Limited evidence for intranasal fentanyl in the emergency department and the prehospital setting – a systematic review

Morten Sejer Hansen & Jørgen Berg Dahl

ABSTRACT

INTRODUCTION: The intranasal (IN) mode of application may be a valuable asset in non-invasive pain management. Fentanyl demonstrates pharmacokinetic and pharmacodynamic properties that are desirable in the management of acute pain, and IN fentanyl may be of value in the prehospital setting. The aim of this systematic review was to evaluate the current evidence for the use of IN fentanyl in the emergency department and prehospital setting.

METHOD: Reports of trials of IN fentanyl in emergency department and prehospital treatment of pain were systematically sought using the PubMed database, Embase, Google scholar, the Cochrane database and the Cumulative Index to Nursing and Allied Health Literature.

RESULTS: Twelve studies of IN fentanyl in the emergency department (ED) and prehospital setting were included in the final analysis. In the ED, analgesic non-inferiority and superiority were demonstrated when comparing IN fentanyl with intravenous (IV) and intramuscular morphine, respectively. Non-blinded, non-controlled studies demonstrated an analgesic effect of IN fentanyl in patients with moderate and severe pain. In the prehospital setting, both analgesic inferiority and non-inferiority were demonstrated when IN fentanyl was compared with IV morphine. Finally, a significant analgesic effect of IN fentanyl was demonstrated when IN fentanyl was compared with methoxyflurane.

CONCLUSION: Only limited quality evidence exists for the efficacy of IN fentanyl in the ED and in the prehospital setting, and more double-blinded, randomised, controlled trials are urgently needed to validate the use of IN fentanyl in this context.

Non-invasive analgesics have increased in popularity in the last couple of years. Intranasal (IN) administration is one of the latest non-invasive modes of analgesic administration, and fentanyl is one of the most extensively investigated IN analgesics in both clinical and pharmacokinetic studies [1].

Gastrointestinal and hepatic pre-systemic elimination can be avoided with IN administration which may allow fentanyl to enter the cerebrospinal fluid via the olfactorial mucosae with an immediate effect on the central nervous system [2]. IN analgesics offer a valuable alternative to patients in whom intravenous (IV) or oral administration is problematic.

With its lipophilic properties and a 50-100-fold higher potency than morphine, fentanyl appears to be ideal for IN administration. Pharmacokinetic studies have demonstrated that the synthetic opioid with selectivity for μ-receptors has a bioavailability of 71-89%, a time to maximal arterial concentration (T_{max}) of approximately 6-7 min, an onset time of 6-8 min and a duration of analgesia of approximately one hour [1, 3-5]. The kinetic and dynamic properties of IN fentanyl are desirable for the management of acute pain, and IN fentanyl may be of value in the prehospital setting. However, evidence from pharmacokinetic studies does not always validate the use of IN fentanyl in daily clinical practice. The heterogeneity of the patients, the simple problems of epistaxis, accidental swallowing and blocked nose may result in suboptimal administration, which will entail decreased bioavailability, uncertainty concerning fentanyl plasma concentration and, finally, limited analgesic effect. Recent systematic reviews of IN fentanyl have evaluated its use in the paediatric population [6], as an analgesic for cancer patients with breakthrough pains [7] and in the treatment of acute pain [8].

Furthermore, recent reports demonstrate that IN fentanyl is beginning to be used in the prehospital setting, both nationally and internationally. The aim of this systematic review was to evaluate the current evidence for the use of IN fentanyl as an analgesic in the emergency department (ED) and prehospital setting.

METHOD

Reports of trials of IN fentanyl in emergency departmental and prehospital treatment of pain were systematically sought using the PubMed database, Embase, Google scholar, the Cochrane database, and the Cumulative Index to Nursing and Allied Health Literature without language restrictions. Free-text combinations including the following search terms were used: nasal, intranasal, spray, pain, fentanyl, emergency, prehospital and analgesia. Reference lists from retrieved articles were searched for additional papers. The last search was performed on 9 February 2012.

SYSTEMATIC REVIEW

Department of Anaesthesia 4231, Centre of Head and Orthopaedics, Rigshospitalet

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TABLE 1

Data from included studies.

