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Title: Acute and chronic pain after cardiac surgery

Issue Date: 2014-09-02



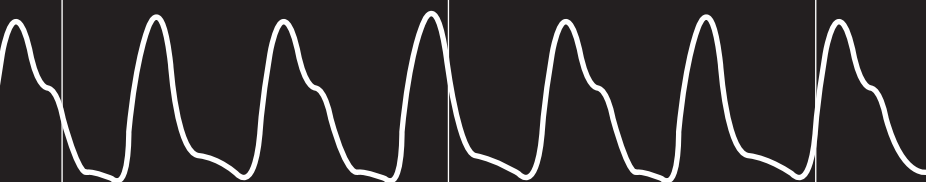
ECG

80



SpO₂

98%



ART

167
69



Pain?

EFFICACY OF AN INTRAVENOUS BOLUS OF MORPHINE 2.5 VERSUS MORPHINE 7.5 MG FOR PROCEDURAL PAIN RELIEF IN POSTOPERATIVE CARDIOTHORACIC PATIENTS IN THE INTENSIVE CARE UNIT: A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL

CH. 4 section II



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Eur J Anaesthesiol. 2010 Oct;27(10):900-5

Abstract

Background and objectives: As pain in the intensive care unit (ICU) is still common despite important progress in pain management, we studied the efficacy of an intravenous bolus of morphine 2.5 versus 7.5 mg for procedural pain relief in patients after cardiothoracic surgery in the ICU.

Methods: In a prospective double-blind randomised study, 117 ICU-patients after cardiothoracic surgery were included. All patients were treated according to a pain titration protocol for pain at rest, consisting of continuous morphine-infusions and paracetamol, which is applied during the entire ICU stay. On the first postoperative day, patients were randomised to intravenous morphine 2.5 (n=59) or 7.5 mg (n=58) at thirty minutes before a painful intervention (turning of the patient and/ or chest drain removal). Pain scores using the numeric rating scale (NRS, range 0-10) were rated at rest (baseline), and around the painful procedure.

Results: At rest (baseline), overall incidence of unacceptable pain was low (NRS $\geq$ 4; 14% vs. 17%, $P=0.81$) for patients allocated to morphine 2.5 mg and 7.5 mg respectively. For procedural related pain, there was no difference in incidence of unacceptable pain (NRS $\geq$ 4; 28% vs. 22%, $P=0.53$) and mean pain scores (2.6 [95%CI 2.0-3.2] vs. 2.7 [95%CI 2.0-3.4]) between patients receiving morphine 2.5 and 7.5 mg, respectively.

Conclusions: In intensive care patients after cardiothoracic surgery with low pain levels for pain at rest, there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

Introduction

Despite important clinical progress in pain management [1], patients after cardiothoracic surgery in the intensive care unit (ICU) may suffer from postoperative pain [2-3]. Procedural related pain is the most common form of health care induced pain [4], of which turning of the patient and chest drain removal have been identified as the most painful procedures [5-6]. More specifically, patients recall repeated painful procedures as strong negative memories of the time in intensive care unit [7]. Additionally, it has been demonstrated that postoperative pain is a predictor for the development of chronic thoracic pain [8]. When receiving adequate pain relief, ICU patients are reported to be more comfortable, thereby also improving patients' outcome like mortality or morbidity [9].

For pain at rest, recent studies [2,10-11] showed that a pain training programme, in which pain scores were systematically recorded by trained personnel, results in a successful reduction in the occurrence of unacceptable pain at rest. In the study conducted in our ICU [11], 46% of the patients treated after the introduction of the pain training programme, experienced at least one unacceptable pain event at rest during their stay. In order to reduce this incidence, a pain titration protocol for pain management at rest is implemented in our ICU, because individualized titration of analgesia is associated with shorter ICU- and hospital length of stay a lower mortality [12].

Apart from pain at rest, ICU patients may suffer from routine health care painful procedures. However, according to available evidence, procedural pain is difficult to treat, in which one part of the patients will experience unacceptable pain despite treatment [13-15]. No studies are available in which a bolus of analgesics is studied for procedural pain relief in ICU patients who are already treated with individualized titration of analgesia for pain at rest. Therefore, we designed a randomized controlled study to compare the efficacy of a bolus of intravenous morphine 2.5 versus 7.5 mg for procedural pain relief in postoperative patients after cardiothoracic surgery in the ICU, who were already treated according to a pain titration protocol for pain at rest.

