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## **HYDROXYZINE FOR LOWERING PATIENT'S ANXIETY DURING PREHOSPITAL MORPHINE ANALGESIA: A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY.**

Running head: Hydroxyzine associated with morphine for pain relief

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**Conflicts of interest:** none declared

**Authors contributions:** VHC and VB conceived the study, designed the trial, and obtained research funding. CHHC, FB, VHC, JM, FB and VB supervised the conduct of the trial and data collection. CHHC, VHC and VB undertook recruitment of participating centers and patients and managed the data, including quality control. VHC provided statistical advice on study design and analyzed the data; VB chaired the data oversight committee. VB drafted the manuscript, and all authors contributed substantially to its revision. CHHC takes responsibility for the paper as a whole.

## **Abstract**

Study objective: Hydroxyzine is an antihistamine drug used for symptomatic relief of anxiety and tension. We hypothesized that managing the anxiety of patients with severe pain by adding hydroxyzine to a conventional intravenous morphine titration would relieve their pain more effectively.

Methods: This was a randomized, double-blind, controlled group study of prehospital patients with acute pain scored greater than or equal to 6 on a 0-10 verbal numeric rating scale (NRS). Patients' anxiety was measured with the self-reported Face Anxiety Scale (FAS) ranking from 0 to 4. The percentage of patients with pain relief (NRS score  $\leq 3$ ) 15 minutes after the first injection was the primary outcome.

Results: One hundred forty patients were enrolled. Fifty-one percent (95% CI 39% to 63%) of hydroxyzine patients versus 52% (95% CI 40% to 64%) of placebo patients reported a pain numeric rating scale score of 3 or lower at 15 minutes. Ninety-one percent (95% CI 83% to 98%) of patients receiving hydroxyzine reported no more severe anxiety versus 78% (95% CI 68% to 88%) of patients with placebo ( $p > 0.05$ ). Adverse events were minor, with no difference between groups (6% in hydroxyzine patients and 14% in placebo patients).

Conclusion: Addition of hydroxyzine to morphine in the prehospital setting did not reduce pain or anxiety in patients with acute severe pain and therefore is not indicated based on our results.

## **Introduction**

Obtaining high-quality analgesia in prehospital patients with severe pain is an important treatment objective for medical teams. Opioids are commonly used to treat severe pain. Recommended initial analgesia for patients with severe acute pain, defined as a verbal numerical rating scale (NRS) score of 6/10 or higher, in a prehospital setting in France consists of the administration of intravenous morphine by the medical staff of mobile intensive care units [1]. Nevertheless, even when using high dose boluses and aggressive titration protocols, pain relief remains inconsistent for some patients [2,3,4]. An explanation could be that unexpected acute pain in an emergency setting causes anxiety, insecurity, and stress that can diminish perceptions of control over pain and diminish ability to decrease pain [5]. This may interfere with the opioid treatment and raises the question of whether an anxiolytic drug added to the morphine titration could help relieve pain and/or anxiety. Hydroxyzine is used primarily as an antihistamine drug for the treatment of itching, allergies, motion sickness-induced nausea, and insomnia. It is a first-generation antihistamine and is widely used for symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested [6,7,8]. Due to its sedative and anxiolytic action, this drug may then be of interest as an adjunctive to the treatment of acute pain in an emergency setting.

There is no study, to our knowledge, assessing the clinical efficacy of hydroxyzine added to morphine in an emergency setting. This randomized double-blind clinical trial was then designed to determine the efficacy and safety of hydroxyzine in addition to a conventional intravenous morphine titration protocol for adult patients with severe traumatic acute pain. We hypothesized that by adding an anxiolytic as hydroxyzine pain relief would be enhanced.

## **Materials and Methods**

### Study design

The study (ClinicalTrials.gov number NCT01151696) was a prospective, randomized, double-blind, controlled, parallel group study designed to compare two intravenous morphine regimens, one using hydroxyzine as an adjuvant, the other one using morphine and an intravenous placebo for medical prehospital treatment of severe acute pain. Enrollment began in May 2010 and finished when the desired number of patients was reached in August, 2013. The regional ethics committee (CPP Sud Ouest et Outre-Mer II, France, n°2009-780) approved this study, and all patients provided written informed consent. We reported findings of this study in accordance with the Consolidated Standards of Reporting Trials Group (CONSORT, appendix 1).