Reference	Design	Clinical issue	n	Basic analgesia to active and control	Dosing, type of intranasal administration, concentration of formula	Outcome parameters, pain	Effect on pain	Effect on analgesic requirements	Side-effects	Baseline pain
Emergency department studies										
Borland et al [18]	IN fentanyl 50 µg/ml vs IN fentanyl 300 µg/ml	Age 3-18 Acute, closed long-bone fractures	91 vs 98	ND	Atomiser 1.5 µg/kg Conc. 50 µg/ml and 300 µg/ml	VAS or FPS-R at 0, 10, 20, and 30 min.	Reduced pain score at all time points No differences between the two groups	Increased use of supplemental analgesia in 50-µg/ml-group	NS	80 mm / 77.5 mm (VAS)
Younge et al [12]	IN fentanyl vs IM morphine (0.2 mg/kg)	Age: 3-10 Fracture of upper or lower limb	24 vs 23	ND	Spray 1.0 µg/kg Conc. 50 µg/ml	WBF at 0, 5, 10, 15, 20, and 30 min.	Reduced pain at 10 min. in IN fentanyl group compared with IM morphine	NS	No difference between the two groups	ND
Borland et al [13]	IN fentanyl vs IV morphine	Age 7-15 Acute long-bone fractures	32 vs 33	ND	Atomiser 1,7 µg/kg Conc.: 150 µg/ml	VAS at 5, 10, 20, and 30 min. after administration	No difference between the two groups	NS	3 children in fentanyl-group reported bad taste	68 mm (VAS)
Saunders et al [14]	IN fentanyl administration	Age 3-18 Fracture	81	ND	Atomiser 2 µg/kg Conc. 50 µg/ml	WBF or VAS at 10, 20, and 30 min. after administration	63 patients had significant reduction in pain score 30 min. after administration	19 patients needed rescue analgesia	NS	5 (WBS)/70 mm (VAS)
Cole et al [15]	IN fentanyl administration	Age 1-3 Acute injury (fracture, burn, fingertip, soft tissue, other)	46	ND	Atomiser 1.5 µg/kg Conc. 50 µg/ml	FLACC at 10 and 30 min. after administration	Median FLACC reduced from 8 to 2 at 10 min. and to 0 at 30 min.	ND	NS	8 (FLACC)
Finn & Harris [16]	IN fentanyl administration	Age 1-16 Acute injury (Fracture, burn, crushed digit, abdominal pain, other)	81		Atomiser 1.5 µg/kg Conc. 50 µg/ml	VAS at 0 and 30 min. after administration	VAS reduced at 5 min. from 91 mm-52 mm, and at 30 min. to 16 mm	ND	NS	91 mm (VAS)
Crellin et al [19]	IN fentanyl administration	Age 5-18 Upper limb injury	36		Type of administration: ? 1.5 µg/kg Conc. 50 µg/ml	VAS or Bieri face scale at 5, 10, 15, 20, and 30 min.	Reduced VAS at all time points	ND	NS	7 (VAS)
Borland et al [17]	IN fentanyl administration	Age 3-12 Acute pain	32	ND	Spray 1.5 µg/kg 100 µg/ml	VAS or WBF at 5, 10, 15, 20, 25, and 30 min. after administration	Pain reduced at 10, 15, 20, 25, and 30 min. after administration	ND	ND	61.3 mm (VAS) / 4 (WBS)
Ambulance studies										
Rickard et al [20]	IN fentanyl vs IV morphine (2,5-5 mg)	Age: 18-65 VRS ≥ 5 (cardiac pain) or ≥ 2 (non-cardiac pain)	127 vs 100	Cardiac pain: glycerol trinitrate; non-cardiac: methoxyflurane	Mucosal atomizer 180 µg Conc. 300 µg/ml	VRS at baseline, before each dose of analgesia, and at destination	No significant differences between the two groups	NS	No difference between the groups	8.2 (VRS)
Middleton et al [21]	IN fentanyl vs IV morphine vs methoxyflurane	Age 16-100 Patients with moderate to severe pain	42,844	ND	Atomiser 240 µg Conc. 300 µg/ml	NRS before and after administration	IV morphine is superior to IN fentanyl in terms of pain reduction	ND	ND	8.4 (VRS)
Bendall et al [22]	IN fentanyl vs IV morphine vs methoxyflurane	Age 5-15 Moderate to severe pain	3,312	ND	Atomiser 45-180 µg Conc. 300 µg/ml	VRS before and after administration	No difference in initial pain score reduction between IN fentanyl and IV morphine	ND	ND	8 (VRS)
Johnston et al [23]	IN fentanyl vs methoxy flurane vs IN fentanyl + methoxyflurane	Visceral pain	1,024	ND	Type of administration: ? < 5 years: 15 µg; 6-10 years: 30 µg; 11-15 years: 45 µg; Adults: 180 µg Conc. 300 µg/ml	VAS at 5 min. after administration and at arrival at hospital	VAS reduced from 8.1 (initial) to 6.2 (5 min.) and to 5.5 (hospital)	ND	ND	8.1/7.6/8.8 (VRS)

