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Original Article

# Low-dose S-ketamine for prehospital pain relief

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## ABSTRACT

**INTRODUCTION.** S-ketamine is increasingly used as an adjunct to opioids for prehospital traumatic pain, but data on patient experience and safety in civilian paramedic practice remain limited. We evaluated low-dose S-ketamine, alone or with fentanyl, in a Danish prehospital setting.

**METHODS.** This was a prospective observational study including adult prehospital patients with pain from significant trauma, suspected fractures of long bones, spine or pelvis, or joint dislocations. Paramedics administered intravenous S-ketamine, usually after fentanyl, and recorded pain using a numerical rating scale (NRS) and an electronic questionnaire on efficacy, side effects and patient experience. Data completeness was ensured by twice-weekly electronic record searches and follow-up.

**RESULTS.** Among 348 patients, 320 (92.0%) reported effective pain relief, with a median NRS reduction of five points. In the combination group, the median fentanyl dose was 150 µg (IQR: 100-200 µg), and the median ketamine dose was 10 mg (IQR: 10-20 mg). In the monotherapy group, the median ketamine dose was 15 mg (IQR: 10-20 mg). Hallucinations occurred in 30.0% (23.9% positive, 6.0% negative) and diplopia in 9.2%. Blood pressure changes > 20 mmHg occurred in 10.1% and tachycardia in 8.0%, with no serious adverse events. Overall, 93.2% stated they would accept S-ketamine again.

**CONCLUSIONS.** In this prospective observational cohort, low-dose S-ketamine, administered alone or in combination with fentanyl, was associated with effective prehospital analgesia, infrequent and predominantly benign side effects and high patient satisfaction.

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Pain remains a major challenge in prehospital care, where cases with moderate to severe pain are common [1, 2]. Fentanyl has improved analgesic management, and effective pain relief enhances perceived care quality [3]. Even so, over half of patients still experience inadequate relief with fentanyl alone [4]. Given its importance, prehospital analgesia is a key performance indicator in several countries [5].

S-ketamine is well established in military medicine [5] and has been shown to be safe and effective for analgesia in civilian prehospital care, including when administered by trained paramedics [6-9].

Ketamine, a phencyclidine (PCP) derivative acting on N-methyl-D-aspartate (NMDA) receptors, provides analgesia at low doses and sedation at higher doses [10], with additional amnesic and psychosensory effects via non-competitive NMDA antagonism. S-ketamine is known to cause vivid hallucinations and psychometric side

effects [11, 12].

In Denmark, S-ketamine is used by physicians and paramedics in both hospital and prehospital settings. Following administration, it rapidly distributes to the central nervous system (α half-life: 2-4 min.; β half-life: 4-7 h) and is metabolised to nor-S-ketamine, which also modulates μ-, δ- and κ-opioid receptors [11].

In the Region of Southern Denmark, intravenous fentanyl is the first-line analgesic administered by emergency medical technicians (EMTs), paramedics and physicians [3]. As opioids may be insufficient or inappropriate in prehospital care, paramedics were authorised from January 2018 to administer S-ketamine under a local protocol after receiving specific training (see Supplementary File 1).

This study aimed to evaluate the analgesic efficacy and side effects of low-dose S-ketamine (LDK) administered by paramedics in a prehospital setting.

The primary objective was to describe the analgesic efficacy and side effects of LDK administered by paramedics in a prehospital setting. Secondary objectives were to describe patient-reported treatment experience, the occurrence of hallucinations and other adverse effects, and to report outcomes separately for patients treated with S-ketamine alone and in combination with fentanyl.

## Methods

### System setting

In Denmark, prehospital emergency care is a three-tiered system, the core resource being an ambulance staffed by two EMTs or paramedics. Dispatch is coordinated by one of five regional emergency medical dispatch centres, each covering a health region. Dispatchers - typically nurses, EMTs or paramedics - may deploy: an ambulance alone; an ambulance with a paramedic in a rapid response vehicle; or an ambulance with a mobile emergency unit staffed by an EMT or paramedic and an anaesthesiologist. Mobile units are either ground-based mobile emergency care units (MECUs) or airborne helicopter emergency medical services (HEMS), with four helicopters operating nationwide [11].

