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Intranasal sufentanil given in the emergency department triage zone for severe acute traumatic pain: a randomized double-blind controlled trial

Fabien Lemoel[1] · Julie Contenti[1,2] · Charles Cibiera[1] · Jocelyn Rapp[1] · Céline Occelli[1,2] · Jacques Levraut[1,2]

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Abstract

The goal of our study was to determine if an intranasal (IN) dose of sufentanil delivered in the ED triage zone would improve the management of severely painful patients. We performed a randomized, double blind and placebo-controlled trial on adult patients suffering from an acute severe pain (≥ 6/10) consecutive to an isolated limb injury. We compared 2 analgesic strategies: the usual pain treatment with IV-only multimodal analgesics (IVMA) including IV opioids if needed (control group) and another strategy (active group) based on a single dose of IN sufentanil (0.4 µg/kg) given at triage and followed by IV multimodal analgesia. Our primary outcome was the proportion of patients reaching pain-relief (≤ 3/10) 30 min after IN injection at triage. Secondary outcomes were rates of adverse events, frequency of clinical interventions required by these events, and satisfaction of patients. A total of 144 adult participants completed the study, 72 in each group. Compared with usual IV-only pain management, the analgesic strategy initiated in triage zone with a dose of IN sufentanil increased the proportion of patients reaching pain relief in 30 min: 72.2% versus 51.4%, in our trial ($p = 0.01$ and number needed to treat of 5). There was no serious adverse event (AE) in both groups. Patients who received IN sufentanil experienced more frequently minor opiate side effects. Proportion of respiratory AEs was higher in the active group (12.5% of bradypnea < 10 cycles per minute versus 1.4%) but these events were of mild severity, as only 2 participants (one in each group) received temporary low dose oxygen therapy, and none required naloxone. Lengths of stay in the ED were similar in both groups, as well as satisfaction of patients (above 9/10) and pain scores at discharge (< 2/10). We found that a single dose of IN sufentanil delivered in the ED triage zone significantly increases the proportion of severely painful patients reaching painrelief in 30 min, compared to usual analgesia with IV-only multimodal analgesia.

Keywords Intranasal · Sufentanil · Non-invasive · Acute severe pain · Emergency department · Triage nurse · Limb injury · Pain relief delay · Time to analgesia

Introduction

Acute pain is one of the most common complaints among emergency department (ED) patients, but for various reasons and despite extensive research, education and recommendations, pain management remains suboptimal and often delayed [1–4].

Intravenous (IV) opioids, the mainstay of severe acute pain treatment, can be ordered and delivered in most EDs only after the patient has been triaged, installed on a stretcher in an individual ED room, and once an IV line has been established. But venous catheter insertion is time-consuming, and requires skilled staff that might be occupied elsewhere. Scarcity of available health care providers is, therefore, a reason why ED overcrowding is associated

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✉ Fabien Lemoel
fablemoel@yahoo.fr

[1] Emergency Department, Hôpital Pasteur 2, Centre Hospitalier Universitaire de Nice, 30 voie Romaine, Nice 06000, France

[2] School of Medicine, Université Côte d'Azur, Nice, France

with poor and delayed care for severely painful patients [5, 6]. As attendance grows every year in EDs worldwide, efficient, safe, and non-invasive alternatives to IV analgesia may be interesting.

Intranasal (IN) analgesia is easy, efficient, and, therefore, increasingly studied and employed by ED physicians and researchers. By this route of administration that does not require specialized skills, opioids can be delivered earlier [7], the number of unnecessary IV line placements can be reduced [8, 9], and time to pain relief might be improved.

For its favorable biodisponsibility and the limited volume of administration needed for adult patients, IN sufentanil in its highest concentration (50 µg/ml) seems effective and promising for pain management in emergency [10, 11] and postoperative [12] settings. To date, IN sufentanil analgesia delivered in the ED triage zone has never been directly investigated.

Our study intends to evaluate if a single dose of IN sufentanil delivered in the triage zone would improve the management of severely painful adult patients with a limb injury receiving an IV multimodal analgesia (including opioids if needed). Other outcomes were rates of adverse events, frequency of clinical interventions needed by these events, and satisfaction of patients.

Methods

Study design and setting

We performed a randomized, double-blind, controlled study, within a tertiary adult ED with an annual census of 80,000 visits. The trial was promoted by Nice University Hospital, approved by our institution's ethics committee, and registered in ClinicalTrials.gov (NCT01954368). The referring doctor of our ED triage zone thoroughly evaluated every eligible patient, and confirmed each inclusion in the trial. All participants provided informed consent.

