Effect of intranasal sufentanil on acute post-traumatic pain in the emergency department: a randomised controlled trial

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ABSTRACT

Background Intranasal sufentanil is a potent opioid which can be used in patients with traumatic injuries presenting to the ED. Although previous studies have demonstrated the superiority of intranasal sufentanil over intravenous morphine in terms of pain relief, its clinical superiority in patients with traumatic injuries receiving adequate multimodal analgesia with acetaminophen and non-steroidal anti-inflammatory drugs is uncertain. We compared pain relief offered by intranasal sufentanil with that offered by oral and intravenous opioids in patients with acute traumatic injuries also receiving a specified regimen of non-opioid treatment.

Methods In this single-centre, open-label, parallel-group, randomised controlled superiority trial conducted between January 2020 and February 2022, trauma patients presenting to the ED with a pain score of ≥7 on a visual analogue scale (VAS) were randomised to receive either intranasal sufentanil or other oral/intravenous opioids alongside oral/intravenous acetaminophen and non-steroidal anti-inflammatory drugs. The primary outcome was reduction in VAS score 15–20 min after randomisation.

Results An intention-to-treat analysis included 170 out of 205 patients screened for inclusion. The intranasal sufentanil group (83 patients) showed a significantly greater reduction in pain when compared with the oral/intravenous opioid group (87 patients) 15–20 min after randomisation (reduction in VAS score 3.0 (IQR 1.7–5.0) vs 1.5 (IQR 0.9–3.0); p<0.001). Similarly, a greater reduction in pain was observed in the intranasal sufentanil group 60 min after randomisation (5.0 (IQR 3.0–7.0) vs 3.0 (IQR 2.0–5.3); p<0.001). However, side effects were more frequent in the intervention group (71.1% vs 23%; p<0.001).

Conclusions Intranasal sufentanil was associated with more effective pain relief than oral/intravenous opioids in patients with traumatic injuries treated with coanalgesia. Intranasal sufentanil could be considered for the management of pain in patients with traumatic injuries associated with severe pain.

Trial registration number NCT04137198

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intranasal sufentanil is associated with good pain control in patients with trauma presenting to the ED. A previous randomised controlled trial of trauma patients suggested that intranasal sufentanil might be superior to intravenous morphine for pain control, but the results may have been affected by variation in coanalgesia.

WHAT THIS STUDY ADDS

⇒ In this open-label, randomised controlled trial using a multimodal analgesia strategy, intranasal sufentanil was associated with faster and better pain control than other oral or intravenous opioids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study supports the utilisation of intranasal sufentanil as an alternative to intravenous and oral opioids for the treatment of acute traumatic pain. Further research should focus on the optimal initial dose for intranasal sufentanil, as well as pharmacological and patient selection strategies to minimise side effects.

INTRODUCTION

Pain is the most common symptom in adults visiting the ED, with 60% of patients complaining of pain, of which 30% are injured.[1] Despite its frequency, pain is often underappreciated and undertreated in the ED.[2–6] Moreover, treatment is often delayed, which may lead to a risk of chronic long-term pain sequelae.[7] Therefore, pain levels should be assessed on arrival using validated pain scales and adequate treatment using appropriate analgesia should be rapidly started.[2 6 8]

The intranasal route uses the nasal mucosa, a highly vascularised region, to bypass the hepatic first-pass effect.[9] The intranasal route is an accepted route for drug delivery, particularly for analgesia and in paediatric settings.[9–11] The intranasal route is rapid, easy and is associated with fewer complications than an intravenous cannula, making it a suitable option for treatment administration in the ED.[12 13]

Sufentanil is an opioid that is 7–10 times more potent and twice as lipophilic as fentanyl, with a short onset and a 45 min duration of action, making it suitable for intranasal administration.[14] Intranasal fentanyl use, compared with sufentanil, is

supported by a large body of evidence and is relatively cheaper. In Belgium, sufentanil costs €3 per 250 μg 5 mL vial, while fentanyl costs €0.5 per 500 μg 10 mL vial. Sufentanil is more potent than fentanyl, an advantage for the intranasal route, as it requires lower volumes. Intranasal sufentanil (INS) might offer some advantages because it has no active metabolites, and shows a higher therapeutic index and a lower frequency of respiratory suppression than fentanyl.[15] Previous studies support INS use in the ED for traumatic pain; however, definitive evidence for its use is lacking given the absence of adequately powered randomised controlled trials comparing INS to opioids in addition to recommended coanalgesia.[16–20]

The aim of this study was to assess the efficacy of INS in the management of traumatic pain in an ED setting. We hypothesised that among patients with acute traumatic injury receiving coanalgesia, INS would provide superior analgesia when compared with oral/intravenous opioids.