Materials & Methods

Design

A prospective, double-blind, randomised clinical trial was performed in a 30-bed surgical/medical intensive care unit (ICU) in a teaching hospital, Nieuwegein, The Netherlands. The study was approved by the local Ethics Committee of the St. Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the patients before the cardiothoracic surgical procedure. The study was registered at ClinicalTrials.gov (identifier NCT00558090).

Patients

During a 10-month period, patients admitted to the ICU after cardiothoracic surgery though sternotomy, between 18-85 years old and weighting between 45-140 kg were included. Exclusion criteria were planned postoperative admission to the postoperative anaesthesia care unit (PACU) instead of ICU (depending on their co-

morbidities), pregnancy or breast-feeding, a language barrier, coma or brain death, patients with a known morphine or paracetamol allergy and patients who refused informed consent. Participant flow is summarized in the CONSORT diagram (Figure 1). Of 528 patients who were scheduled for cardiothoracic surgery and assessed for eligibility, 393 were excluded and 135 patients were enrolled in the study. The 42 patients who were excluded because they were not present on the ward during inclusion rounds due to medical examination, did not differ from included study patients in terms of demographic characteristics, i.e. mean age ($68 \text{ years} \pm 15$ vs. $69 \text{ years} \pm 11$, $P=0.51$), mean BMI ($26 \text{ kg/m}^2 \pm 3$ vs. $27 \text{ kg/m}^2 \pm 4$, $P=0.14$), and mean baseline pain scores (NRS 1.4 ± 1.5 vs. 1.5 ± 1.7 , $P=0.93$) or incidence of unacceptable pain scores at baseline (NRS ≥ 4 ; 10% vs. 13%, $P=0.78$).

Of the 135 patients enrolled in the study, 16 patients were excluded before randomisation of the study medication (Figure 1). Random allocation resulted in 61 patients assigned to 2.5 mg morphine and 58 patients assigned to the 7.5 mg morphine group. In the patients receiving 2.5 mg morphine, one patient was excluded from analysis, because the pain score during the painful procedure was not recorded. One patient was excluded because the intervention was not executed according study protocol.

Intra-operative anaesthetic technique during cardiothoracic surgery

In all patients, midazolam or diazepam, fentanyl and propofol was used for induction of anaesthesia. All patients were paralyzed with pancuronium. Anaesthesia was maintained with propofol, sevoflurane, nitrous oxide and either fentanyl or remifentanyl as preferred by the attending anaesthesiologist.