Population

We enrolled patients aged 18–75 years, admitted to our ED for a recent (< 6 h) isolated limb injury, and a persistent severe pain despite immobilization (pain score ≥ 6 on a 0–10 verbally administered numerical rating scale, VNRS).

Patients were not included if they had received opioids within 4 h of arrival in the ED; had sustained a thoracic, abdominal, spinal or head injury; had a clinically obvious dislocated articulation or another orthopedic injury clearly indicating a procedural sedation; had respiratory or hemodynamic instability (blood pulse > 110/min, systolic < 90 mmHg or oxygen saturation < 95% in room air); had chronic respiratory, cardiac or renal failure; were intoxicated; were allergic to opiate analgesics; or had a stuffy nose or a facial injury. Pregnant women, prisoners, IV drug users or patients unable to understand or communicate a pain score were also excluded.

Study protocol

Eligible patients willing to participate were randomized to either the active group or the control group, using a fixed 1:1 allocation ratio determined by a computer-generated randomization list, maintained in the pharmacy (located outside of the ED). Small, random block sizes of 8 were used to ensure equal allocation to each treatment arm. Following the allocation list, the pharmacist prepared in advance and dispatched sealed indistinguishable study kits to the emergency department. The content of the sealed study kits was not revealed to study participants, emergency physicians, and ED nurses, to maintain the double-blind. The pharmacist was not involved in direct patient care or data collection.

Each study kit included a fulfilled 1-ml lauer-lock syringe (containing sufentanil or normal saline solution, depending on the study arm), a study-specific weight-based schedule and an intranasal mucosal atomization device (MAD Nasal™, Teleflex®, Wayne, Pennsylvania, USA). The 0.1 ml dead space of the MAD was taken into account in the weight-based schedule displayed in each kit, and the volume of medication injected in each patient's nostril never exceeded 0.4 ml. Prior to any inclusion, each nurse had received detailed practical information on nasal administration with the MAD.

Once the participant's consent was obtained, the triage nurse had to take the syringe inside the study kit, ask the patient his or her body weight, check the study-specific weight-based schedule, and withdraw from the syringe the unnecessary volume of study medication. Unaware of the patient's study arm, the triage nurse then had to connect the MAD to the syringe, and spray half of its volume in each patient's nostril. The timing of this double-blind IN injection in triage zone defined time zero (*t*0).

At time zero (*t*0), patients in the active group received 8 µl/kg of IN sufentanil in its highest concentration (50 µg/ml), corresponding to 0.4 µg/kg of IN sufentanil. Patients in the control group received at *t*0 the same weight-based intranasal volume (8 µl/kg) of normal saline solution, as placebo. Unlike IN midazolam, discomfort and bad taste are unusual with IN sufentanil or saline solution, making these products almost impossible to distinguish.

Immediately after IN administration in triage zone, each participant was installed on a stretcher in an individual ED room, and as soon as possible a nurse (unaware of patients' study arm) had to establish an IV line, prepare and deliver via a protocol IV multimodal analgesics (IVMA), guided by current French pain management recommendations [13].

Every participant received 1 g of IV acetaminophen and 100 mg of IV ketoprofen (if not contraindicated).

In both groups, in addition to these IV analgesics, only the patients still declaring a VNRS ≥ 6/10 at this time of the trial received IV morphine titration using 3 mg increments every 5 min (2 mg if the patient's body weight was less than 60 kg), until reaching pain relief (VNRS ≤ 3/10).

As patients allocated to the control group received an IN placebo at *t*0, our institution's ethics committee approved not to differ the initiation of IV multimodal analgesics, to treat these patients as soon as possible and according to current French pain management guidelines [13]. For these ethical reasons and because of the double-blind, we, therefore, could not apply a security period between *t*0 and the beginning of IV morphine titration, for the patients in the active group (IN sufentanil at *t*0) who were still in severe pain (VNRS ≥ 6/10) at the time of venous catheter insertion.

A dedicated research assistant followed each patient during his or her entire ED stay, and recorded time at each step of participants' ED care, as well as pain scores, vital signs, and adverse events every 5 min from *t*0 to *t*0 + 120 min. Using a Nellcor® N-85 Monitor (Medtronic, Dublin, Ireland), continuous respiratory rate, heart rate, and pulse oximetry were monitored and recorded every 5 min in this 2-h period. Participants did not receive systematic oxygen therapy.

Measures

Our primary outcome was the proportion of patients reaching pain relief, defined as a pain score ≤ 3 on a 0–10 verbally administered numerical rating scale, 30 min after the intranasal injection of study medication at *t*0 in the ED triage zone (*t*0 + 30 min).