### Setting

In France, management of out-of-hospital medical emergencies is the responsibility of the Service d'Aide Médicale Urgente (SAMU). Mobile intensive care units are staffed by an attending physician, a nurse, a trained ambulance driver and, sometimes a medical student. All physicians have at least 2 years of practice and are emergency physicians or anesthesiologists. Mobile intensive care units are distributed throughout France, providing a comprehensive coverage of prehospital advanced life-support services. The decision to provide opioid analgesia including titration of subsequent doses of opioid is the responsibility of physicians, according to local titrated intravenous analgesia protocols based mostly on morphine. The prehospital emergency service of the University Hospital of Purpan (Toulouse, France) located in an urban area participated in this study.

### Selection of participants

Patients were eligible for inclusion if they were aged 18 years or older with a severe traumatic acute pain defined by an NRS score of 6 on a scale of 0 (no pain) to 10 (most severe pain) or higher at randomization. Exclusion criteria included the presence of patient-reported history of chronic respiratory, renal, or hepatic insufficiency, known opioid or hydroxyzine allergies, recent treatment with opioids or anxiolytics, incapacity to understand the NRS, hypotension (defined as a systolic blood pressure <90 mm Hg), bradypnea of less than 12/min, oxygen desaturation of less than 90%, seizures or a Glasgow Coma Scale score of less than 14, pregnancy and drug addiction. Patients who had already received an opioid analgesic or an anxiolytic within 6 hours (either by self-administration or by another physician) were also excluded. Investigators enrolled participants once they had provided written informed consent.

#### Intervention

A computer random numbers list was generated, using a restricted randomization scheme with a 1:1 allocation equilibrated by blocks of 4 to ensure roughly equal numbers in each group. Group assignments were sealed in numbered opaque envelopes and opened sequentially by the nurse at the time of patient inclusion. Eligible patients were randomly allocated to receive either intravenous hydroxyzine 1mg/kg (with a maximum of 100mg) or intravenous placebo at the beginning of the morphine titration protocol, and intravenous morphine 0.15 mg/kg then 0.05 mg/kg if necessary, every 5 minutes. The drugs were administered by the physician from syringes of similar appearance prepared by the nurse in the ambulance who was not otherwise involved in the study, thus both physicians and patients were blinded to the drug administered. The investigator / physician completed a case report form on-site. Patients were followed up until hospital admission.

#### Methods of measurement

Before initial treatment (baseline, T0) and at 5, 10, 15 and 30 minutes postbaseline (T5, T10, T15 and T30), the emergency physician asked the patients to rate their pain intensity on a

verbally numeric rating scale (NRS), ranging from “0” (no pain) to “10” (worst imaginable pain). This scale has been validated for assessment of acute pain in the ED [9]. The physicians also recorded oxygen saturation by pulse oximetry, blood pressure, pulse rate, a respiratory rate and asked patients about the presence or absence of nausea, vomiting and pruritus at T0, T5, T10, T15 and T30. They determined the level of sedation by using a modified Ramsay Sedation Scale (0, patient is awake; 1, patient is with intermittent sleeping; 2, patient is sleeping, awakened by verbal stimulation; 3, patient is sleeping, awakened by tactile stimulation; 4, patient is not aroused by stimulation) at these periods [10]. The patients’ anxiety was measured at T0, T15 and T30 using the Face Anxiety Scale (FAS), a self-report measure of state of anxiety including 5 faces with different levels of anxiety. Responses were scored 0 (no anxiety) to 4 (extreme anxiety) [11].

Throughout the study, a clinical research assistant collected the case report forms, checked out the accuracy and the consistency of the data, and entered them into Microsoft Excel (version 2010; Microsoft, Redmond, WA). The data were then verified by another research assistant to ensure no errors were entered in the database.