MATERIALS AND METHODS

Overview

This was an open-label, balanced (1:1), randomised clinical trial including adult patients presenting to the ED from January 2020 to February 2022, with acute post-traumatic pain and a pain score on arrival of 7/10 or more according to an 11-point visual analogue scale (VAS). All patients received a single dose of a combination of analgesics (non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen). Oral consent was obtained concomitantly to VAS measurement followed by randomisation. Patients in the treatment arm received INS, whereas those in the control group received oral or intravenous opioids. Patients were asked to rate their pain using the VAS at 0, 15–20 and 60 min after the initial evaluation. The study was registered at ClinicalTrials.gov (NCT04137198) before patient enrolment. All the participants provided written informed consent. Data[21] were collected between January 2020 and February 2022, with a pause during the COVID-19 pandemic.

Study setting

This study was conducted in the ED of Saint Pierre University Hospital, an urban teaching hospital with more than 80 000 emergency visits annually, located in the city centre of Brussels, Belgium.

Participant selection

Patients older than 18 years presenting to the ED with acute post-traumatic pain (<24 hours from injury) in the extremities, spine or thorax were considered for inclusion. Eligible patients required a VAS pain score of at least 7. Patients were excluded if they had received any opioids within the previous 8 hours. The other exclusion criteria were injuries more than 24 hours old, chronic or acute opiate drug use, alcohol intoxication, allergy or intolerance to opiates, renal or hepatic insufficiency, a body weight of less than 50 kg, hypoxia and haemodynamic instability. Prisoners, pregnant and breastfeeding women and patients presenting with lesions or pain in the head, face or abdomen were excluded.

Interventions

Screening and randomisation were performed at first contact with the patient. For allocation of the participants, a computer-generated list of random numbers without permuted blocks was used. Randomisation was achieved using sealed numbered envelopes that were opened after obtaining patient consent. Patients were enrolled in the study and assigned to the intervention group by the care providers. All patients rated their pain prior to randomisation (T0), at 15–20 (T15) and 60 min (T60) after randomisation.

All study patients were prescribed a single dose of a combination of analgesics (oral diclofenac and acetaminophen or intravenous ketorolac and acetaminophen) that was adjusted according to patient NSAID and acetaminophen use before randomisation. Patients in the intervention arm received an intranasal loading dose of sufentanil of 0.5 μg/kg given at baseline, immediately after randomisation. In cases of insufficient pain control, further opioid doses, according to the randomisation arm, were administered at predetermined measurement points, that is, 15 and 60 min after baseline. Subsequent doses of INS were of 0.3 μg/kg. Patients in the control group received an oral or intravenous opioid according to the clinical judgement of the clinician in charge. Oral oxycodone was administered at a fixed dose of 5 mg that could be repeated while intravenous morphine was administered at a recommended dose of 0.1 mg/kg followed by a titration dose of 0.05 mg/kg.

Outcome measures

Pain was assessed visually using an 11-point VAS, in which a score of 0 indicated no pain and a score of 10 indicated the worst imaginable pain.[22] The VAS is used in our ED to assess initial pain at triage and changes in pain levels during evaluation and treatment. The VAS was assessed by the nurse or doctor looking after the patient. The primary study outcome was the between-group difference in the mean change in the VAS pain score between the two groups, measured 15–20 min after randomisation. Secondary outcomes included between-group differences in mean VAS scores at 60 min and the proportion of patients experiencing side effects. The minimum clinically important difference was defined, a priori, as a difference of 1 on the VAS . Additional outcomes not described in the original protocol included the proportion of patients who received rescue analgesia.