Secondary outcomes were the proportion of patients experiencing somnolence (sedation > 3 on Ramsay's sedation scale [14]); emesis (nausea or vomiting); or respiratory depression defined as respiratory rate < 10 cycles per min, central apnea > 6 s or hypoxia (oxygen saturation < 90% in room air). Clinical interventions required by any adverse events were monitored. Time intervals and pain scores were recorded at each step of patients' ED care, and satisfaction of patients was assessed on 10-cm visual analogic scales.

Primary data analysis

In accordance with the previous data [10, 15], we assumed that half of the patients in the control group (strategy with IV-only multimodal analgesics including opioids if needed) would reach pain relief (VNRS ≤ 3/10) at *t*0 + 30 min. We anticipated a clinically meaningful 50% increase of this proportion for participants in the active group (strategy with 0.4 µg/kg IN sufentanil at triage + IV multimodal analgesics in ED room).

With a power of 90% and an alpha of 5%, 132 participants were required. We chose to include 144 patients to consider eventual impossibility or issues in the assessment of the 30-min pain control. To limit the attrition bias, we analyzed the data for the main outcome using an intention-to-treat (ITT) method. In case of missing data concerning the primary outcome, we chose to apply the worst-case scenario approach: pain relief at *t*0 + 30 min in the control group (IN placebo at triage + IVMA including IV opioids if needed), and the contrary in the active group. The calculations were performed using MedCalc (MedCalc Statistical Software, version 14.8.1) and the R software (http://www.R-project.org).

Continuous data were expressed as mean ± SD, or medians ± IQR, depending on the data distribution, and categorical data were presented as percentage. Data were compared with Student's *t* test or Mann–Whitney test, as appropriate for continuous variables, and Chi square tests for categorical data. The confidence intervals (CIs) of the differences in proportions were calculated using an online calculator accessible at http://vassarstats.net/prop2_ind.html. The CIs of the differences in medians of two independent samples were calculated using a stratified bootstrap method. Cumulative proportions of pain-relieved patients in each group were compared using a Kaplan–Meir method; the log-rank test was applied for overall comparison, and Wilcoxon test was used for the initial segment of the curves. A *p* value of 0.05 was considered as being significant.

Results

A total of 144 patients were included, 72 in the active group (IN sufentanil followed by IV analgesics) and 72 in the control group (IN placebo followed by IV opioids).

Because of psychological and understanding issues, the participation of one patient allocated to the control group had to be stopped immediately after inclusion and IN administration, and no data could be recorded. To respect ITT analysis for the primary outcome, we considered this patient as pain relieved (VNRS ≤ 3/10) at *t*0 + 30 min, according to the worst-case scenario approach.

Patient flow during the study period (January 2014–March 2016) is shown in Fig. 1. Baseline pain scores and patients' characteristics were similar between groups (Table 1). No patient included in the study had a long-term opioid treatment.

For our primary outcome shown in Fig. 2, 30 min after IN administration in triage zone, significantly more patients reached pain relief (VNRS ≤ 3/10) in the active group (IN sufentanil followed by IV analgesics) than in the