Conc. = concentration; FLACC = face, legs, activity, cry, consolability scale; FPS-R = Faces Pain Scale-Revised; IN = intranasal; IM = intramuscular; IV = intravenous; n = number of patients in the trial; ND = no description; NS = non-significant; VAS = visual analogue scale; VRS = visual rating score; WBF = Wong-Baker-Faces scale.

TABLE 2

Randomization, blinding, control groups and study design of included trials.

Study	Randomisation	Blinding	Control	Design
Borland et al [18]	Adequate randomization, adequate description	Double-blinded	IN-fentanyl low conc. vs IN fentanyl high conc.	Prospective interventional, comparative
Younge et al [12]	Adequate randomization, no description	No blinding	IN fentanyl vs IM morphine	Prospective, interventional, comparative
Borland et al [13]	Adequate randomization, no description	Double-blinded	IN fentanyl vs IV morphine	Prospective interventional, comparative
Saunders et al [14]	No randomization	No blinding	No control group	Prospective, interventional, non-controlled
Cole et al [15]	No randomization	No blinding	No control group	Prospective, interventional, non-controlled
Finn & Harris [16]	No randomization	No blinding	No control group	Prospective, interventional, non-controlled
Crellin et al [19]	No randomization	No blinding	No control group	Prospective, audit, non-controlled
Borland et al [17]	No randomization	No blinding	No control group	Prospective, interventional, non-controlled
Rickard et al [20]	Adequate randomization, adequate description	No blinding	IN fentanyl vs IV morphine	Prospective, interventional, comparative
Middleton et al [21]	No randomization	No blinding	IN fentanyl vs IV morphine vs methoxyflurane	Retrospective, comparative, observational
Bendall et al [21]	No randomization	No blinding	IN fentanyl vs IV morphine vs methoxyflurane	Retrospective, comparative, observational
Johnston et al [23]	No randomization	No blinding	IN fentanyl vs methoxyflurane	Retrospective, comparative, observational

Conc. = concentration; IN = intranasal; IV = intravenous.

Reports of IN fentanyl were considered for inclusion if they had prehospital treatment of pain as an endpoint, were evaluated by validated pain score or as effect on analgesic requirements. Furthermore, we chose to include studies of analgesic treatment in the ED conducted with patients not yet examined by a doctor. We required full journal publication or summary clinical trial reports published in English for inclusion. Consequently, abstracts were excluded. Only studies with pain or supplemental analgesic consumption as an endpoint were included in the final analysis. Databases were screened for any ongoing but unpublished studies [9]. All sites were last visited on 9 February 2012.

Each of the identified trials were independently read by the authors and assessed for eligibility. Data from the included studies were extracted onto a data sheet (**Table 1**). These data included: study design; clinical issue; number of patients in the intervention and control groups; basic analgesic regimen; dosing, type of IN administration and concentration of fentanyl formula; pain scores; effect on pain; possible side effects; and baseline level of pain and/or level of pain in the control group.

The Cochrane criteria for evaluation of adequate blinding and randomization were followed [10] (**Table 2**). Data concerning volume of dose were also extracted from the included studies (**Table 3**).

Qualitative analysis of analgesic efficacy was evaluated by assessment of significant difference in pain relief and analgesic consumption between the study groups, or between baseline and post-treatment pain ($p < 0.05$ as reported in original paper). We planned to perform quantitative analysis of combined data by calculating the mean differences (MDs) of pain scores (primary endpoint) and the MD of cumulated use of supplemental analgesics (secondary endpoint) between the study groups whenever sufficient data were provided in the original papers.

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed [11].

RESULTS

The search yielded 14 studies of IN fentanyl in the ED and prehospital setting, and one ongoing trial. Twelve studies met the inclusion criteria and were included in the final analysis (**Figure 1**). The included studies did not present a sufficiently homogenous group of trials to perform a meta-analysis. Consequently, only a qualitative analysis was conducted.