Sample size calculation

The sample size calculation was based on a between-group difference for change in the mean VAS pain score of at least 1. A two-sided significance level of 0.05, a power of 90% (β=0.10) and a within-group SD of 1.9, based on estimates of variability from our prior work,[23] were used to calculate the sample size. Using these parameters, we estimated that 84 patients would be required per group. Considering that 2% of patients would be non-evaluable, target recruitment was 172 patients (86 per arm).

Statistical analysis

All analyses were performed on an available case analysis using an intention-to-treat principle according to the statistical analysis plan. No imputation method was used for missing data.

Continuous baseline variables were summarised using the mean (SD) or median (IQR) according to their distribution. Categorical variables were summarised as counts (proportions).

Continuous variables were compared using the t-test or Kruskal-Wallis test according to variable distribution and reported as absolute differences (95% CI). Categorical variables were compared using χ^2 test or Fisher's exact test and reported as differences in proportion (95% CI). The primary analysis was a Wilcoxon-Mann-Whitney test for testing the null hypothesis that there is no difference in the effect of the medications on the mean change in pain from baseline to 15–20 min, with a

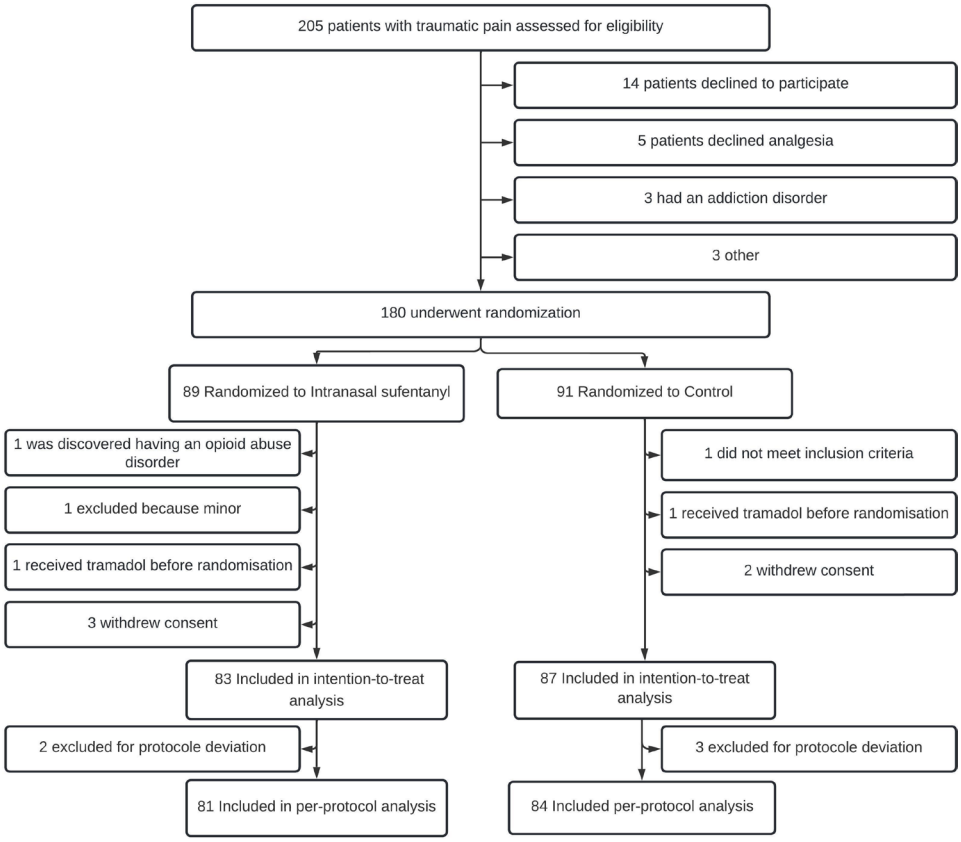

Figure 1 Trial flow chart. A total of 205 patients were assessed for eligibility; 25 patients were excluded because they did not meet the criteria for inclusion or did meet the criteria for exclusion. 180 patients underwent randomization at the time of enrollment. After enrollement 5 additional patient were excluded because they did not meet the criteria for inclusion or did meet the criteria for exclusion. In addition, 5 patients withdrew their consent to the study.170 patients were included in the intention-to-treat analysis. After review of protocol adherence, 5 patients were excluded for protocol violation, leaving 165 patients for the per-protocol analysis.

significance level of 0.05. We performed a secondary analysis on the primary outcome using the analysis of covariance (ANCOVA) test to correct for imbalances in baseline VAS.