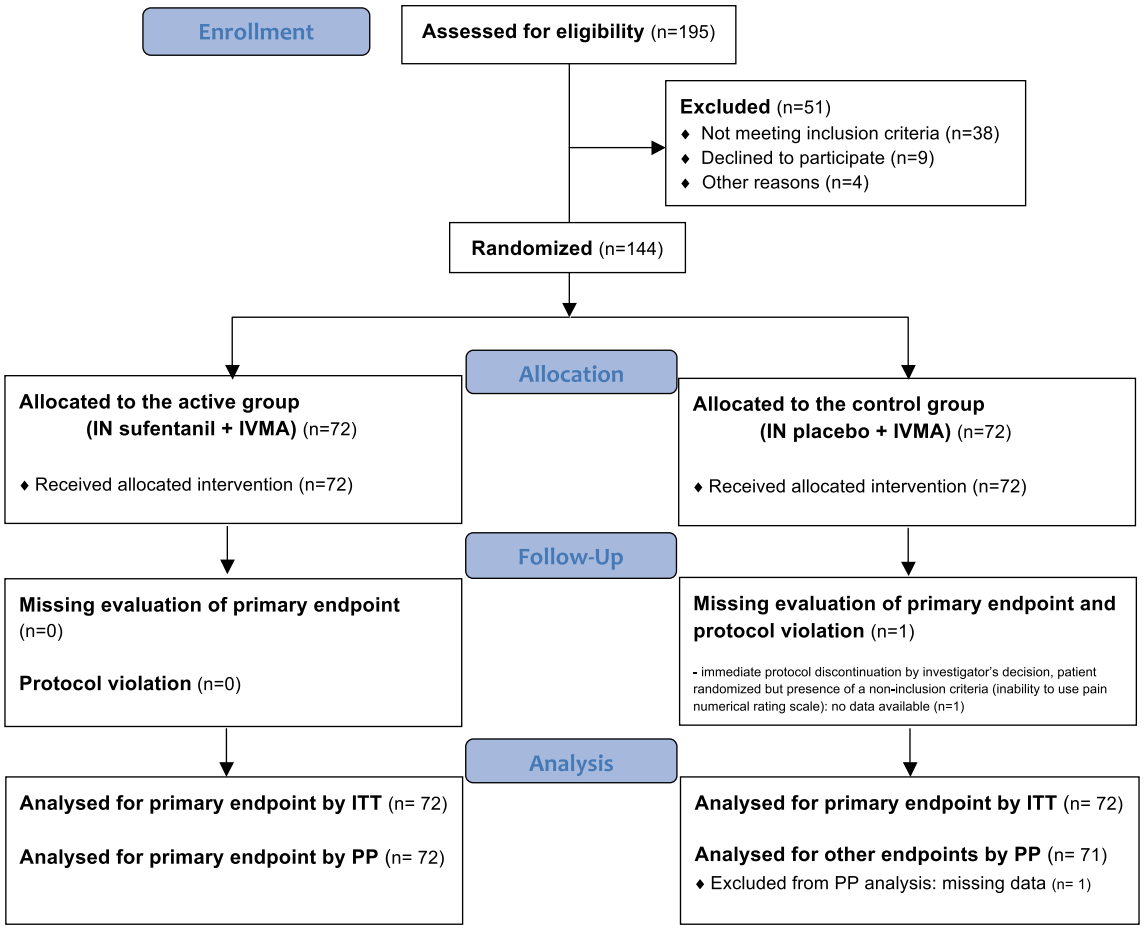

Fig. 1 The CONSORT flowchart. *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed), *ITT* intention-to-treat, *PP* per protocol

control group (IN placebo followed by IVMA including IV opioids if needed): 72.2% versus 51.4% (difference 20.8%, 95% CI 4.0–36.2%, $p = 0.01$). According to this absolute increase, the number needed to treat is five.

From IN administration at triage ($t0$) until discharge from the ED, median times at each step of patients' care were similar in both groups (Table 2). Median time from $t0$ to initiation of IV multimodal analgesia (IVMA) was 17 min in the active group, versus 18 min in the control group (difference − 1 min, 95% CI − 3.5–4.5 min).

Patients in the control group received protocol-ordered IV morphine titration more frequently than patients in the active group (Fig. 3): 53.5% versus 31.9% (difference 21.6%, 95% CI 4.4–37.2%). Table 3 shows pain scores at each step of patients' care in the ED: at the time of venous catheter insertion in individual ED room, mean VNRS of patients in the control group was higher than in the active group (6.3 versus 5.1, respectively, difference 1.2, 95% CI 0.5–1.9), but pain scores were similar at discharge: 1.5 in the active group and 1.3 in the control group (difference 0.2, 95% CI − 0.4–0.6).

The Kaplan–Meier curves shown in Fig. 4 illustrate the cumulative proportions of pain-relieved (VNRS ≤ 3/10) patients in both groups, during the first 120 min of the study. Globally, using a log-rank test on the whole period of 120 min, these proportions were similar ($p = 0.14$). However, the Wilcoxon test reveals a significant difference of these cumulative proportions in the initial follow-up of patients ($p < 0.01$), this difference staying significant until $t0 + 48$ min.

Table 4 shows frequencies of opiate adverse events. There was no serious event in both groups. The composite proportion of patients who experienced temporary respiratory depression, emesis or somnolence was almost three times higher in the active group than in the control group. The severity of these AEs was, however, mild, as frequencies of clinical interventions needed to treat these events were very low and similar between groups. For respiratory adverse events, more patients in the active group experienced bradypnea (< 10 cycles per min): 12.5% vs. 1.4% (difference 11.1%, 95% CI 1.5–21.6%). Proportions of hypoxia (saturation < 90%, in room air), apnea (> 6 s), and clinical