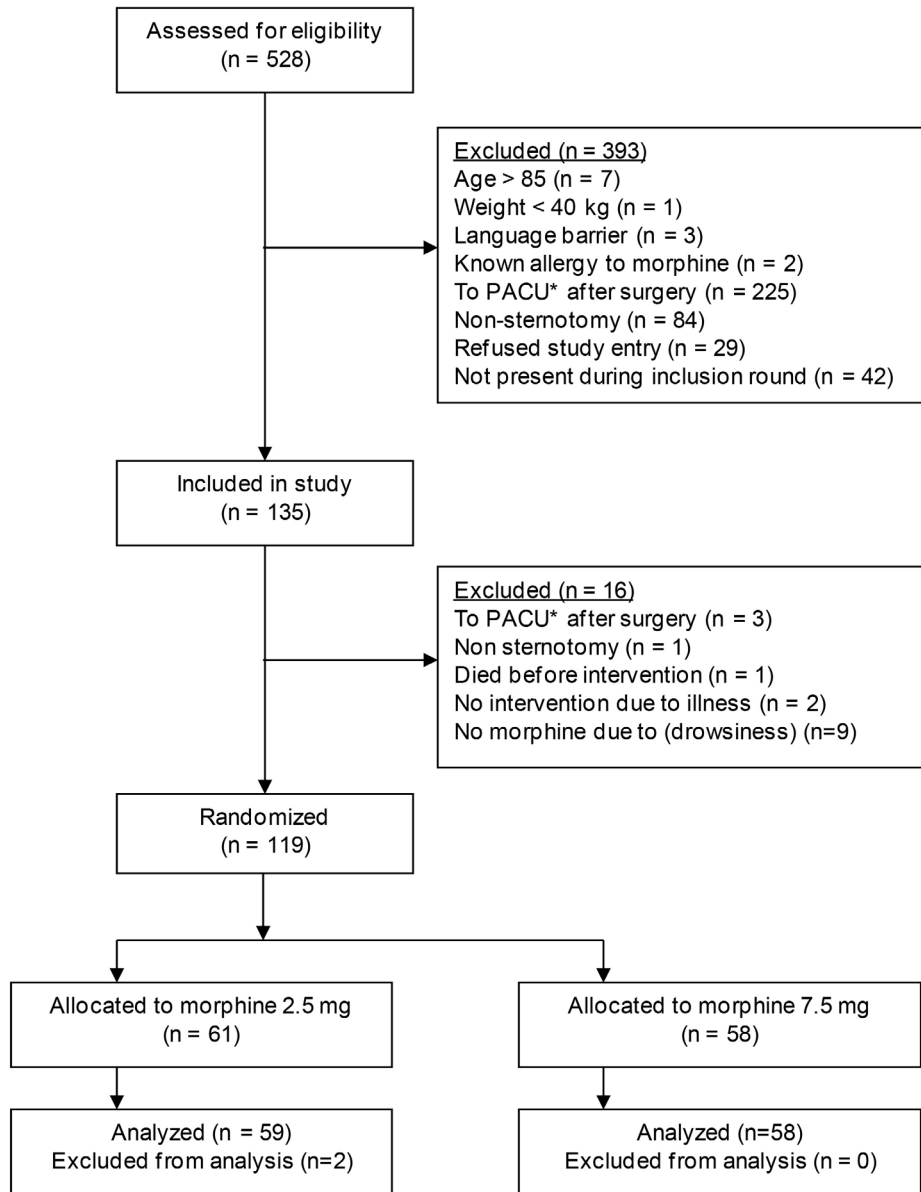
Pain measurements instruments

The NRS was scored by the patient which is considered the gold standard for pain measurement [16]. The NRS was explained to participating patients before cardiothoracic surgery. The NRS is based on a scale from 0 to 10; 0 represents no pain, and 10 represents worst possible pain [17-18]. The NRS has a maximal acceptable pain score of 3 [19]. Severe pain was defined as a NRS ≥ 7 [20]. The minimum clinically significant difference in pain reduction has been determined to be 1.3 to 1.5 [21-22]. In case the patient was not able to report his or her pain, the NRS was scored by the nurse, which has been proven to be a reliable measure [23]. There was no difference between mean NRS scores by the patient and mean NRS scored by the nurse before administration of the study dose morphine (1.7 [95%CI $1.3-2.0$] vs. 1.3 [95%CI $0.7-1.9$]; $P=0.38$) and during intervention (2.7 [95%CI $2.2-3.2$] vs. 2.3 [95%CI $1.5-3.0$]).

Standard pain titration protocol for treatment of pain at rest

For basic pain relief, a standard pain titration protocol (Figure 2), consisting of intravenous morphine infusions and intermittent paracetamol, was used in all patients, which is current practice in this ICU since 2007. When patients had an NRS score of ≥ 4 , the attending nurse together with the responsible physician administered additional analgesic medication.

Figure 1: CONSORT diagram



* PACU = Post Anesthesia Care Unit

Study procedures

According a standard pain titration protocol for pain at rest, patients were treated with continuous morphine infusions. The painful intervention took place during routine healthcare procedures on the first postoperative day after cardiothoracic surgery (day 1), between 7.30 a.m. and 9.30 a.m.. Patients received either morphine 2.5 or 7.5 mg intravenously, 30 minutes prior to an unavoidable painful routine intervention, i.e. turning of the patient and/ or chest drain removal, which were both described as painful by patients [5,24]. Pain levels using the NRS were assessed at rest (baseline, before administration of a bolus morphine 2.5 or 7.5 mg), and 5 minutes before, during and 5 minutes after the painful intervention. If necessary, rescue medication (fentanyl) could be administered.