#### Outcome measures

The protocol-defined primary outcome measure was the percentage of patients with pain relief (with a NRS score of 3/10 or lower) 15 minutes after the first injection. As secondary outcomes were assessed the percentage of patients (1) with pain relief at T5, T10 and T30, (2) with no more severe anxiety at T15 and T30. No more severe anxiety was defined as a score 0, 1 or 2 and a patient was considered still severely anxious with a score of 3 or 4. The percentage of patients with no more pain and no more severe anxiety at T15 (combined criteria) were evaluated as well as the proportion of adverse events, such as nausea, vomiting, dizziness, agitation or pruritus. Adverse events were classified as minor, moderate and severe. Severe events included hospitalization, subject dropout, life threatening situation and disability or

permanent damage. Minor or moderate events are based on clinical appreciation. Finally, an overall patient and investigator satisfaction evaluation on analgesia was asked, based on a score rated from 1 (highly dissatisfied), 2 (dissatisfied), 3 (satisfied) and 4 (highly satisfied). Then, the score was recategorized dichotomously into 0 (dissatisfied) and 1 (satisfied).

## Data Analysis

The sample size was calculated on the basis of preliminary data obtained in our center. In a 5-month prospective randomized study conducted on 106 patients, we found that 48% of the patients receiving morphine experienced pain relief at 15 minutes [2]. In another 3-month pilot study of 30 patients, we found that adding hydroxyzine to the morphine titration improved the level of analgesia at 15 minutes up to 75%. Taking these data into account, the clinically important difference in pain relief used for the calculation was 27% (e.g. 75%-48%) that is above the minimal clinically important difference of changes in pain intensity found in the literature (reduction of 15.0% in the NRS) [12].

The approach for our study design was a superiority design, so a sample size of 126 was therefore calculated with a 2-sided test with a 0.05 type I error and a power of 90%. We decided nevertheless to include 140 patients for those lost to follow-up.

Descriptive statistics are reported as means with SDs, medians with interquartile ranges (IQR), and proportions with exact binomial 95% confidence intervals (CIs). Proportions were compared using Chi2 tests or Fisher's exact test when appropriate. All participants who underwent random assignment were analyzed according to group assignment in an intention-to-treat fashion. For purposes of analysis, physician and patient satisfaction scores were each recategorized dichotomously. Stata (Statistical Software: Release 12.0. Stata Corporation, College Station, Texas, U.S.A) was used for data analysis.



## Results

### Characteristics of Study Subjects

Between June 2010 and August 2013, 172 potential cases were screened for eligibility. Figure 1 shows the trial profile; 140 patients were randomly assigned to treatment, the main reasons for non inclusion were inclusion criteria not met ( $n = 19$ ) and refusal to participate ( $n = 11$ ).

The assessment at 15 minutes was missing for 2 patients, one withdrew his consent just after inclusion time and the other one interrupted his participation 10 minutes after inclusion time after having received 16 mg morphine.

No significant differences between treatment groups were observed in any of the patient demographics or clinical characteristics including age, sex, height, weight, primary diagnoses (Table 1), or baseline scores of pain or anxiety. There were no differences between groups with regards to systolic blood pressure, heart rate, or oxygen saturation at T0. We found differences in baseline characteristics between the groups concerning diastolic blood pressure ( $p=0.03$ ) and respiratory rate ( $p=0.004$ ), none of them was clinically meaningful.

Fifteen minutes after the injection, 35 out of 69 patients (51%; 95% CI 39% to 63%) in the hydroxyzine group had a pain numeric rating scale score of 3 or lower versus 36 out of 69 (52%; 95% CI 40% to 64%, one missing data) of those in the placebo group ( $p = 0.5$ ; OR 0.94 %; 95% CI 0.46 to 1.94). We found that 58 of 64 patients (91%; 95% CI 83% to 98%, 5 missing data) of the patients in the hydroxyzine group had no more severe anxiety versus 50 out of 64 (78%; 95% CI 68% to 88%, 6 missing data) of those in the placebo group (OR 2.71; 95%CI (0.94-7.7,  $p>0.05$ ). At 5, 10 and 30 minutes, there was no difference in pain relief between the 2 groups (Table 2). Results show a greater numeric decrease of anxious patients in the hydroxyzine group (64% to 9%) than in the Placebo group (51% to 22%) between T0 and 15 minutes.