The prehospital services of the Region of Southern Denmark include 73 ambulances, seven paramedic rapid response units and six anaesthesiologist-staffed MECUs and HEMS units.

All prehospital patient encounters are documented by the attending personnel in a nationwide electronic Prehospital Medical Record (ePMR) system. This system records clinical findings and treatments, including pharmacological interventions, and incorporates dedicated electronic modules to support research and quality assurance initiatives [11].

### Study design

This was a prospective observational descriptive study of consecutive prehospital patients receiving S-ketamine administered by paramedics.

Data were collected prehospital and immediately upon arrival at the hospital, prior to the transfer of care to hospital staff.

### Inclusion criteria

In accordance with the established protocol, indications for the administration of S-ketamine included adult patients experiencing pain resulting from severe trauma, including joint dislocations and suspected fractures of major bones, the spine or the pelvis. Paramedics were instructed to administer fentanyl prior to S-ketamine unless the patient had a known allergy to opioids or declined opioid treatment for any reason.

### Exclusion criteria

Exclusion criteria included patients under 18 years of age, those with known or suspected allergies to S-ketamine and patients who received S-ketamine from prehospital physicians.

In all instances where S-ketamine was administered by paramedics, the dosage, along with the patient's vital signs and numerical rating scale (NRS) score, had to be documented in the ePMR. Additionally, paramedics were instructed to complete a questionnaire integrated into the ePMR system whenever S-ketamine was administered.

Paramedics used the tablet-based ePMR to document clinical findings and interventions [13]. After each S-ketamine administration, they completed a 16-item questionnaire (Supplementary File 2) that captured patient-reported experience, satisfaction, perceived and observed side effects, and their own professional assessment. Pain scores were obtained using an NRS before and after administration at intervals determined by clinical judgement.

To ensure data completeness, questionnaires were required for all S-ketamine cases. Twice-weekly, automated searches of the ePMR identified eligible records (detailed in Supplementary File 3). Discrepancies or incomplete questionnaires were resolved through follow-up telephone interviews with the responsible paramedic; remaining gaps were supplemented by an investigator review of the ePMR, classifying S-ketamine outcomes as: 1) effective analgesia; 2) no analgesia; 3) effect unknown; or 4) side effects reported.

### Data analysis

Data were managed using Microsoft Excel (Redmond, Washington, USA) as a case report form, and analysed using STATA BE 18.0 (StataCorp LLC, College Station, Texas, USA). Results are presented as medians with IQRs to account for data skewness and the presence of potential outliers. Data were summarised using medians with interquartile ranges for continuous variables and counts with percentages for categorical variables. Outcomes are presented for the overall cohort and stratified by treatment regimen (S-ketamine monotherapy versus S-ketamine combined with fentanyl). No formal hypothesis-testing between treatment groups was planned, and no a priori sample size calculation was performed, as this study was designed as a descriptive quality-assurance project.

### Ethics

This paper is part of an internal audit of an instituted treatment and, as such, does not require ethics approval. The project was prospectively approved as a quality assurance study by the Director of the Prehospital Administration in the Region of Southern Denmark (Ref. no: 21/35411).

### Data sharing

The datasets generated and/or analysed during this study are not publicly available due to patient confidentiality considerations. Anonymised data in the form of an Excel data file are available from the corresponding author upon reasonable request. The individual patient charts cannot be anonymised.

*Trial registration:* not relevant.

## Results

### Study population

Between 1 March and 2 September 2023, all prehospital contacts in the Region of Southern Denmark were