All tests were two sided, and statistical significance was set at $p<0.05$. Statistical analyses were performed using the Stata software (V.15.0; StataCorp).

Patient and public involvement

There was no patient involvement in the design or conduct of the trial.

RESULTS

Group characteristics

During the 23-month period between January 2020 and February 2022, two hundred and five patients were screened for inclusion, 180 underwent randomisation and 170 were included in the intention-to-treat analysis (figure 1), with 83 and 87 subjects randomised to the intervention group and control group, respectively.

The characteristics of the patients in the two groups were well balanced at baseline in terms of demographics, medical history, vital signs, ambulance admission, admission complaints and baseline VAS pain assessment (table 1). We observed a lower rate of NSAID administration at baseline in the intervention group (77.1% vs 89.7%; $p=0.03$). Intravenous coanalgesia was similar in the intervention group and control group (3.6% vs 8.1%; $p=0.22$). Intravenous access was established, throughout study observation, less frequently in the intervention group (7.2% vs 17.2; $p=0.04$). All patients except one in the intervention group received non-opioid coanalgesia.

The most frequent complaint was upper limb trauma, followed by lower limb trauma. At discharge, the most common diagnosis was bone fracture, followed by contusion (table 1).

Main results

Pain intensity decreased over time in both groups. After 15–20 min from randomisation, the VAS pain score decreased by 3.0 (IQR 1.7–5.0) in the intervention group and by 1.5 (IQR 0.9–3.0) in the control group ($p<0.001$) (table 2).

The median VAS pain score was lower in the intervention group 15–20 min after randomisation (5.0 (IQR 3.5–6.5) vs 6.6 (IQR 5.0–7.3); $p=0.002$) (figure 2). Results were concordant after adjustment using ANCOVA for baseline VAS with a greater reduction of the VAS in the intervention group ($p=0.002$).

After 1 hour, the VAS pain score decreased by 5.0 (IQR 3.0–7.0) in the intervention group and by 3.0 (IQR 2.0–5.3) in the control group ($p<0.001$) (table 2). The median VAS pain score was lower in the intervention group 1 hour after randomisation (3.0 (IQR 2.0–5.0) vs 4.8 (IQR 3.0–6.0); $p<0.001$) (figure 2).

No differences in coanalgesia were observed between the two groups.

Forty patients received rescue analgesia during the observation period, and these were similarly distributed between the intervention and control groups (24.1% vs 23%, respectively; $p=0.87$).

Table 1 Demographic and clinical characteristics of the 170 patients at study inclusion

	Intervention	Control
	Intranasal sufentanil	Oral/intravenous opioid
Observations (n)	83	87
Age, median (IQR), years	45 (32–54)	38 (28–48)
Female, n (%)	38 (45.8)	34 (39.1)
Weight, median (IQR), kg	70 (60–82)	75 (65–85)
Height, mean (SD), cm	170 (9)	172 (9)
BMI, median (IQR), kg/m^2	24.2 (21.1–28.4)	24.3 (21.8–27.7)
History of motion sickness, n (%)	8 (9.6)	5 (5.8)
HR (IQR), bpm	80 (73–91)	83 (72–96)
Systolic BP (IQR), mm Hg	132 (120–142)	126 (116–142)
Diastolic BP (IQR), mm Hg	79 (71–90)	81 (72–90)
Oxygen saturation (IQR), %	99 (98–100)	100 (98–100)
VAS at admission (IQR)	8 (7.5–9)	8 (7–9)
Ambulance admission, n (%)	17 (20.7)	21 (24.1)
Admission complaint, n (%)		
Upper limb trauma	45 (54.9)	53 (60.9)
Lower limb trauma	32 (39.2)	29 (33.3)
Spinal trauma	2 (2.4)	3 (3.5)
Chest trauma	3 (3.7)	2 (2.3)
Treatment, n (%)		
Level 1 coanalgesia*	82 (98.8)	87 (100)
Oral acetaminophen	76 (91.6)	79 (90.8)
Intravenous acetaminophen	3 (3.6)	7 (8.1)
Oral NSAID	64 (77.1)	71 (81.6)
Intravenous NSAID	0 (0)	7 (8.1)
Intravenous morphine	0 (0)	12 (13.8)
Any intravenous treatment	6 (7.2)	15 (17.2)
Diagnosis at discharge, n (%)		
Fracture	32 (39)	35 (40.2)
Contusion	23 (28.1)	20 (23)
Sprain	11 (13.4)	14 (16.1)
Dislocation	9 (11)	11 (12.6)
Wound	5 (6.1)	5 (5.8)
Other	1 (1.2)	1 (1.2)