There was no difference in the 15-minute combined criteria (analgesia and no more severe anxiety) among the groups (Table 2). The median morphine dose injected until 15 minutes was 0.2 mg/kg (IQR 0.15-0.25) in the hydroxyzine group and 0.21 mg/kg (IQR 0.16-0.25) in the placebo group.

Concerning patient satisfaction with analgesia, 52 of 55 patients (95%) in the study group and 49/53 (92%) in the placebo group described analgesia as excellent or good. Moreover, 50/57 (88%) of physicians described analgesia as excellent or good in the hydroxyzine group versus 53/58 (91%) in the Placebo group.

All of the reported adverse effects were mild to moderate in severity. There were no severe adverse effects, hospitalizations, or subject dropout due to adverse events. We noted a higher but non-significant rate of adverse events in the placebo group (10 (14%) versus 4 (6%)) for the hydroxyzine group),  $p=0.07$  (Table 2). Patients in the placebo group did experience more than three times the incidence of nausea (7 versus 2 for the hydroxyzine group), without a significant difference. The other adverse events were dizziness (2 in the placebo group versus 1 in the hydroxyzine group), one moderate decrease in SpO<sub>2</sub> in the hydroxyzine group with no need of oxygen administration and one agitation in the placebo group. It is of note that one patient died of cardiac arrest one day after his hospital admission, but his death was not deemed as attributable to the study and the study drugs administered. In no cases were the drug regimens stopped because of bothersome adverse effects, and none of these adverse events required naloxone to antagonize opioid effects.

## **Discussion**

This is the first study, to our knowledge, to assess the use of a non benzodiazepine ~~anxiolytic~~ (hydroxyzine) as an adjuvant to pain and anxiety treatment in the prehospital setting. It refutes our hypotheses that adding hydroxyzine to morphine significantly reduces pain and anxiety in

patients with severe pain. In addition, we found no difference in the incidence of adverse effects, and no severe complications appeared, although large doses of morphine were used. Moreover, final patient and physician satisfaction was high for both groups.

Despite our findings, other studies suggest that treatment of anxiety in patients with severe pain helps reduce pain and anxiety. Emergency situations are significant sources of anxiety for patients [13]. Most times, patients experience long waiting time, uncertainty about the diagnosis, possible additional tests or exams or hospitalization. Kapoor et al. studied in 2015 the association between pain intensity in ED and the anxiety state, using an anxiety evaluation self-questionnaire, the STAI Y-A [12]. This test assesses the emotional reactions involving tension, apprehension, nervousness and anxiety at a given moment, and is an indicator of transient changes in anxiety caused by therapeutic or aversive situations. They showed that pain intensity was significantly and positively associated with the anxiety state. Some other studies have shown such relationship, usually demonstrating that patients with untreated anxiety report higher pain scores and lower satisfaction during the ED visit despite similar doses of opioid pain medications [14,15]. Wells et al described in 2018 that ED patients experiencing pain and receiving a treatment for their anxiety reported greater improvement in their pain scores [16]. Other studies, most often dealing with post-operative pain or analgesic management in the emergency department, have sought a relationship between pain and anxiety. and all have concluded that there is a relationship between these two entities [17,18]. Thus, treatment of anxiety using non pharmacologic methods, such as relaxation [19], music therapy [20], acupuncture [21], etc. have proven their utility in achieving effective analgesia.

## **Limitations**

Inferences that can be drawn from these data are limited in several respects. The study was conducted in a prehospital physician staffed setting in trauma patients, so the results may not be generalizable to other emergency or patient settings. The nurses who prepared the medication were unblinded, but we believe that this could not have affected enrollment, because patients and physicians were blinded to the randomization results and nurses were no longer involved in the study to avoid any adverse influence on enrollment. Finally, it is always possible that factors affecting analgesia may be more or less prevalent in treatment groups despite randomization. Although we relied on randomization to balance baseline differences that are measured and unmeasured and thus reduce confounders known and unknown, groups were slightly different concerning initial anxiety rates (64% in the hydroxyzine group versus 51% in the placebo group), showing a real significant difference only for the subgroup of anxious patients. We do not believe that this would alter our results, as screening anxious patients when beginning analgesic treatment and treating specifically those who express high anxiety scores may be the most efficient current strategy.