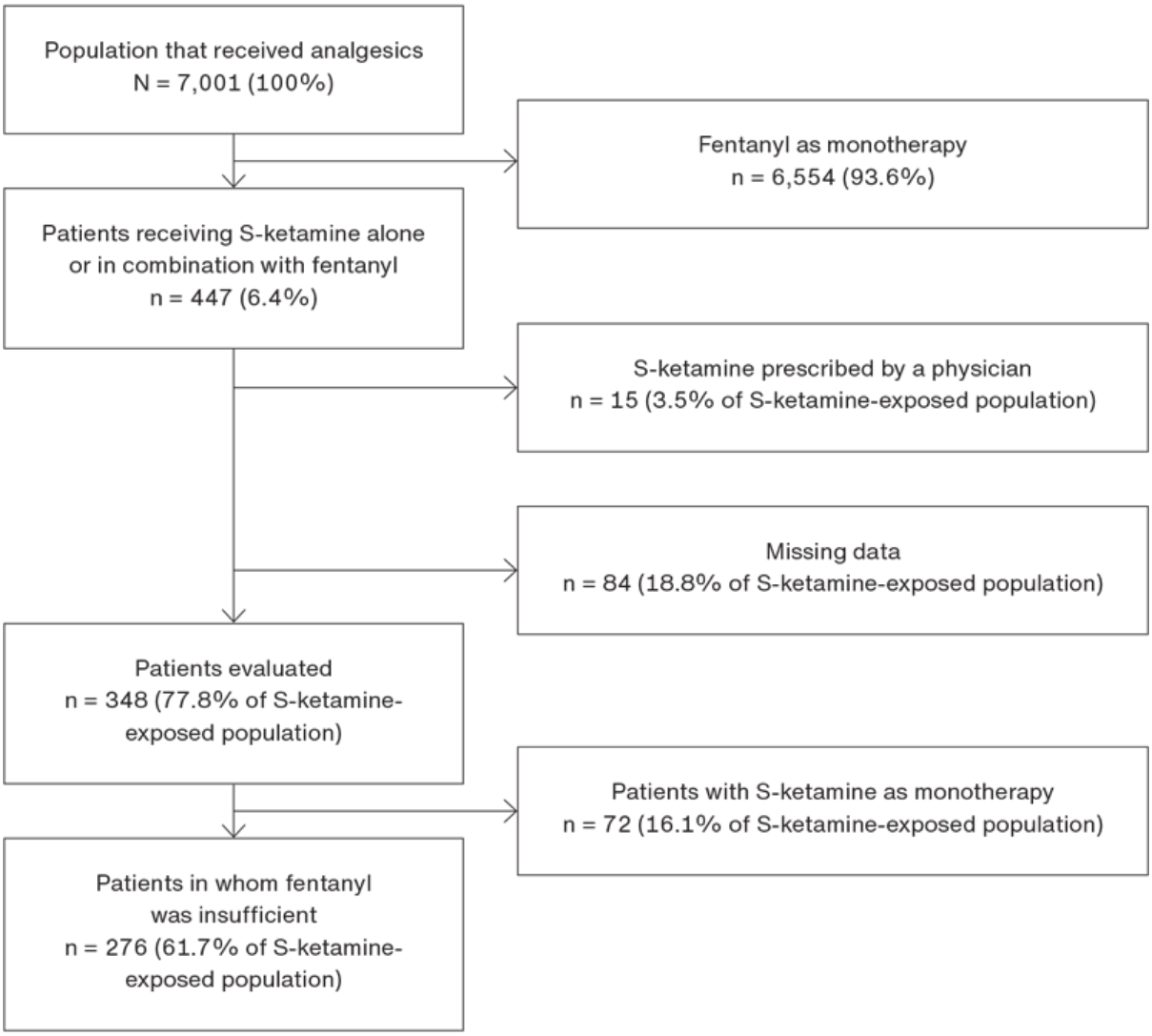
screened. In this period, 7,001 patients received analgesic treatment with fentanyl, S-ketamine or both. Among these, 6,554 received fentanyl alone and were excluded from our study. A total of 447 patients received S-ketamine, either as monotherapy or in combination with fentanyl, and formed the study cohort. Eighty-four had missing data, and in 15 cases, S-ketamine was administered by a prehospital physician. Thus, 348 patients were analysed.

- 276 patients reported insufficient pain relief from fentanyl alone, prompting S-ketamine administration

- 72 patients received S-ketamine without prior fentanyl.

See **Figure 1** (flow chart).

**FIGURE 1** Study flow chart of patients receiving fentanyl and/or S-ketamine.




Fentanyl and S-ketamine doses were administered by protocol (Supplementary File 1). The initial dose of fentanyl in this protocol was 1-2 µg/kg and a total maximum of 4 µg/kg, if fentanyl was to be repeated.

The initial dose of S-ketamine was 5 mg (for patients weighing 30-60 kg) or 10 mg (> 60 kg). Additional doses were 0.125 mg/kg, based on the patient's weight. In 24 cases, three or more doses were needed to obtain clinical pain relief.