As illustrated in Table 1, we divided the included studies into two groups: ED studies and Ambulance studies. ED studies were defined as studies investigating the use of IN fentanyl in patients not yet examined by a doctor.

Intranasal fentanyl in the emergency department

Eight trials of IN fentanyl in the ED were identified [12-19]. The included studies were of varying design and quality. Only three were randomized studies [12, 13, 18] and only two studies were adequately double-blinded [13, 18] (Table 2). All studies investigated pain in patients below the age of 18 years.

One randomized, double-blinded study investigating pain following acute long-bone fractures [13], demonstrated no difference in pain scores or supplemental analgesic consumption when comparing IN fentanyl with IV morphine. Another randomized, open-label trial investigating pain following upper- or lower limb fracture demonstrated a significantly reduced pain score 10 min after administration of IN fentanyl compared with IM morphine. Four non-controlled, prospective trials were

TABLE 3

Dose volume of included trials.

Study	Dose volume
Borland et al [18]	200 µl
Younge et al [12]	100 µl
Borland et al [13]	N/A (1.7 µg/kg → 11 µl/kg)
Saunders et al [14]	N/A (2 µg/kg → 40 µl/kg)
Cole et al [15]	N/A (1.5 µg/kg → 30 µl/kg)
Finn & Harris[16]	N/A (1.5 µg/kg → 30 µl/kg)
Crellin et al [19]	N/A (1.5 µg/kg → 30 µl/kg)
Borland et al [17]	N/A (1.5 µg/kg → 15 µl/kg)
Rickard et al [20]	300 µl
Middleton et al [21]	150-600 µl
Johnston et al [23]	50-200 µl

N/A = not applicable, administered dose volumes depending on the weight of the patient.

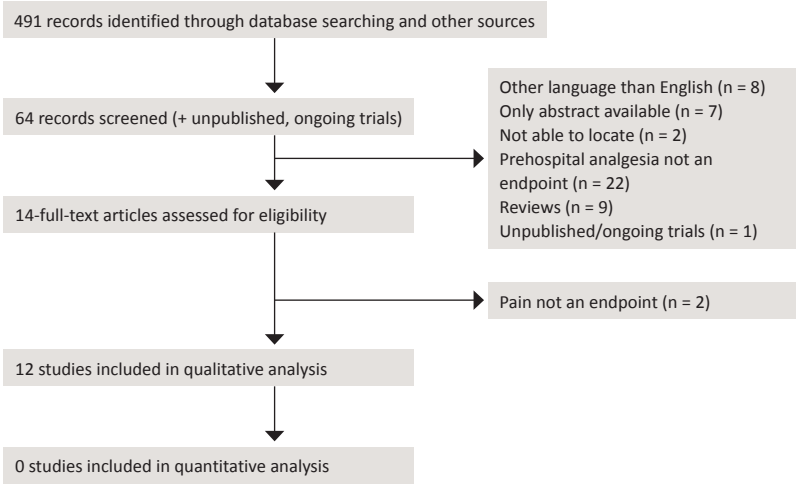
identified. One trial demonstrated a significant reduction in pain scores in 63 of 81 patients 30 min after administration of IN fentanyl for the treatment of post-fracture pain [14]. Another trial investigating pain following acute injury in 1-3-year-old patients demonstrated a significant reduction in pain scores ten and 30 min after administration of IN fentanyl [15]. Finn & Harris investigated pain following acute injury and demonstrated a significantly reduced pain score five and 30 min after administration of IN fentanyl [16]. Likewise, Borland et al demonstrated significantly reduced pain scores following IN administration of fentanyl in treatment of acute pain [17].

One study, a prospective audit, investigating pain after upper-limb injury, demonstrated reduced pain scores from five to 30 min after administration of IN fentanyl [19].

In a recent trial [18] investigating pain following long-bone fractures, Borland et al demonstrated reduced pain scores ten to 30 min after administration of IN fentanyl, with no significant differences between IN fentanyl in a standard concentration of 50 µg/ml and a high concentration of 300 µg/ml. However, the group receiving the 50-µg/ml dose had an increased use of supplemental analgesia. No major side effects were reported in any of the studies.

FIGURE 1

Flow chart of retrieved, excluded and analysed trials.