*Level 1 coanalgesia is defined as having received acetaminophen or an NSAID.
BMI, body mass index; bpm, beats per minute; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale.

Table 2 Visual analogue scale (VAS) pain scores and reduction by treatment group

	VAS pain score*, median (IQR)		
	Intervention	Control	P value
Patients (n)	83	87	
Baseline VAS score	8 (7.5–9)	8 (7–9)	0.13
Primary endpoint: reduction in VAS score after 15–20 min	3 (1.7–5)	1.5 (0.9–3)	<0.001
Reduction in VAS score after 60 min	5 (3–7)	3 (2–5.3)	<0.001
VAS score after 15–20 min	5 (3.5–6.5)	6.6 (5–7.3)	0.002
VAS score after 60 min	3 (2–5)	4.8 (3–6)	<0.001
	VAS pain score* ≤3, n (%)		
Proportion of patients with a VAS score ≤3 after 15–20 min	19 (23.5)	8 (9.8)	0.02
Proportion of patients with a VAS score ≤3 after 60 min	45 (57.7)	25 (30.1)	<0.001

*Pain intensity was assessed through an 11-point VAS in which 0 indicates no pain and 10 indicates the worst imaginable pain.

No statistically significant differences were observed between the two groups in terms of the administration of repeat analgesic doses at either T15 or T60.

Adverse events

Adverse events were observed more frequently in the intervention group (71.1% vs 23%; p<0.001) (table 3). Severe adverse events were more common in the intervention group although the difference was not statistically significant (7.2% vs 3.5%; p=0.27).

One patient in the intervention group and no one in the control group developed hypoxaemia defined as a $SatO_2$ <90% (p=0.3). Two patients in the intervention group and one patient in the control group developed hypotension, defined as a mean arterial pressure below 65 mm Hg (p=0.53).

Supplementary per-protocol analysis concurred with the intention-to-treat analysis showing a faster decrease in the VAS in the intervention group, and this is reported in online supplemental document 1. A nested post hoc analysis comparing patients receiving intravenous morphine to patients receiving INS is presented in online supplemental document 2 and showed similar rates of pain reduction in this nested control group.

DISCUSSION

This study has demonstrated that adult patients who presented to the ED with acute traumatic pain and who underwent intranasal administration of sufentanil experienced a significantly greater reduction in pain than those who followed the conventional protocol using other intravenous and oral opioids. These results were consistent both at the primary endpoint (15–20 min after randomisation) and at the secondary endpoint (1 hour after randomisation). Absolute VAS pain scores were also significantly lower in the sufentanil group at 15–20 min and 1 hour after randomisation.

The use of intanasal sufentanil resulted in a clinically significant and statistically faster decrease in pain scores. The between-group difference in the VAS pain score reduction of 1.5 at 15–20 min favouring INS is clinically significant as it is higher than the 'a priori' threshold of a 1 point reduction and the empirical recommendation of 1.4.[24]

The intranasal route offers several advantages, such as simple and rapid access both in-hospital and during prehospital care. The intranasal route circumvents the need for placement of an intravenous cannula,[25] which might delay treatment and may be challenging in some patient groups.[11] Altogether, these factors may have contributed to the faster decline in the VAS scores observed in the intervention group.