Sample size calculation

With an incidence of unacceptable pain ($\text{NRS} \geq 4$) of 60% [13] during a painful intervention, the sample size needed for a 25% reduction in incidence of unacceptable pain, is 120 patients. The sample size was calculated with a power of 0.80 and an alpha of 0.05, two sided. Turning of the patient and drain removal have been identified as the most painful routine procedures performed for adults [5-6], in which pain intensity between chest drain removal and turning of the patient was comparable ($\text{NRS } 6.5 \pm 3.9$ vs. $\text{NRS } 4.1 \pm 3.4$) [6]. In our study, there was no difference in pain intensity between turning of the patient and chest drain removal as well ($\text{NRS } 2.2 \pm 2.0$ vs. 3.1 ± 2.7 respectively; $P=0.07$).

Study medication

Morphine 2.5 and 7.5 mg syringes were prepared using morphine HCl 10 mg = 1 ml solution for injection (Pharmachemie, Haarlem, The Netherlands), which was diluted with sodium chloride 0.9% for a final concentration of morphine 2.5 mg = 10 ml and morphine 7.5 mg = 10 ml respectively. The preparation, packaging and labelling was performed by the Department of Clinical Pharmacy. Syringes were blinded for patients, nurses, physicians and researchers.

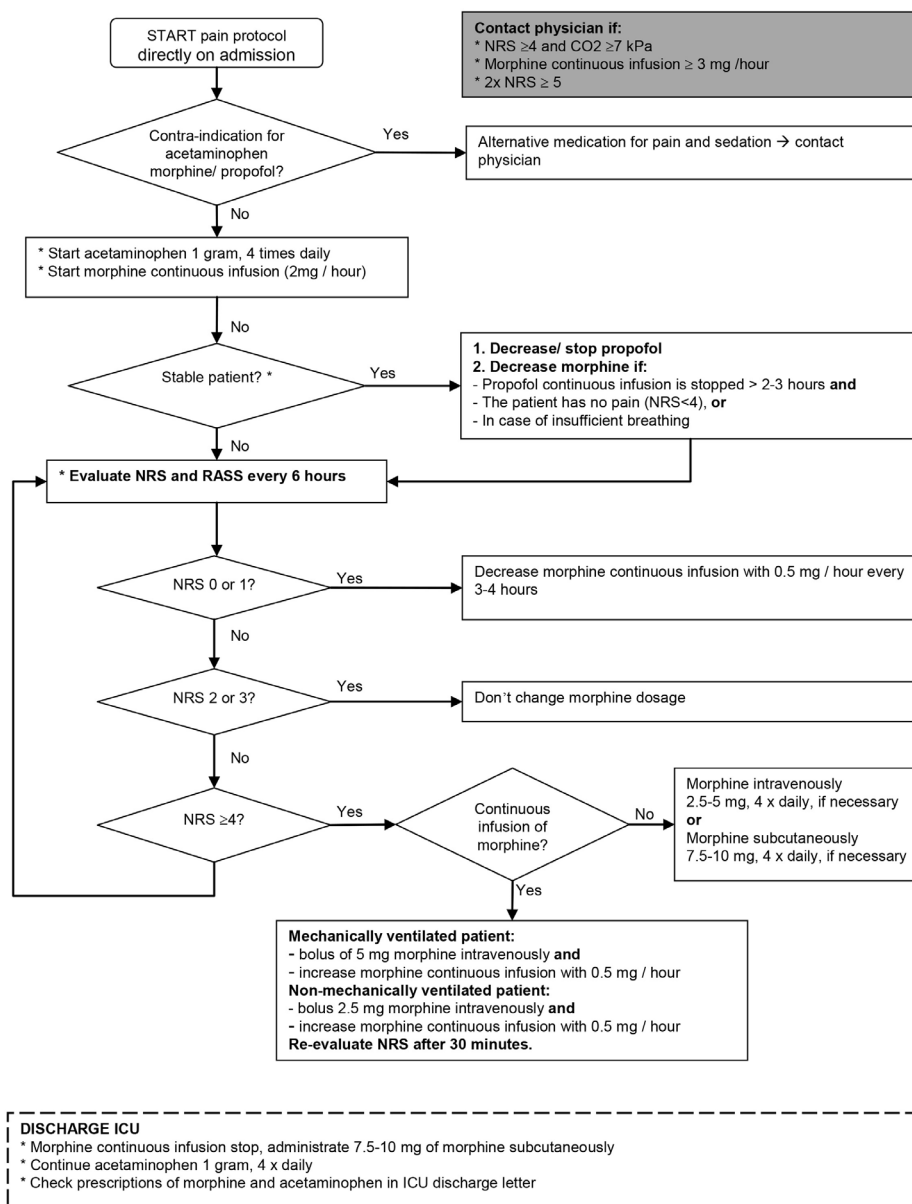
Randomization to morphine 2.5 or 7.5 mg before the painful Intervention