Intranasal fentanyl in the ambulance

Four studies of the use of IN fentanyl as analgesia in the ambulance were identified. The studies were of various designs and quality (Table 2) with one prospective randomized trial and three retrospective studies.

In a prospective randomized trial, Rickard et al demonstrated no significant differences between IN fentanyl and IV morphine treatment to reduce acute pain [20]. In a large retrospective study, IV morphine was demonstrated to be superior to IN fentanyl in treatment of acute pain [21]. In another retrospective trial, Bendall et al demonstrated no significant differences in initial pain score reduction between IN fentanyl and IV morphine [22]. In a retrospective trial, Johnston et al compared the volatile gas methoxyflurane with IN fentanyl in the treatment of presumed visceral pain, and demonstrated a higher initial pain score reduction with methoxyflurane. However, administration of IN fentanyl resulted in a significantly higher pain score reduction upon arrival at the hospital compared with methoxyflurane [23].

No major side effects were reported in any of the studies.

DISCUSSION

We conducted a systematic review of IN fentanyl in the ED and as a prehospital analgesic. In our systematic search, we located 12 studies for inclusion in our qualitative analysis. Eight trials of IN fentanyl in the ED were located. In two studies, analgesic non-inferiority and superiority were demonstrated when IN fentanyl was compared with IV and IM morphine, respectively [12, 13]. Four non-blinded, non-controlled studies [14-17] and one observational audit [19] all demonstrated significant reductions in pain from baseline values when investigating patients with moderate and severe pain (Table 1). One trial comparing standard concentration IN fentanyl with high concentration IN fentanyl demonstrated analgesic non-inferiority [18].

Four trials of IN fentanyl in the ambulance were identified. One randomized, non-blinded trial [20] and one retrospective study [22] demonstrated no significant differences in pain score between IN fentanyl and

IV morphine. Conversely, one large retrospective study [21] demonstrated that IV morphine was superior to IN fentanyl and, finally, one study demonstrated a reduction in pain when IN fentanyl was compared with methoxyflurane [23].

Our systematic search of trials concerning the use of IN fentanyl in the ED and the prehospital setting demonstrated a clear lack of high-quality trials with only four randomized investigations of which only two were blinded. In order to strengthen the evidence base, we decided that the inclusion criteria should contain no requirements concerning study design and methodological approach. However, to evaluate the possible risk of bias and to investigate the methodological validity, we applied the Cochrane criteria for evaluation of blinding and randomization [10] (Table 2).

As discussed in a recent editorial [24], head-to-head comparisons of analgesics without a placebo group can be difficult to interpret. A comparable outcome with no statistically significant difference between two active drugs can occur if the baseline pain in the two groups is too low to demonstrate an analgesic effect, if an insufficient number of patients has been included in the trial, or if both drugs are equally effective or ineffective [24].

Of the 12 studies included in this review, no trials were placebo-controlled, and seven trials compared IN fentanyl with another analgesic. Of the seven trials, four trials were prospective and three retrospective. One study had no report of baseline pain [12], the remaining 11 studies all reported moderate-to-severe baseline pain (Table 1). IN fentanyl in the ED was investigated by eight of the included studies. Borland et al [13] and Younge et al [12] both demonstrated an analgesic effect of IN fentanyl compared with IV morphine and IM morphine, respectively. However, in the study by Younge et al, no sample size calculation was performed, and no baseline pain was evaluated, wherefore it is difficult to conclude whether IN fentanyl is comparable to IM morphine. Five prospective trials demonstrated some analgesic effect of IN fentanyl in the treatment of acute pain in the ED [14-17, 19]. However, none of the trials were blinded, randomized or controlled.

Four trials investigated the use of IN fentanyl in the ambulance. They demonstrated significant analgesic qualities of IN fentanyl. Rickard et al [20] demonstrated no difference between IN fentanyl and IV morphine. However, because of their non-blinded design and the fact that no placebo group was introduced, no firm conclusions are possible.

Three retrospective studies investigated IN fentanyl versus IV morphine and/or the volatile gas methoxyflurane [21-23]. All three studies demonstrated a significant analgesic effect of IN fentanyl; however, one very large study demonstrated analgesic inferiority of IN fentanyl compared with IV morphine [21]. Middleton et al [21] and Bendall et al [22] both performed large retrospective studies. However, no estimation of the time of pain measurement after administration of IN fentanyl was described. We therefore cannot determine if the T_{max} of IN fentanyl has been achieved. This could potentially result in reduced efficacy evaluation and therefore a lower "true" analgesic effect of IN fentanyl.