To date, few studies have tested the efficacy of INS for treating acute traumatic injuries. Two single-centre, randomised controlled trials have compared INS to placebo. One protocol compared a single dose of 0.4 μg/kg of INS (or placebo) in addition to usual intravenous pain treatment with multimodal analgesics (including intravenous opioids if needed).[20] This study showed a higher proportion of patients with pain relief, defined as achieving a numerical pain rating scale score ≤3, when treated with INS (72.2% vs 51.4%). However, INS was administered in addition to multimodal intravenous analgesics, including opioids. Another study compared a single dose of 0.7 μg/kg of INS with 0.1 mg/kg of intravenous morphine in adult patients presenting to the ED. This study did not find any difference in the numerical rating scores between the two groups at

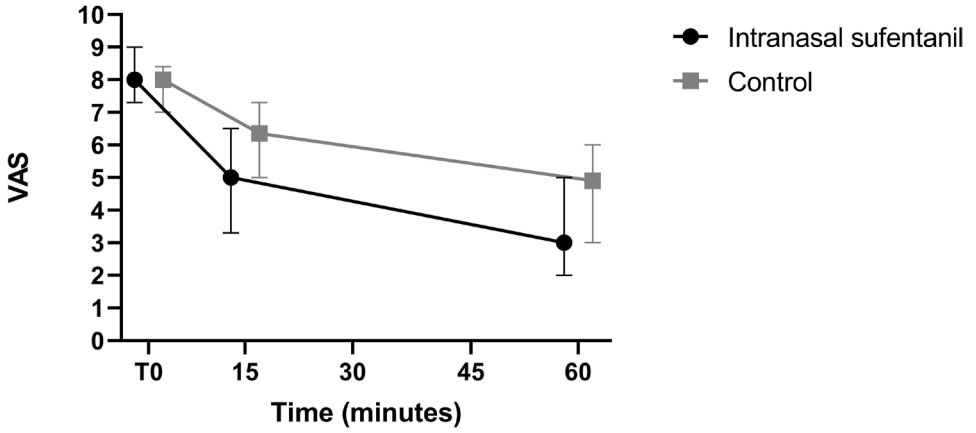

Figure 2 Changes from baseline to 60 minutes in the primary endpoint. Analyses are based on the treatment policy and reflect the intention-to-treat analysis population. Shown are the observed changes from baseline in the median visual analogue scale (VAS; scores range from 0 to 10, with higher scores indicating more intense pain). Bars indicate the interquartile range.VAS, visual analogue scale.

10, 20 or 30 min after drug administration,[18] but the study may have been underpowered.

Finally, a randomised, multicentre, double-blind study suggested better pain reduction at 30 min in patients with acute traumatic pain with INS (−4.1 vs −5.2; p=0.03), despite having some limitations in terms of low rates of coanalgesia.[16] Our study reported a similar superior analgesic effect with INS. Almost all patients in our study received concomitant non-opioid analgesia, avoiding the bias observed in previous studies and complying with usual pain management guidelines.[26] Our protocol was designed to pragmatically assess the performance of multimodal analgesia based on INS versus the current best practice, which includes acetaminophen and NSAIDs, and using the VAS, a patient-centred primary outcome. Given its pragmatic design, the superiority of INS might have been driven by either its ease of administration (usually faster than intravenous drugs) or the pharmacological properties of sufentanil itself.

Consistent with previous evidence,[16] we observed a significantly higher proportion of mild side effects while using INS, whereas no significant differences were observed in terms of severe side effects (7.2% vs 3.5%; p=0.27). Mild side effects of INS were observed in the majority of patients (71.1%), with a higher proportion than previously reported[16 18]; this might be associated with the dose administered. Loading doses were already reduced compared with those in the pilot study.[23] Although we observed a similar effect on pain reduction, we also observed a similarly high incidence of side effects, suggesting that the effectiveness of even lower doses should be investigated. Another possible explanation for the higher than previously reported incidence of side effects might be the significant proportion of patients with contusions and sprains in our study, exposed to strong opiates because of their pain rating, despite the absence of severe injury. Finally, while frequent, most of the observed side effects were mild, with dizziness and sweating being the two most frequently observed side effects in the intervention group.