Randomization to one of the two groups was performed using a random allocation schedule generated in blocks of 6 using SPSS. Randomization was performed in blocks of 6 patients to ensure that the morphine 2.5 mg group and 7.5 mg group would be of approximately equally size through the course of the study. The studied dose of 7.5 mg was chosen because it corresponds - in combination with the baseline morphine dosage according to the pain titration protocol - to the morphine dosage of 0.15 mg/kg, which was shown to be effective for pain relief in patients with severe pain [20]. The studied dose of 2.5 mg results from our hypothesis that a pain titration pain protocol combined with a low dose or placebo is sufficient to prevent or treat procedural pain.

Endpoints

Primary endpoint of the study was the percentage of patients with an unacceptable pain score ($\text{NRS} \geq 4$) at baseline and during painful intervention, in both the group receiving morphine 2.5 mg or 7.5 mg. Secondary endpoints were mean NRS scores

Figure 2: Pain titration protocol for pain at rest



* Hemodynamically stable, acceptable leakage through thoracic drains, adequate time after muscle relaxation, adequate core temperature

during intervention, extreme pain ($\text{NRS} \geq 7$) during painful intervention, and clinically relevant decrease or increase in the NRS during intervention compared with the NRS before intervention.

Data-analysis

The SPSS statistical package (version 15.0.1 for Windows; SPSS, Chicago, IL) was used for the statistical analyses. Analysis was conducted in patients allocated to receive morphine 2.5 mg and 7.5 mg, although at baseline (at rest), patients still had to receive the study medication. Descriptive statistics are reported as means with SDs, medians with ranges, and proportions. Means were compared using a t-test for normally distributed data or the non-parametric Mann Whitney two-sample rank sum test for data not fitting the assumptions of parametric testing. Proportions were compared by using chi-square tests or Fisher's exact test when appropriate. A P-value of less than 0.05 was considered statistically significant.

Results

Baseline patient characteristics

Baseline demographic and clinical characteristics of patients are described in Table 1. Patients allocated to 7.5 mg morphine were significantly older ($72 \text{ years} \pm 9$ vs. $66 \text{ years} \pm 12$, $P < 0.002$), had a higher median euroSCORE (8 [range 0-13] vs. 6 [range 2-12], $P = 0.03$), and were less often exposed to the combination of turning and drain removal (22 patients vs. 36 patients, $P = 0.03$).

NRS scores at baseline (before administration of a bolus morphine 2.5 or 7.5 mg)

At rest (baseline), overall incidence of unacceptable pain ($\text{NRS} \geq 4$) was low (16%), and comparable between patients planned for randomization to morphine 2.5 mg and 7.5 mg (14% vs. 17%, $P = 0.81$) (Table 2, Figure 3). Mean baseline NRS scores at rest were not different between patients receiving 2.5 mg and 7.5 mg morphine (1.5 [95%CI 1.2-2.0] vs. 1.7 [95%CI 1.1-2.2]; $P = 0.62$). Patients planned for randomization to morphine 7.5 mg received significantly less morphine ($13.1 \pm 5.9 \text{ mg}$ vs. $15.9 \pm 5.5 \text{ mg}$, $P = 0.03$) compared to the patients planned for randomization to morphine 2.5 mg.

Pain scores before, during and after the painful intervention in patients randomized to receive morphine 2.5 mg versus 7.5 mg

During intervention, overall incidence of unacceptable pain ($\text{NRS} \geq 4$) was low (25%), and comparable between patients allocated to morphine 2.5 and 7.5 mg (28% and 22% respectively) (Table 3, Figure 3). In both the 2.5 morphine and 7.5 morphine groups, mean NRS scores were low (2.6 [95%CI 2.0-3.2] vs. 2.7 [95%CI 2.0-3.4]). 8% and 14% of the patients experienced severe pain ($\text{NRS} \geq 7$) during the intervention in the morphine 2.5 and 7.5 mg group, respectively. There were no significant differences in mean NRS scores 5 minutes before, during and 5 minutes after the painful intervention between patients receiving morphine 2.5 mg and patients receiving morphine 7.5 mg (Table 3, Figure 3).