Pharmacokinetic studies have demonstrated that a high concentration and a low dose volume of intranasal drugs are important to achieve optimal analgesic effect [1, 3-5]. With fentanyl administration by simple aqueous solutions, drop-by-drop method, nasal sprays and atomizers, there is a risk of dripping from the nose and/or pharyngeal run-off, which results in decreased analgesic efficacy and inconsistent dose-response estimates. Pharmacokinetic studies have demonstrated that in order to avoid pharyngeal run-off, the maximum volume of IN application is 150 millilitres per nostril [1].

In this review, six of the 12 included studies [12, 14-19] investigated the analgesic effect of IN fentanyl at a rather low concentration of 50 µg/ml. Borland et al compared the analgesic effect of IN fentanyl at a concentration of 50 µg/ml versus 300 µg/ml. They demonstrated no significant differences in pain score, however, the "low concentration" group had a higher consumption of supplemental analgesia in the.. All six studies, two studies comparing 50 µg/ml IN fentanyl with IM morphine and high-concentration IN fentanyl, and four non-controlled studies, demonstrated an analgesic effect of 50 µg/ml fentanyl. However, as four of the six studies are non-controlled (Table 2) and current pharmacokinetic studies support use of high concentration IN fentanyl, it remains difficult to assess the non-inferiority of low-concentration (50 µg/ml) compared with high-concentration IN fentanyl.

The mode of intranasal administration and the dose volume are variables that have significant effects on the end-plasma fentanyl concentration. Two types of nasal

TEXT BOX

Intranasal fentanyl is the most extensively investigated intranasal analgesic.

The kinetic and dynamic properties of intranasal fentanyl are desirable for the management of acute pain.

Simple problems such as epistaxis, blocked nose and accidental swallowing may result in suboptimal administration and decreased analgesic effects.

Eight studies investigated intranasal fentanyl in the emergency department and four studies in the prehospital setting.

Due to a rather low scientific quality of studies performed in these settings, it is not currently possible to recommend intranasal fentanyl as routine care.

Emergency ambulance and Emergency Response Unit. The photo was kindly provided by the Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet.

administration were investigated in the included trials: mucosal atomiser and nasal spray (Table 1). None of the included studies used penetration enhancers such as pectin or chitosan [25]. The dose volume in the included trials differs (Table 3). Furthermore, in the studies where dose volume was calculated according to the patient's weight or age, the dose volumes differ between the individual study participants as well. This makes inter- and intra-study comparisons difficult, and as only three studies administered IN fentanyl at dose volumes below 200 µl, there is a risk of decreased analgesic efficacy in these high-volume studies.

Our analysis has certain limitations. We did not include studies not written in English and did not contact authors regarding trial protocols and full trial information. Furthermore, we did not contact authors for the full trial information of the identified abstracts.

Pharmacokinetic studies have demonstrated that IV fentanyl has a lower T_{max}, a higher maximum arterialconcentration (C_{max}), and, as demonstrated in oral surgery studies, a shorter onset time and time to meaningful pain relief [4, 5]. IN fentanyl may therefore be inferior to IV fentanyl when administered under standardized conditions. However, the conditions in the daily clinical practice are not standardized. In order to administer IV fentanyl, an intravenous access is needed, and in patients where intravenous access is difficult to achieve, the time to pain relief with IV fentanyl may be inferior to that of pain relief with IN fentanyl. It is not suggested that IN fentanyl should replace IV fentanyl as an analgesic. Still, we must consider that in patients where IV access is difficult to achieve, IN fentanyl may be a valuable alternative in the acute analgesic treatment.

In conclusion, only a limited number of studies with sufficient scientific quality exist to document the efficacy of IN fentanyl in the ED and in the prehospital setting. Of the 12 studies included in this review, only two studies were randomised and double-blinded, which emphasizes the fact that further well-performed double-blinded randomised controlled trials are urgently needed to validate the use of IN fentanyl in this context.

CORRESPONDENCE: *Morten Sejer Hansen*, Anæstesi- og Operationsklinik 4231, HovedOrtoCentret, Rigshospitalet, 2100 Copenhagen, Denmark.

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