## **Conclusions**

Why hydroxyzine did not significantly reduce pain and anxiety in our study is unclear. It is possible that our study have been underpowered to detect a significant difference in anxiety. It is also possible that a different agent, such as benzodiazepine, would have been more effective. In conclusion, while identification and treatment of anxiety in patients with severe pain is important, addition of hydroxyzine to morphine in the prehospital setting did not reduce pain or anxiety in patients with severe pain.

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## Figure legends

Figure 1. Flow diagram of patients

Table 1. Characteristics of the patients at baseline

Table 2. Analgesia, anxiety and safety outcomes among study participants



Figure 1. Flow diagram of patients

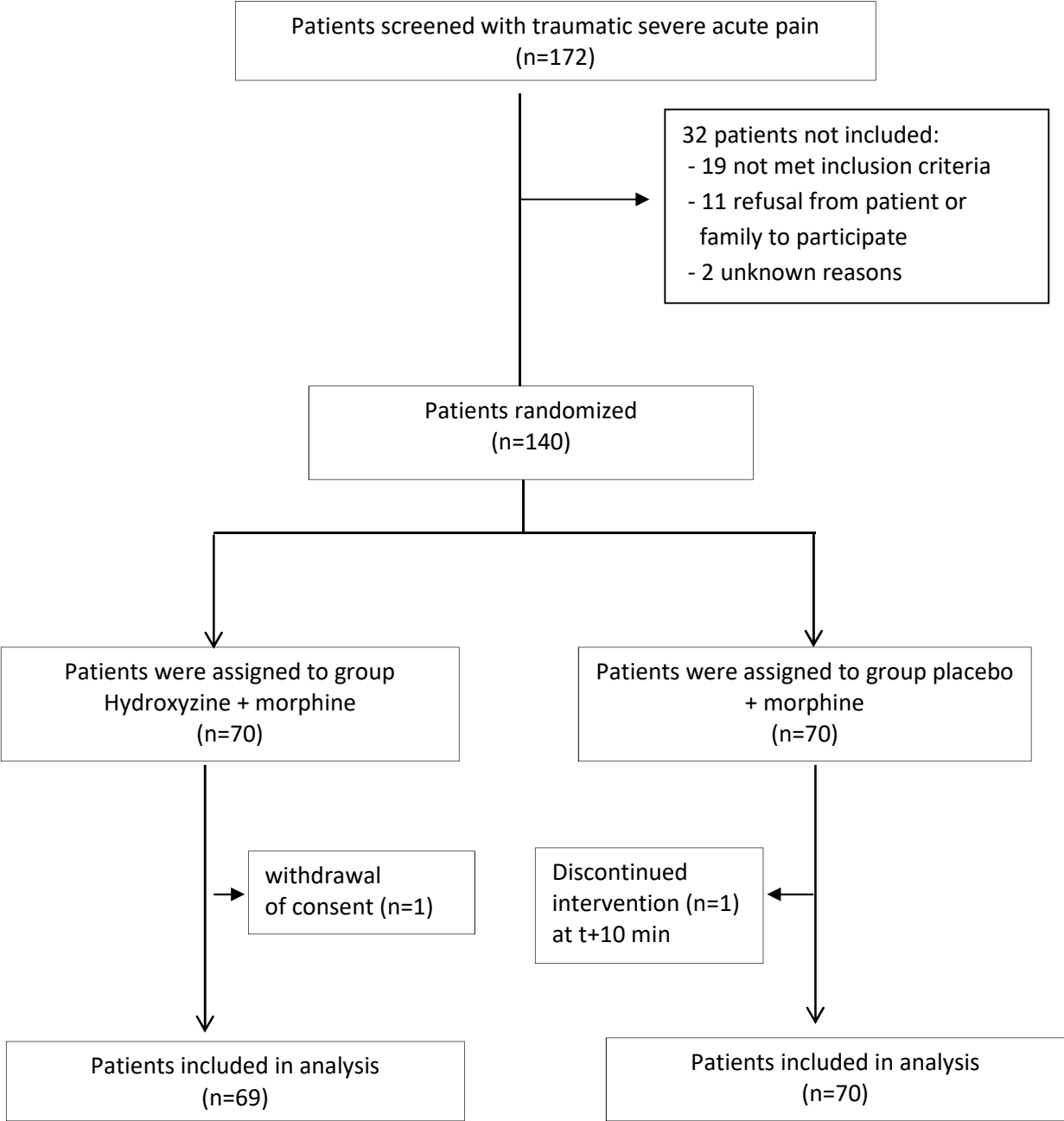


Table 1. Characteristics of the patients at baseline

	Placebo + morphine (n=70)	Hydroxyzine + morphine (n=69)
<b>Age, y</b>	54 (29-65)	46 (29-63)
Gender No. (%)		
Males	38 (54)	44 (64)
Weight, Kg	70 (65-80)	72 (65-87)
NRS <sup>§</sup> pain	8 (7-10)	8 (7-10)
Face anxiety scale*	3 (2-3)	3 (2-4)
Patient with severe anxiety <sup>±</sup> , No (%)	36 (51)	44 (64)
<b>Etiology of pain No. (%)</b>		
Lower limb	38 (57)	37 (54)
Upper limb	20 (30)	26 (38)
Chest injury	3 (4)	1 (1)
Spinal injury	5 (7)	4 (6)
Cephalic injury	1 (1)	
<b>Physiology</b>		
Systolic blood pressure (mmHg)	135 (126-147)	140 (122-160)
Diastolic blood pressure (mmHg)	80 (76-88)	83 (79-97)
Heart rate (bpm)	82 (70-95)	87 (75-95)
Respiratory rate (breaths/min)	16 (15-20)	20 (16-24)
Spo2 (%)	99 (98-100)	99 (98-100)

Quantitatives values are median (IQR, interquartile range) unless otherwise stated.