No difference was found between the groups morphine 2.5 and 7.5 mg in clinically relevant ($\Delta\text{NRS} \geq 1.3$) decrease (0% vs. 3%; $P = 0.24$) or increase (42% vs. 38% $P = 0.71$) in NRS scores. There was also no difference in mean change in NRS scores between both groups (1.5 [95%CI 1.1-1.9] vs. 1.4 [95%CI 0.1-2.6] respectively, $P = 0.64$) (Table 4).

Table 1: Baseline characteristics of patients receiving morphine according to the pain titration protocol for pain at rest and a bolus of morphine 2.5 or 7.5 mg thirty minutes before a painful intervention.

	Pain titration protocol + Morphine 2.5 mg	Pain titration protocol + Morphine 7.5 mg	P
Male gender, n (%)	46 (78%)	41 (71%)	0.40
Age (years)	66 [63-69]	72 [70-74]	0.002
Body Mass Index (kg/m ²)	27 [26-28]	27 [26-29]	0.68
History of sternotomy, n (%)	5 (8%)	10 (17)	0.17
History of Diabetes Mellitus, n (%)	10 (17%)	9 (16%)	1.00
History of pain ^a , n (%)	11 (18%)	16 (28%)	0.28
Preoperative Pain score NRS ≥ 4 n (%)	3 (5%)	9 (16%)	0.12
Preoperative chronic use, n (%)			
Benzodiazepines [#]	7 (12.3%)	10 (18%)	0.30
Analgesics ^{b#}	7 (10.3%)	12 (21%)	0.22
Median euroSCORE (range)	6 (2-12)	8 (0-13)	0.03
Intraoperative dose fentanyl			
Total dose (mg)	1.7 [1.5-1.9]	1.6 [1.5-1.7]	0.35
Dose (mcg/kg)	21.1 [19.0-23.2]	20.0 [18.6-21.4]	0.45
Intraoperative dose remifentanyl			
Total dose (mg)	1.1 [0.7-1.4]	1.2 [0.9-1.5]	0.49
Dose (mcg/kg)	13.2 [9.1-17.3]	15.2 [11.6-18.9]	0.46
Surgery in the morning/ afternoon	44/15	34/24	0.08
Median RASS score before intervention (range)	0 (-4-2)	0 (-5-1)	0.41
Intervention			
Turning/ Turning & Drain removal, n	23/36	35/23	0.03
Mechanical ventilation, n (%)	9 (15%)	11 (19%)	0.63
NRS scored by patient / nurse, n	48/11	49/9	0.81
Duration between bolus morphine 2.5/7.5 mg and procedural intervention (min)	32 [28-35]	30 [28-32]	0.42

Data are mean [95%CI], median (range), number (percentage) or number/number. a Includes chronic back pain, rheumatoid arthritis, polyneuropathy, Herniated Nucleus Pulposus (HNP). b Includes paracetamol, NSAID's and opioids. euroSCORE = European System for Cardiac Operative Risk Evaluation score [25]; RASS = Richmond Agitation and Sedation Scale [32]; NRS = numeric rating scale

Table 2: Baseline NRS scores at rest and baseline morphine consumption in patients planned for randomization to morphine 2.5 mg (n=59) vs. 7.5 mg (n=58)

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Baseline (at rest)			
NRS ≥ 4, n (%)	8 (14%)	10 (17%)	0.81
NRS ≥ 7, n (%)	0 (10%)	3 (5%)	0.12
Mean NRS [95% CI]	1.5 [1.2-2.0]	1.7 [1.1-2.2]	0.62
Median NRS [IQR]	1 [0-3]	1 [0-3]	0.95
Baseline cumulative dose morphine on day of intervention (mg)	15.9 ± 5.5	13.1 ± 5.9	0.03
Baseline cumulative dose morphine on day of intervention (mg/kg)	0.19 ± 0.08	0.15 ± 0.08	0.03
Dose bolus morphine 2.5 / 7.5 mg (mg/kg)	0.03 ± 0.005	0.09 ± 0.016	<0.001

Data are expressed as number (percentage), mean (95%CI) or median (interquartile range [IQR])
NRS = numeric rating scale

Figure 3: Mean NRS scores (95%CI) and the percentage of patients with unacceptable pain (NRS≥4) at rest (baseline) and before, during and after intervention in patients randomised to receive 2.5 mg (n=59) or 7.5 mg morphine (n=58).