Table 1 Characteristics of the study subjects

	Active group (IN sufentanil + IVMA) ($n = 72$)	Control group (IN placebo + IVMA) ($n = 72$)
Age (years)		
Median (IQR)	45 (28–58)	39 (25–54)
Range	18–75	19–78
Age distribution (years), no. (%)		
18–21	6 (8.3)	8 (11.1)
22–49	36 (50.0)	41 (56.9)
50–74	28 (38.9)	21 (29.2)
75 or older	2 (2.8)	2 (2.8)
Male, No. (%)	31 (43.1)	23 (31.9)
Weight, mean (SD), kg	74.0 (15.0)	70.6 (14.6)
ASA class, no. (%)		
Class 1	56 (77.8)	56 (77.8)
Class 2	16 (22.2)	15 (20.8)
Class 3	0 (0.0)	1 (1.4)
Type of injury, no. (%)		
Contusion	16 (22.2)	15 (20.8)
Sprain	16 (22.2)	16 (22.2)
Fracture	35 (48.6)	39 (54.2)
Dislocation	5 (6.9)	2 (2.8)
Localization of injury, no. (%)		
Upper limb	32 (44.4)	33 (45.8)
Lower limb	40 (55.6)	39 (54.2)
Baseline pain, mean (SD)		
VNRS	7.8 (1.2)	8.0 (1.4)

IN intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed), *IQR* interquartile range, *ASA* American Society of Anesthesiologists, *SD* standard deviation, *VNRS* verbal numerical rating scale

interventions required by any of these respiratory events were similar between groups. No patient required naloxone use, and only two participants required temporary low-dose oxygen therapy, one in each group.

Assessed on 10-cm visual analogic scales at discharge, mean satisfaction scores of participants are similar in both groups: 9.1 ± 1.3 cm in the active group and 9.3 ± 0.3 cm in the control group (difference -0.2 cm, 95% CI -1.0–0.7).

Discussion

To the best of our knowledge, our trial is the first to investigate the advantage of a single dose of IN sufentanil delivered at triage, to adult ED patients suffering from a limb injury with severe pain. In our randomized, double-blind, placebo-controlled study, we find that this strategy, compared with usual analgesia (IV-only multimodal analgesia including IV opioids if needed), determines a 20% absolute increase in proportion of patients reaching pain relief (VNRS $\leq$ 3/10) 30 min after their contact with the ED triage nurse ($p = 0.01$ and number needed to treat = 5).

Although our trial cannot prove it, this difference in time to pain relief may even be greater in case of ED overcrowding, as venous catheter insertion and IV analgesics would in this case be delayed because of limited available staff. The impact of ED crowding on time to pain relief has already been pointed out [6], so efforts to limit this impact with alternative, fast and non-invasive approaches are needed, and will probably be welcomed by our patients.

In the control group, mean baseline pain intensity was high (VNRS = 8/10), patients received an IN placebo in the triage zone, and subsequently were treated in an ED room via a protocol IV multimodal analgesia after venous catheter had been inserted by the nurse. At this time of the trial (median time of 18 min after *t*0), only one half (53.5%) of these patients received IV morphine, because they were still experiencing severe pain (VNRS $\geq$ 6/10). This early reduction in pain intensity in our control group is probably the result of a significant placebo effect, combined with the first results of IV multimodal analgesia. The strong placebo effect suspected in our trial might be explained by contributing factors already described in the literature: expectation, suggestion, and anxiety reduction [16, 17]. In our trial, the early initiation of sham analgesia in the triage zone, the unusual route of administration (intranasal), and the constant presence of a research assistant with participants during their ED stay may have triggered these contributing factors.

One half of the patients in the control group reached pain relief (VNRS $\leq$ 3/10) 30 min after their contact with the ED triage nurse. This result is in accordance with the previously published data. Lvovshi et al. [15] analyzed time to analgesia and time to pain relief on 625 severely painful adult patients (mean initial VNRS = 8/10) treated by IV morphine titration. The median time between arrival in the ED and pain relief (VNRS $\leq$ 3/10) was about 45 min in this trial. But much longer periods have also been quoted in literature, especially in real-life setting and overloaded EDs. Pines et al. [5] show on more than 13,000 severely painful ED patients (mean initial VNRS = 9/10) that only one half received pain medication, and in a mean time from triage of around 75 min. The authors' conclusions were that a significant association exists between ED crowding and oligoanalgesia (both delays and nontreatment) in large academic EDs. Again, in similar overcrowded circumstances with such delays in IV pain medication delivery, it is likely that intranasal analgesia would be particularly efficient and desirable.