<sup>§</sup> Numerical rating scale from 0 (no pain) to 10 (worst imaginable pain)

\*Face anxiety scale (FAS) is scored from 0 (no anxiety) to 4 (extreme anxiety)

<sup>±</sup> A patient was defined severely anxious with a FAS score of 3 or 4.

There were no significant differences in baseline characteristics between the groups with the exception of diastolic blood pressure (p=0.03) and respiratory rate (p=0.004).

Table 2. Analgesia, anxiety and safety outcomes among study participants

	Placebo + morphine (n=70)	Hydroxyzine + morphine (n=69)	OR (95%CI)	P-value *
	No/. total No. (%)			
<b>Primary outcome</b>				
Analgesia at T15	36/69 (52)	35/69 (51)	0.94 (0.46-1.94)	.5
<b>Secondary criteria</b>				
Analgesia at T5	11/62 (18)	11/61 (18)	1.02 (0.36-2.86)	.57
Analgesia at T10	24/63 (38)	23/64 (36)	0.91 (0.42-1.99)	.47
Analgesia at T30	31/46 (67)	28/48 (58)	0.68 (0.27-1.7)	.24
<b>No more severe anxiety at T15</b>	50/64 (78)	58/64 (91)	2.71 (0.94-7.7)	.05
	38/45 (84)	44/46 (96)	4.05 (0.7-41.6)	.07
No more severe anxiety at T30	28/70 (39)	31/69 (45)	1.19 (0.57-2.48)	.31
Combined criteria	10/70 (14)	4/69 (6)	0.37 (0.08-1.37)	.08
Adverse events	7/10 (70)	2/4 (50)		
Nausea	2/10 (20)	1/4 (25)		
dizziness	1/10 (10)	0/4		
agitation	0/10	1/4 (25)		
desaturation				
	Median (IQR)			
Total morphine dose at T15 (mg/kg)	0.21 (0.16-0.25)	0.20 (0.15-0.25)		.57
Total morphine dose at T30 (mg/kg)	0.25 (0.17-0.27)	0.22 (0.18-0.27)		.83

\* Chi 2 test

Analgesia, proportion of subjects experiencing NRS pain score  $\leq 3$

No more severe anxiety, proportion of subjects with a FAS score = 0, 1 or 2.

Combined criteria, Analgesia and no more severe anxiety at T15