Emergency physicians prescribing INS could engage patients in shared decision-making by providing patients with details about its superiority in terms of pain control, while explaining the higher risk of adverse effects.

Policy implications in terms of cost-effectiveness should be investigated further as this technique may be cost saving and time saving in a crowded ED environment. The cost-effectiveness of this particular form of analgesia should be investigated.

Table 3 Side effects and rescue analgesia by study group

	n (%)		
	Intervention	**Control**	**P value**
Patients (n)	81	84	
Any side effects	59 (71.1)	20 (23)	<0.001
Dizziness	45 (54.2)	14 (16.1)	<0.001
Nausea	16 (19.3)	10 (11.5)	0.16
Sweating	17 (20.5)	7 (8.1)	0.02
Vomiting	6 (7.2)	0 (0)	0.01
Xerostomia	3 (3.6)	0 (0)	0.08
Any severe side effect	6 (7.2)	3 (3.5)	0.27
Hypotension (MAP <65 mm Hg)	2 (2.4)	1 (1.2)	0.53
Hypoxia (SpO_2 <90%)	1 (1.2)	0 (0)	0.3
Bradypnoea	4 (4.8)	2 (2.3)	0.38
Bradycardia (<45 bpm)	0 (0)	0 (0)	–
Rescue analgesia*	20 (24.1)	20 (23)	0.87
Ketamine	2 (2.4)	7 (8.1)	0.10

* defined as a supplemental dose of any analgesic beyond the initial dose
bpm, beats per minute; MAP, mean arterial pressure.

Limitations

As this study was conducted at a single centre, the external validity of the results might be limited.

The patients and caregivers were not blinded, which might have introduced some bias into the study. Moreover, for some patients, the caregivers assessing the outcome were the investigators, and this might have introduced a bias, as the latter may have been intellectually vested in the outcome.

Therapeutic interventions other than analgesic administration conducted between T0 and T60 were not documented during data collection. Nonetheless, procedures such as dislocation reduction and cast application reduce pain and therefore may affect the pain scores.[27]

Another limitation of the study was the assessment of pain levels using the VAS before administering analgesia. The VAS is considered the most complicated pain assessment scale for patients to use while having excellent performance for evaluating the evolution of pain during analgesic treatment.[20 22] VAS use during this stressful event may have been associated with some bias in the assessment of pain.

Finally, the intervention protocol was compared with a standard hospital protocol based on the recommendations of the European Society of Emergency Medicine. In terms of coanalgesia, the protocol allowed for choice among drugs, their potential associations and their routes of administration. This may have introduced confounding factors that could have accounted for the observed differences between the groups. This risk was low as a higher proportion of patients received coanalgesia in all possible forms and intravenous treatment in the control group than those in the intervention group.

CONCLUSION

For patients presenting to the ED with acute traumatic pain, significant reduction in pain was observed at 15–20 min and at 1 hour after randomisation among patients treated with INS compared with those treated with other intravenous and oral opioids, although side effects were greater. Further research is required to assess the impact of adverse events on patient selection, optimal dosing and external validity.

Contributors SM contributed substantially to the conception and design of the study; to the acquisition, analysis and interpretation of the data. SM drafted the manuscript and approved the final version, which has been submitted for publication. PYT contributed substantially to the design of the study and the acquisition and interpretation of the data. TL contributed substantially to data acquisition and interpretation. F-ZB contributed substantially to the data analysis and interpretation. APl and APa contributed significantly to data acquisition and interpretation. MB contributed substantially to the data interpretation. BK substantially contributed to the conception and design of the study as well as the acquisition and interpretation of the data. PYT, TL, F-ZB, APl, APa, MB and BK critically revised and approved the final version of the manuscript for publication. SM is the garantor of the study, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the local ethics committee (Comité d'Ethique du CHU Saint-Pierre, reference number: CE/19-07-08). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available at the following address: https://doi.org/10.6084/m9.figshare.22348558.v1.

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Supplementary document 1

Per-protocol analysis

Group characteristics

During the 23-month period between January 2020 and February 2022, 205 patients were screened for inclusion, 180 underwent randomisation, and 165 were included in the per protocol analysis after excluding 35 patients (Figure 1), with 84 and 81 subjects randomised to the control and intervention group, respectively.