Our trial demonstrates a high percentage of respiratory adverse events in the active group (0.4 µg/kg of IN sufentanil followed by IV analgesics): 16.7% of patients experienced

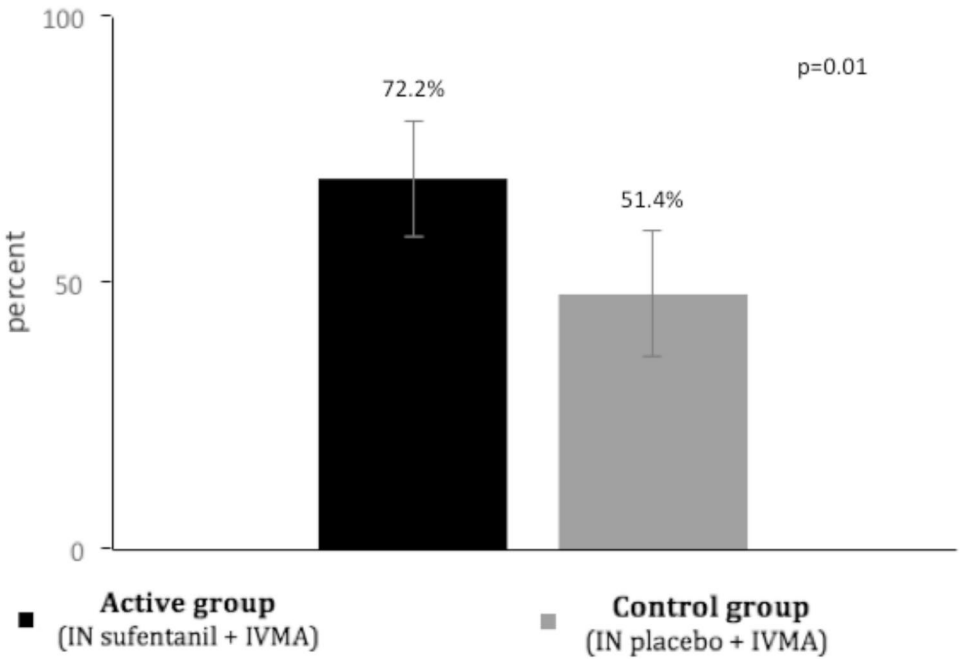

Fig. 2 Primary outcome: percentage of patients declaring VNRS ≤ 3/10, 30 min after IN pulverization (*t*0). *VNRS* verbal numeric rating scale, *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed)

Table 2 Median time intervals (IQR) in minutes, at each step of patients'ED care, from *t*0 to discharge

	Active group (IN sufentanil + IVMA) ($n = 72$)	Control group (IN placebo + IVMA) ($n = 71$)	Difference (95% CI)
Triage zone: IN administration (*t*0)	0	0	0
Delay between *t*0 and installation in individual ED room	4 (3.75–7)	4 (3–6.5)	0 (−2–0)
Delay between *t*0 and venous catheter insertion	14 (10–22)	15 (10–18.5)	−1 (−4–0.5)
Delay between *t*0 and start of IV multimodal analgesia	17 (13–23.75)	18 (14–22)	−1 (−3.5–4.5)
Delay between *t*0 and departure to the imaging department	45 (34–55)	47 (39–54)	−2 (−9–2.5)
Delay between *t*0 and return from the imaging department	70 (58–84)	72 (63–84)	−2 (−9–7.5)
Delay between *t*0 and discharge from the ED	179.5 (121–273.25)	161 (111–226)	18.5 (−17–61)

IQR interquartile, *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed)

bradypnea (< 10 cycles per min), hypoxia (oxygen saturation < 90%) and/or apnea (> 6 s), compared to 2.8% in the control group (difference 13.9%, 95% CI 3.0–25.1%).

On adult patients suffering from limb injury and severe pain, Steenblik et al. [10] employed a dose higher than in our study (0.5 µg/kg of IN sufentanil) and found 2.5% proportion of patients experienced hypoxia (oxygen saturation < 88% in room air). But as the authors did not use continuous respiratory monitoring with capnography or permanent clinical survey, respiratory events may have been underestimated in their trial. In our study, the continuous monitoring of vital signs (with capnography) and the constant presence of a research assistant with every participant during the first 120 min may have detected false positives or respiratory events of very low clinical significance. Indeed, severity analysis of this outcome shows that no respiratory event led to subsequent trouble, sequelae, increased ED stay, unplanned hospitalization or naloxone use. Only one participant in the active group (and another patient in the control group) required temporary low-flow oxygen therapy. In less monitored and real-life setting, the percentage of clinically detectable and significant respiratory depression would probably be much lower than the proportions detected in our trial.