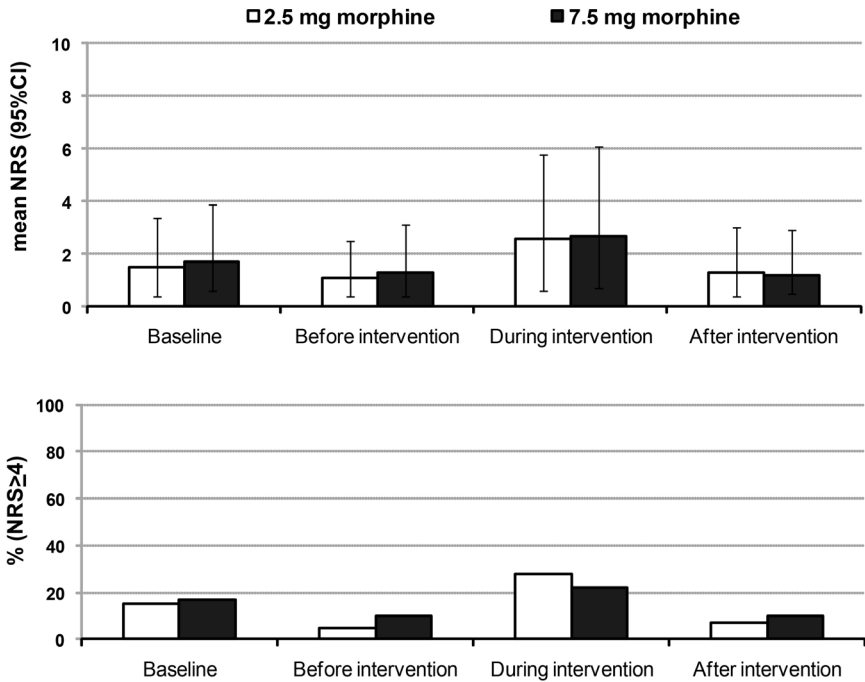


Table 3: NRS scores before, during and after the painful intervention (turning and/or drain removal) in patients randomised to receive morphine 2.5 mg (n = 59) vs. 7.5 mg (n = 58).

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Before painful intervention (5 minutes before intervention)			
NRS ≥ 4, n (%)	2 (5%)	6 (10%)	0.16
NRS ≥ 7, n (%)	0 (0%)	1 (2%)	0.50
Mean NRS [95% CI]	1.1 [0.7-1.4]	1.3 [0.9-1.8]	0.35
Median NRS [IQR]	1 [0-2]	1 [0-2]	0.66
During painful intervention			
NRS ≥ 4, n (%)	17 (28%)	13 (22%)	0.53
NRS ≥ 7, n (%)	5 (8%)	8 (14%)	0.39
Mean NRS [95% CI]	2.6 [2.0-3.2]	2.7 [2.0-3.4]	0.86
Median NRS [IQR]	2 [1-4]	2 [1-3]	0.81
After painful intervention (5 minutes after intervention)			
NRS ≥ 4, n (%)	3 (7%)	6 (10%)	0.32
NRS ≥ 7, n (%)	0 (0%)	2 (3%)	0.24
Mean NRS [95% CI]	1.3 [0.9-1.7]	1.2 [0.7-1.7]	0.70
Median NRS [IQR]	1 [0-2]	0 [0-2]	0.21

NRS=numeric rating scale

Table 4: Change in mean NRS scores in patients randomised to receive morphine 2.5 mg (n = 59) vs. 7.5 mg (n = 58).

