 minutes of initial dose administration in both groups, a marked reduction in pain intensity was observed. Reduced respiratory rate, pruritus and decreased O2 saturation were common AE's observed, which were comparatively higher among patients receiving morphine as compared to ketamine.

**Conclusion:** The efficacy of morphine (opium) and LDK is similar in alleviating pain in an emergency setting, however, LDK is visibly safer than its opioid counterpart and thus may be used as a safer alternative.

## Keywords

Low Dose Ketamine, Opioid Analgesic, Analgesic, Acute Pain, Oxygen Saturation.

## Introduction

Pain is among the most frequent complaints presented at the ED[1], its effective management plays significant role in patient satisfaction and reduces the probability of associated adverse physical and mental complications like persistent pain syndrome and anxiety which further leads to high levels of patient distress[2].

Mostly commonly preferred choice for treating acute pain at the ED is intravenous opium (derivative)[3]. The provably strong analgesic effect of opioid derivate, its easy availability and cost-effectiveness are the major reasons behind its use as an ideal emergency option worldwide. However, like every other pharmacologic agent, the benefits come together with some adverse events (AE's), heavy sedation and depression of the respiratory system are among common AE's associated with opioids[4]. Which can be modified and controlled by dose regulation but lowering the dose results in compromised effectiveness[5]. Whereas, Ketamine has been under constant utilization as analgesic agent and manifests a wide array of pharmacological effects, others than its chief objective, which include sedation, somatic analgesia, catalepsy and bronchodilation[6]. The quick onset of analgesic action even at low doses without any serious incumbent risk of respiratory distress has widely promoted its use in EDs and various other areas for pain management[7].

Intravenous Ketamine is given in the dose less than 1 mg/kg as LDK[8]. A thorough literature search identified that supplementary administration of LDK in addition to morphine, aids in decreasing the dose of opioid derivatives that are needed to limit the AE's and also maintaining effectiveness[9]. By lowering opioid tolerance and manifests a prominent opioid-sparing effect[10]. Therefore, ketamine is formally recommended for pain alleviation in many different clinical scenarios including postoperative conditions and cancer-associated instances[11]. Furthermore, detailed research attempting to investigate the effects of ketamine in varied settings such as gastroenterology[12], anesthesia[13] and emergency medicine[14], have demonstrated that the efficacy of LDK as an analgesic, as a sole pharmacologic agent or as an adjunct pharmacologic agent to opioids. A study conducted at ED-affiliated mobile intensive care units in France showed that LDK had an opioid-sparing effect in trauma patients with acute pain[15].

To the best of our knowledge, locally no reports of LDK administration in the ED for the treatment of pain and a direct comparison of LDK with opioid alternatives has not been reported and published in the medical literature. This study may be the first to compare efficacy and safety of two common analgesics, intravenous LDK and morphine (opioid) for treatment of acute pain among patients presented to ED at a tertiary care hospital, Karachi – Pakistan.

## Methodology

This prospective cohort study was conducted at ED, Ziauddin University Hospital, Karachi. A total 280 patients presented with the complaints of acute pain were enrolled in the study after attained written informed consents. Patients irrespective of gender were included in the study sample and randomly divided into two groups with 140 patients in each group. The 1st group received 0.2 mg/kg of LDK while the 2nd group received 0.1 mg/kg of intravenous morphine (opioid).

Non-consenting patients and patients presented with instable vital signs, head injury, chronic opiate abusers and psychiatric disabilities were excluded from the study. Patients with any major systemic diseases

(cardiac or metabolic), hypersensitivity to ketamine or morphine, patients presently pregnant and/or lactating and patients with renal or hepatic insufficiency or those with contraindications to use both medications (including hypersensitivity or upper respiratory infections or hypersensitivity) and those with GCS score less than 15 were also kept under exclusion criteria.

The data obtained was recorded by means of a structured questionnaire inquiring patients' demographic details. The pain intensity and AE's were monitored after every 15 minutes, from admission to 60 mins. Pain was assessed using the VAS score where 0 represents no pain and the scale progression is indicative of increasing paint intensity. Recorded data was analyzed using SPSS Version 21 & Microsoft Excel 2016.