As previously mentioned, our ethics committee permitted to treat as soon as possible with IV multimodal analgesics every participant of the study, in order not to delay the pain management of patients in the control group who received an IN placebo at *t*0. Because of the double-blind, we could not respect a security period for patients in the active group, between IN sufentanil at *t*0 and the administration of IV analgesics in ED room (including for some

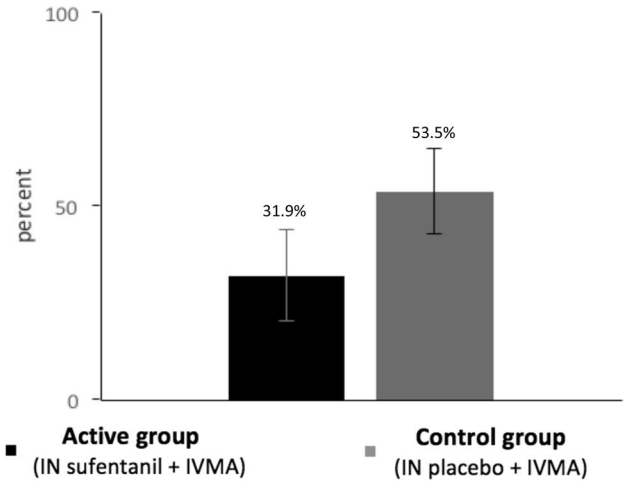

Fig. 3 Proportions of patients who required IV opioids for their pain management in ED room. *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed)

patients, IV morphine). This methodology determined short time to pain relief in both groups of the study, but might have artificially increased the incidence of respiratory depression in the active group. In real-life setting, proportions of opiate AEs would be much lower since ED physicians would respect a pharmacokinetic-based security period between IN sufentanil administration and subsequent (if needed) IV morphine titration.

Satisfaction scores are similar in both groups, even if patients in the active group (IN sufentanil) reached pain relief sooner. One could argue that the high proportion of opiate adverse events experienced by participants in this arm may have limited their satisfaction. We believe on the contrary that patients in the control group, even if reaching pain relief later, were still highly satisfied because of the strong placebo effect showed in our trial, and by the fact that a research assistant stayed nearby them constantly, and could answer their interrogations or expectations easily. As previously quoted, appropriate communication with health care providers, empathy, timeliness of care and information dispensation are major proven elements related to patient satisfaction [18]. These elements may

Table 3 Pain scores (VNRS) at each step of patients' ED care, from *t*0 to discharge

	Active group (IN sufentanil + IVMA) ($n=72$)	Control group (IN placebo + IVMA) ($n=71$)	Difference (95% CI)
Triage zone: participation agreement	7.8 (1.2)	8.0 (1.4)	−0.2 (−0.6 to 0.2)
Triage zone: intranasal administration (*t*0)	7.8 (1.2)	8.0 (1.4)	−0.2 (−0.6 to 0.2)
Installation in individual ED room	6.8 (1.9)	7.4 (1.7)	−0.6 (−1.1 to 0.1)
Venous catheter insertion	5.1 (2.3)	6.3 (2.1)	−1.2 (−1.9 to −0.5)
Discharge from the ED	1.5 (1.5)	1.3 (1.5)	0.2 (−0.4 to 0.6)

Data are reported as means (SD)

VNRS verbal numeric rating scale, *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed), *CI* confidence interval, *SD* standard deviation