The characteristics of the patients in the two groups were well balanced at baseline in terms of demographics, medical history, vital signs, ambulance admission, admission complaints, and baseline VAS pain assessment.

The most frequent complaint that led to ED visits was upper limb trauma, followed by lower limb trauma. At discharge, the primary diagnosis was bone fracture, followed by contusion (Table 1S).

Main results

Pain intensity decreased over time in both groups. After 15–20 minutes the VAS pain score decreased by (3 [interquartile range (IQR) 1.6–5] in the intervention group and by 1.4 (IQR, 0.5–3) in the control group, a reduction that was significantly larger in the intervention group (p<0.001) (Table 2S).

The median VAS pain score was lower in the intervention group 15–20 minutes after randomisation (5 [IQR, 3.4–6.8] vs 6.6 (IQR, [5–7.3]; p=0.002).

After one hour, the VAS pain score decreased by 5 (IQR, 3–6.9) in the intervention group and by 3 (IQR, 2–5) in the control group, and the reduction was significantly higher in the intervention group (p<0.001) (Table 2S). The median VAS pain score was lower in the intervention group one hour after randomisation (3 [IQR, 2–5] vs 4.9 [IQR, 3-6]; p<0.001).

No differences in co-analgesia were observed between the two groups (100% in both groups).

Thirty-nine patients received rescue analgesics during the observation period, who were similarly distributed between the intervention and control groups (24.7% vs. 22.6%, respectively; p=0.75).

No significant differences were observed between the two groups in terms of the administration of repeated analgesic doses at either T15 or T60.

Adverse events

There was no difference in terms of severe adverse events in the two groups (Table 3S). One patient in the intervention group and no one in the control group developed hypoxemia defined as a SatO2<90% (p=0.31). Two patients in the intervention group

and one patient in the control group developed hypotension, defined as a mean arterial pressure below 65 mmHg (p=0.54).

The composite outcome, regrouping all measured adverse events that occurred during the one-hour follow-up period, was observed more frequently in the intervention group (71.6% vs 21.4%; p<0.001) indicating a higher proportion of side effects in the intervention group (Table 3S).

When assessed individually, patients in the intervention group had a significantly higher incidence of dizziness (54.3% vs 15.5%; p<0.001), sweating (21% vs 7.1%; p=0.01), and vomiting (7.4% vs 0%; p=0.01). No significant difference between the two groups was observed in terms of the occurrence of nausea, bradypnea, or xerostomia. Dizziness was the most reported adverse effect in both groups, as outlined in Table 3S. Saturation was higher in the control between groups fifteen minutes after randomization (99 [98; 100] vs. 98 [97; 100], p=0.001) and one hour after randomization (99 [98; 100] vs. 98 [96; 99], p<0.001).

Supplementary document 2

Post-hoc analysis IV morphine vs IN sufentanil

Group characteristics

During the 23-month period between January 2020 and February 2022, within the patients randomized for the study, after applying exclusion criteria, 12 patients were treated with IV morphine and 87 with intranasal sufentanil.

Post-hoc nested analysis on patients receiving IV morphine compared to patient receiving IN sufentanil

Pain intensity decreased over time in both groups. After 15–20 minutes the VAS pain score decreased by (3 [interquartile range (IQR) 1.7–5] in the intervention group and by 1 (IQR, 1–5) in the intravenous morphine group group, a reduction that was larger but not statistically superior in the intervention group (p=0.24).

The median VAS pain score was lower, but not statistically significantly, in the intervention group comparted to the intravenous morphine group 15–20 minutes after randomisation (5 [IQR, 3.5–6.5] vs 7 (IQR, [5–9]; p=0.068).

After one hour, the VAS pain score decreased by 5 (IQR, 3–7) in the intervention group and by 3 (IQR, 2–8) in the intravenous morphine group. the reduction was larger but significantly higher in the intervention group (p=0.37). The median VAS pain score was lower, but not significantly, in the intervention group, compared to the intravenous morphine group (3 [IQR, 2–5] vs 5 [IQR, 0-6]; p=0.3) one hour after randomisation.