The threshold for administering S-ketamine was defined by the indication "*Pain resulting from significant trauma, fractures of long bones, the spine or pelvis and dislocations of joints*" (see Supplementary File 1). Patients who did not receive S-ketamine may have been given fentanyl alone or may have refused analgesic treatment in the prehospital phase.

Although nasal, intramuscular and intravenous administration were all permitted, the predominance of intravenous use meant that stratification by route was not justified.

**Patient characteristics**

The cohort comprised 205 females (58.9%) and 143 males (41.1%). The median age was 65 years (IQR: 42.75-79). Median body weight was 80 kg (IQR: 65-86.75) (**Table 1**).

**TABLE 1** Demographic characteristics of the study population (N = 348).

| | |
|---|---|
| Females, n (%) | 205 (58.9%) |
| Males, n (%) | 143 (41.1%) |
| Age, median (quartiles), yrs | 65 (42.75-79) |
| Weight, median (quartiles), kg | 80 (65-86.75) |

In the combination group, the median fentanyl dose was 150 µg (IQR: 100-200 µg) and the median ketamine dose was 10 mg (IQR: 10-20 mg). In the monotherapy group, the median ketamine dose was 15 mg (IQR: 10-20 mg).

Patient satisfaction with pain relief was 91.7% in the combination group and 93.1% in the S-ketamine group. Hallucinations occurred in 29.1% and 33.3%, respectively. Most patients reported no side effects (62.0% versus 63.9%). Paramedics assessed pain relief as sufficient in 88.8% versus 90.3%. Regarding future preferences, 74.1% versus 77.8% would accept S-ketamine again, whereas 5.1% versus 8.3% would not. The median NRS reduction was six (IQR: 3.75-8) versus five (IQR: 3-6) (p = 0.09) (**Table 2**).

**TABLE 2** The clinical outcomes and patient-reported experiences for the two treatment groups: fentanyl combined with S-ketamine and S-ketamine alone (N = 348).

| | Fentanyl + S-ketamine (n = 276) | S-ketamine (n = 72) |
|---|---|---|
| Fentanyl dose, median (quartiles), µg | 150 (100-200) | 0 |
| S-ketamine dose, median (quartiles), mg | 10 (10-20) | 15 (10-20) |
| Patients satisfied with pain relief, n (%) | 253 (91.7) | 67 (93.1) |
| *Hallucinations[a], n (%)* | | |
| Occurrence of hallucinations | 80 (29.1) | 24 (33.3) |
| Positive hallucinations | 62 (22.5) | 21 (29.2) |
| Negative hallucinations | 18 (6.5) | 3 (4.2) |
| Patient-experienced diplopia, n (%) | 23 (8.3) | 9 (12.5) |
| No patient-experienced side effects, n (%) | 171 (62.0) | 46 (63.9) |
| Paramedic considered sufficient pain relief, n (%) | 245 (88.8) | 65 (90.3) |
| Patient opts for S-ketamine in a similar situation in the future[b], n (%) | 218 (74.1) | 56 (77.8) |
| Patient would opt out of S-ketamine in a similar situation in the future[b], n (%) | 14 (5.1) | 6 (8.3) |
| Reduction in pain score: NRS, median (quartiles)[c] | 6 (3.75-8) | 5 (3-6) |
| Changes in blood pressure > 20 mmHg, n (%) | 25 (9.1) | 10 (13.9) |

NRS = numerical rating scale.
a) Data from 348 patients.
b) Patients' preferences regarding future S-ketamine administration in similar situations: unambiguous data from 294 patients; 54 patients had missing or inconclusive answers.
c) Data from 255 patients.

92.0% of patients reported being satisfied with their pain relief. Hallucinations occurred in 30.0% of patients; among these, 23.9% described them as *positive* experiences, whereas 6.0% described them as *negative*. Diplopia was reported by 9.2%, and 62.4% reported experiencing *no* side effects. Paramedics judged pain relief to be sufficient in 89.0% of cases.

Regarding future treatment, 93.2% (n = 274) stated they would accept S-ketamine again, whereas 6.8% (n = 20) would not. The median reduction in NRS pain score was five (IQR: 3-8). A blood pressure change > 20 mmHg occurred in 10.1% of patients. No difference in the willingness to receive S-ketamine again was observed between patients treated with S-ketamine alone and those receiving S-ketamine combined with fentanyl.