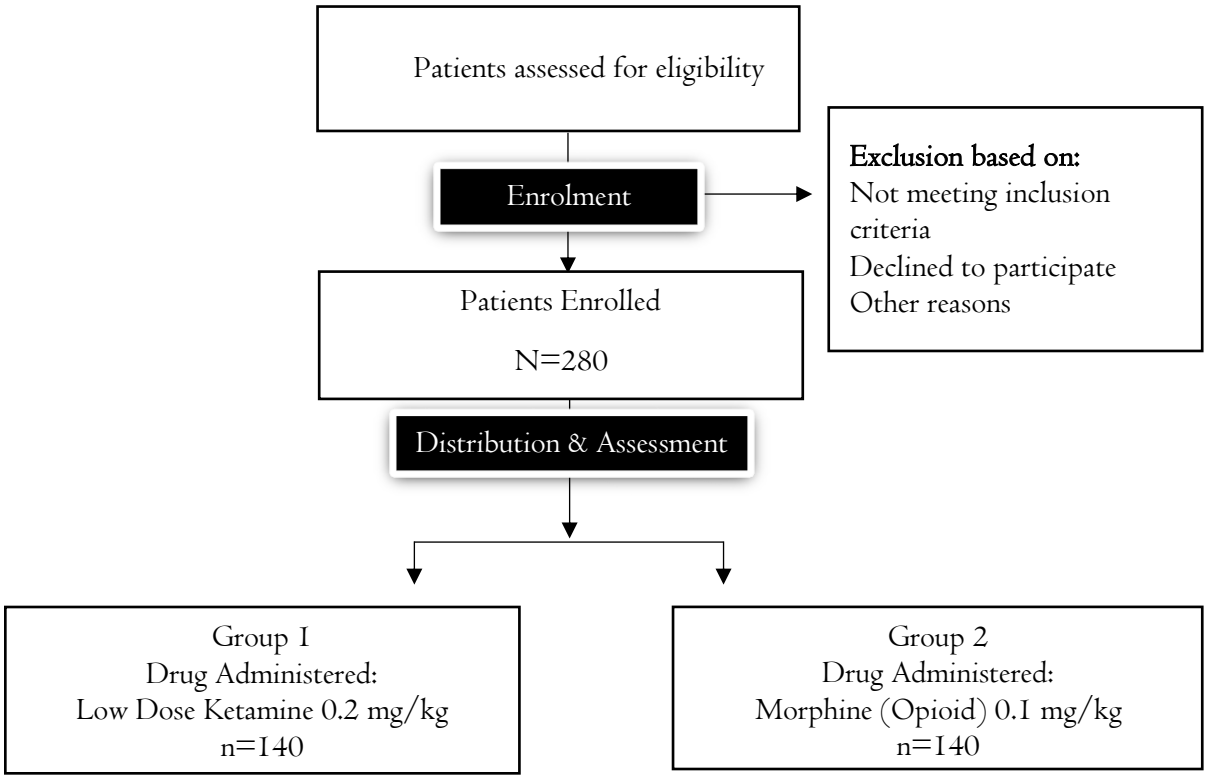


**Figure 1: Enrolment and distribution of patients enrolled in the study.**

## Results

The demographic characteristics of the study patients are given in table I, the patients mean age was 29±7 years. No age and gender restrictions were considered in the study but depending upon the rate of presentation at the ED and consent, there was an overall male majority i.e. 213 out of 280 were male patients.

**Table I: Demographic characteristics of the patients enrolled.**

| Variables | Sub-categories | (n=280) |
|---|---|---|
| Age (Mean ± SD) | | 29±7years |
| Gender [n (%)] | Males | 213(76.07) |
| | Females | 67(23.93) |

Marked reduction in pain intensity was observed within 15 mins of drug administration in both groups. The pain intensity was recorded 5 times (after every 15 minutes) starting from 0 minutes to 60 mins and no significant difference was observed in the efficacy of the two drugs as the decreasing trend of pain intensity was quite similar among patients of both groups (Table 2 & Figure 2).

**Table 2: Comparative drug efficacy in reducing pain intensity among patients of both groups**

| Variables | | LDK | Morphine |
|---|---|---|---|
| Pain Score | Before Intervention | 8.9±1.3 | 9.1±1.1 |
| | 15 min | 5.3±0.9 | 4.9±1.0 |
| | 30 min | 4.7±0.7 | 4.5±1.1 |
| | 45 min | 4.1±0.8 | 4.1±0.9 |
| | 60 min | 3.7±0.7 | 3.6±0.8 |

*Values are given as mean±SD
*LDK-Low Dose Ketamine

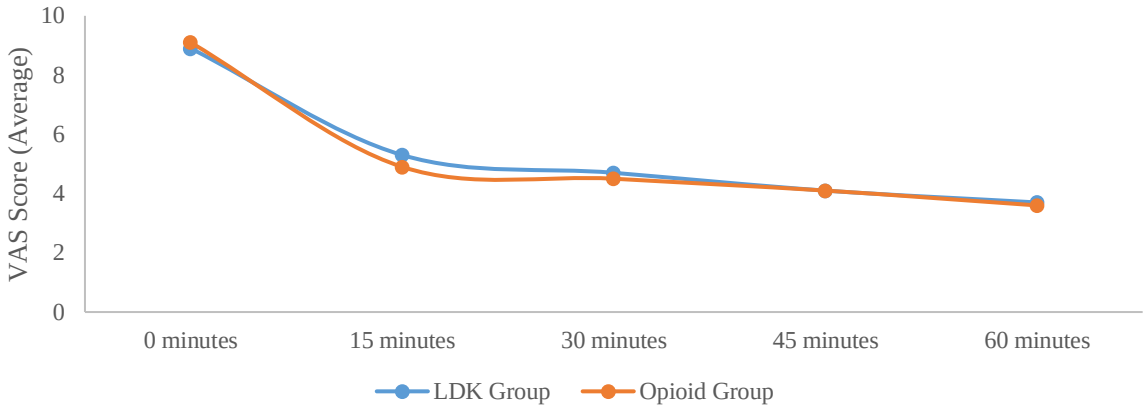


**Figure 2: Changes in mean VAS scores among the two study groups receiving LDK and morphine from admission to 60 minutes.**