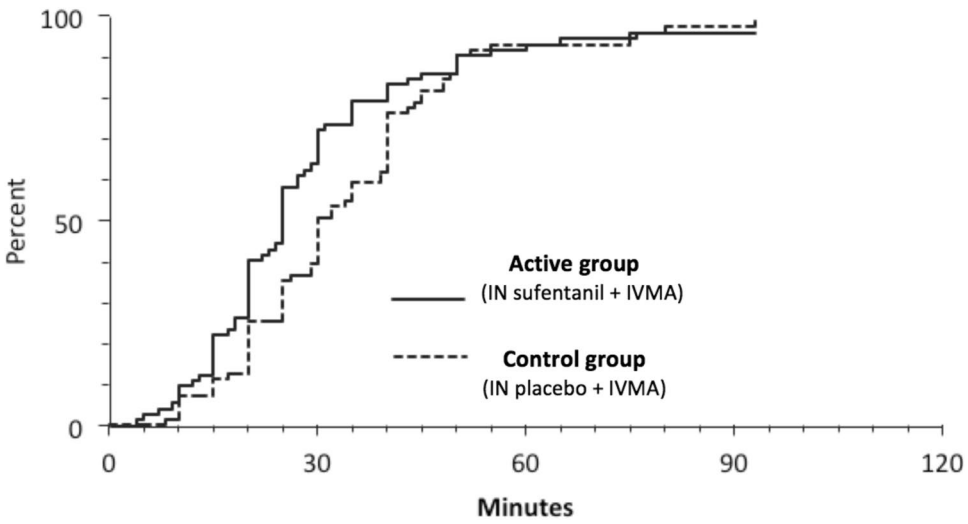

Fig. 4 Cumulative proportions of patients reaching pain relief (VNRS ≤ 3/10), in each group. *VNRS* verbal numerical rating scale, *IN* intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed)

Table 4 Proportions of patients with opiate adverse events, and clinical interventions required, in each group

	Active group (IN sufentanil + IVMA) ($n = 72$)	Control group (IN placebo + IVMA) ($n = 71$)	Difference
Any opioid related adverse event	48 (66.7)	16 (22.5)	44.1 (27.2–57.7)
Any respiratory adverse event	12 (16.7)	2 (2.8)	13.9 (3.0–25.1)
Bradypnea < 10/min	9 (12.5)	1 (1.4)	11.1 (1.5–21.6)
Oxygen desaturation < 90% (room air)	5 (6.9)	1 (1.4)	5.5 (−2.9 to 14.8)
Apnea > 6 s	0	0	0
Temporary oxygen therapy (2 l/min)	1 (1.4)	1 (1.4)	0.0 (−7.4–7.2)
Naloxone use	0	0	0
Excessive somnolence (Ramsay score > 2)	16 (22.2)	5 (7.0)	15.2 (2.5–27.6)
Clinical intervention required	0	0	0
Nausea and vomiting	24 (33.3)	7 (9.9)	23.5 (9.1–36.8)
Intravenous metoclopramide	3 (4.2)	2 (2.8)	1.3 (−7.1–0.1)

Data are reported as No. (%) or percent (95% CI)

IN intranasal, *IVMA* intravenous multimodal analgesia (including IV opioids if needed), *CI* confidence interval

explain why patients in both groups of our double-blind study were similarly highly satisfied, even with different time to pain relief and various adverse event proportions.

Limitations

As we could not perform inclusions 24 h a day and 7 days a week because of our research assistant availability, we have no information on the total number of unrecruited eligible patients during the study period, leaving possibility to selection bias.

This was a single-center study with wide non-inclusion criteria, on a convenience sample of adults aged 18–75 years suffering from a severe acute traumatic pain. Generalization of our data for other EDs, different categories of patients and various clinical conditions is not possible.

Although every effort was made to conceal drug allocation, blinding may not have been complete. As IN sufentanil injection does not induce discomfort or bad taste, and because of the strong placebo effect noticed for patients in the control group, the blinding of participants as well as providers should have been maintained. But ED staff could subsequently have guessed arm allocation for a few patients in the active group experiencing early opiate adverse events in the first 15–20 min after inclusion, before IV line was in place. However, as every IV analgesic treatment was not at the ED physician's discretion but was via strict protocol and driven only by patients' self-reported pain intensity, our results should not have been influenced. We, therefore, believe that our primary outcome at $t0 + 30$ min is valuable.

Conclusion

Delivered in the ED triage zone, an intranasal dose of sufentanil (0.4 µg/kg) accelerates the management of severe pain from limb injury, by increasing the proportion of adult patients reaching pain relief in 30 min, compared to the usual strategy based on IV-only multimodal analgesics (including opioids if needed): 72.2% versus 51.4% in our trial, ($p = 0.01$ and number needed to treat is 5).

Patients who received IN sufentanil experienced adverse respiratory events more frequently (12.5% of bradypnea < 10 cycles per min), but these events were of mild severity, as only two participants (one in each group) received temporary low-dose oxygen therapy, and none required naloxone. Lower doses of IN sufentanil, or other IN non-opioid analgesics should be explored, to enhance the clinical safety of this attractive non-invasive initiation of severe pain treatment in EDs, while maintaining its advantage on time to pain relief.

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Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Statement of human and animal rights This study has been ethically approved by the Comité de Protection des Personnes Sud Mediterranée V (CHU de NICE - Hôpital de CIMIEZ. Bâtiment Grand Hôtel - 5ème étage. 4 avenue Reine Victoria. CS 91179. 06003 NICE CEDEX 1, France).

Informed consent All participants provided informed consent.

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