**Overall side effects**

A total of 217 patients (62.4%) reported no side effects, whereas 131 (37.6%) experienced subjective or objective effects.

Subjective side effects:

- Positive hallucinations (fentanyl combined with S-ketamine): n = 62 (22.5%)

- Positive hallucinations (S-ketamine monotherapy): n = 24 (33.3%)

- Negative hallucinations (fentanyl combined with S-ketamine): n = 18 (6.5%)

- Negative hallucinations (S-ketamine monotherapy): n = 3 (4.2%)

- Diplopia (fentanyl combined with S-ketamine): n = 23 (8.3%)

- Diplopia (S-ketamine monotherapy): n = 9 (33.3%).

Objective side effects:

- Changes in systolic blood pressure > 20 mmHg (fentanyl combined with S-ketamine): n = 25 (9.1%)

- Changes in systolic blood pressure > 20 mmHg (S-ketamine monotherapy): n = 10 (13.9%).

Across groups, 91.7-93.1% of patients reported substantial analgesia, with median NRS reductions of six and five points. Tachycardia occurred in 28 patients (8.0%) with heart-rate changes exceeding ± 20 beats per minute, although no chest pain or clinically relevant cardiovascular events were observed.

## Discussion

In this cohort, S-ketamine administered by paramedics was associated with effective analgesia and high patient satisfaction. Outcomes appeared broadly similar in patients treated with S-ketamine alone and in combination with fentanyl, but the study was designed as a descriptive quality-assurance project and was not intended to formally compare treatment regimens. Pain relief typically occurred within the first two doses, although 24 cases required three or more doses. Few patients declined future treatment, indicating generally acceptable analgesia and tolerability. One study from Iowa, USA, regarding burn patients found a higher patient satisfaction in the S-ketamine group versus opioids prior to hydrotherapy [14].

Our study did not support the perception that S-ketamine frequently induces severe hallucinations requiring pharmacological intervention. Previous work suggests that s(+) enantiomer produces fewer psychotropic adverse effects than racemic ketamine, although at least one study found no significant differences [15]. Emergence reactions at subanaesthetic doses have been reported at around 12% [16], but such effects may be mitigated by low-dose analgesic regimens. In our cohort, most hallucinations were positive, and only 6.0% of patients (21 of 348 patients) experienced negative hallucinations, despite the acute and stressful context.

Evidence suggests that positively framed pre-treatment information can reduce negative experiences and side effects [15]. In line with the regional protocol, paramedics informed patients using positive phrasing, such as: *"Your pain will be relieved; however, some may experience colourful dreams"*, as preparation for perceptual changes lessens the risk of negative experiences.

No difference in side effect incidence was found between patients treated with S-ketamine alone or combined with fentanyl, consistent with Häske et al. [9]. Although this study was not powered to detect significant differences between treatment groups, combined treatment showed a trend towards greater efficacy. Side effects were minor, with positive hallucinations being more frequent than negative ones. Most patients experienced pain relief within the first two doses and reported high satisfaction.

### Limitations

Incomplete NRS data represented the main limitation: in 48 cases (13.8%), post-treatment scores were missing, limiting evaluation of analgesic response. However, 92% of patients reported effective pain relief, documented either in NRS or in free-text notes. Patient-reported outcomes were collected in the ambulance, introducing potential response and observer bias, as the treating paramedic also administered the questionnaire and assessed side effects. Responses may further have been affected by residual fentanyl and/or S-ketamine. Real-time data collection was chosen over retrospective follow-up to minimise recall bias. Dosage was not deemed to

influence responses, though future studies should include post-treatment follow-up to enhance objectivity.

## Conclusions

In this prospective observational cohort, LDK, used alone or in combination with fentanyl, was associated with effective prehospital analgesia, predominantly benign side effects and high patient satisfaction. At doses of 10-15&;mg, side effects were infrequent and predominantly benign. Most patients in our study reported high satisfaction and willingness to receive S-ketamine again. For patients with insufficient analgesia from fentanyl alone, S-ketamine appears to be a safe and effective option for prehospital analgesia.

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**Supplementary material** a08250694-supplementary.pdf

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