Minor AE's were observed among the patients which were slightly greater among patients receiving morphine. Reduced respiratory rate was the most common AE i.e. 6.1% in LDK group and 12.5% in morphine group. Decreased O2 saturation was highest among all the AE's reported in morphine group while in LDK group, it was only observed among 3.3% patients.

Table 3: Safety profile of the two drugs in terms of adverse events

| Adverse Events (AE's) | LDK | Morphine |
|---|---|---|
| Pruritus | 14(5) | 21(7.5) |
| Reduced Respiratory Rate | 17(6.1) | 35(12.5) |
| Decreased $O_2$ Saturation | 09(3.3) | 26(9.3) |
| Urinary Retention | 01(0.4) | 03(1.1) |

*Values are given as n(%)

## Discussion

A number of studies have supported the use of LDK for treatment of both chronic and acute pain. An extensive retrospective case series, revealed that ketamine under 0.3 mg/kg dose alone successfully reduced both acute and chronic pain in ED patients, with only 6% AE's encounters, most of which were non-significant. Thus, providing reaffirmation that LDK is safe and effective pain-relieving agent and is ideal to be used in ED[16].

Another similar research work carried out by Majidinejad et al., compared the effectiveness of 0.5 mg/kg dose of ketamine with 0.1 mg/kg of morphine in more than 100 patients presenting to the ED with severe acute pain following an orthopedic surgery[17]. The study concluded that LDK is a fast-acting pharmacological agent that is capable of manifesting results within minutes of administration[17]. Which when compared to opioids such as morphine which are highly efficacious in pain alleviation but due to high AE's profile and duration of action, LDK might be more preferable. Similarly, Motov and his colleagues also supported the fast-acting theory of LDK over opioid derivatives[18]. Based on our findings, the efficacy profile of opioid was stronger than LDK, similar rate of reduction in the pain score was observed in both groups.

As far as the effectiveness over longer duration is concerned, it is evident that morphine provides significantly long-term effect in comparison to LDK. Also supported by a study, which showed that the patients in morphine group achieved complete pain relief in 100 minutes after initial administration while the patients in LDK group observed a significant pain relief in the first few minutes which then gradually decreased and resulted in weaker long-term impact in comparison to opioid[7]. The pain alleviation score was not very prominent in our data set, same pain score was observed at 45 mins in both groups while at 60 mins, a slight point difference was observed (Table 2). However, the results might have varied if prolonged recordings would have been taken in the current study. But due to safety issues the study conduction was kept precise and the AE's profile was keenly observed.

In addition to efficacy, the safety profile of both the study drugs was also monitored. No life-threatening AE's were associated with LDK and morphine administration. Among minor AE's observed were reduced respiratory rate (16.1% vs 12.5%), pruritis (5% vs 7.5%), decreased O2 saturation (3.3% vs 9.3%) and urinary distention (0.4% vs 1.1%). These incidences were high in morphine group but were temporary and no additional pharmacological interventions were applied (Table 3). In consistent to our results, Mahshidfar et al., also reported nausea,

flushing, dizziness, mood changes, hypotension and $O_2$ saturation as the common AE's associated with both drugs[19]. 16% patients receiving LDK were observed with nausea vs 17% in opium group, no flushing incidences were seen among LDK patients while 36% patients receiving morphine reported flushing incidences, high cases of $O_2$ saturation < 90% were observed in morphine group as compared to LDK group[19].

Thus, the effect of LDK is similar to morphine at 15 minutes after initial administration and the effects continued to fair well against opioid alternative for longer periods as well. An additional fact that our research reaffirms is that the complications encountered following LDK administration were less as compared to those encountered after the opioid administration. Further studies are required in order to consider one of the above drugs as the ideal choice. As there were several aspects in which LDK second morphine in terms of safety while for prolong efficacy both the drugs were producing similar effects.

## Conclusion

After careful consideration, it can be concluded that opium and LDK have similar efficacy profile in alleviating acute pain at ED. However, the safety of LDK is higher than its opioid counterpart and thus LDK may be used as a safer alternative to opioid but the hypothesis needs more firm support of detailed clinical trials approving the comparative safety and efficacy profile of both the drugs in Pakistan.

## Conflicts of Interest

None.

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