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Mean Δ NRS [95%CI]			
Between 'baseline intervention' and 'during intervention'	1.1 [0.5-1.7]	1.0 [0.4-1.6]	0.92
Between 'baseline intervention' and 'before intervention'	-0.4 [-0.7- 0.1]	-0.3 [-0.6 -0.0]	0.59
Between 'before intervention' and 'during intervention'	1.5 [1.0-2.1]	1.4 [0.8-1.9]	0.64
Between 'during intervention' and 'after intervention'	-1.3 [0.8-0.1.8]	-1.5 [1.0-2.0]	0.58
Clinically relevant decrease NRS, n (%)*			
Between 'before intervention' and 'during intervention'	0 (0)	2 (3)	0.24
Between 'during intervention' and 'after intervention'	20 (33)	23 (40)	0.57
Clinically relevant increase NRS, n (%)*			
Between 'before intervention' and 'during intervention'	25 (42)	22 (38)	0.71

Clinically relevant decrease/ increase = Δ NRS> 1.3

Additionally, in patients with unacceptable pain at rest (baseline), the mean change in NRS score was similar between patients allocated to morphine 2.5 and 7.5 mg (-1.1 [95%CI -2.9-0.7] vs. 0.4 [95%CI -2.1-2.9], $P=0.27$). None of the patients received fentanyl rescue medication.

Discussion

In this study, we evaluated the efficacy of morphine 2.5 versus 7.5 mg for the prevention and treatment of a non-avoidable painful intervention in ICU patients after cardiothoracic surgery, who were already treated according to a pain titration protocol for pain at rest. In patients with low pain levels for pain at rest, there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

During the painful intervention, we found a substantially lower incidence of unacceptable NRS scores (25%), compared to previous reports. In these studies, incidences of 32% to 62% were reported during endotracheal suctioning and movement in patients with various morbidities [13-15]. In addition, mean NRS scores during the painful intervention were low (Table 3) compared to other studies, in which mean NRS scores of 5 and 7 were recorded during turning and drain removal, respectively [5-6]. In these studies, pain was managed with standard doses of analgesics for pain relief at rest or during procedural interventions only [26-28], in contrast to our study using a pain titration protocol. As such, the pain titration protocol which is applied during the entire ICU stay may not affect pain scores at rest alone, but may also lead to a decrease of pain intensity during painful procedures. This is partly explained by the study of Aubrun et al. [20], who concluded that patients with an initial visual analogue scale (VAS) ≥ 6 need more often rescue medication after morphine titration compared to patients with VAS < 6 in the treatment of postoperative pain.

The dose of morphine 7.5 mg in our study was in accordance with the described literature for the prevention of procedural pain. Aubrun et al. [20] reported that a threshold of 0.15 mg/kg morphine is needed for pain relief in patients with severe pain (NRS ≥ 7) during postoperative pain titration. A lower dose of 0.10 mg/kg was less effective compared to 0.15 mg/kg for pain reduction in emergency department patients with acute pain. A higher dose of 0.25 mg/kg morphine was reported to lead to respiratory depression compared to 0.15 mg/kg [29]. Our dose of morphine 7.5 mg combined with the standard titration protocol is therefore the most optimal dose as it is in accordance with the maximum dose of 0.15 mg/kg. In contrast, the dose of morphine 2.5 mg results from our hypothesis that a pain titration protocol for managing pain at rest combined with only a low dose morphine is sufficient to prevent or treat procedural pain. However, we cannot exclude that morphine 2.5 mg is comparable to placebo. In that case, the pain titration protocol is more important for procedural pain management than a bolus of morphine.

Concerning pain at rest, previous reports showed that systematic pain measurement reduced incidences of unacceptable pain (NRS ≥ 4) at rest to approximately 40% [2,10-11]. In our study, we were able to reduce the incidence of unacceptable pain at rest to 16%, as result of morphine titration adapted to individual pain. In the group patients allocated to morphine 7.5 mg, similar NRS scores could be achieved by a lower baseline morphine consumption compared to the patients allocated to morphine

2.5 mg. The difference in morphine consumption can be explained by the difference in baseline characteristics, as patients allocated to morphine 7.5 mg were significantly older and had a higher euroSCORE. It is well known that older patients need less analgesics for pain relief than younger patients [30]. Patients with a high euroSCORE are probably more vulnerable for the effects of medication, due to impaired condition of elimination organs, e.g. kidney and liver. This condition may result in a slower elimination of morphine, thereby leading to lower morphine consumption in these patients. Thus, the pain titration protocol leads to an individual dosing regimen of analgesics, thereby resulting in a low incidence of unacceptable pain at rest (16%).

Some remarks must be included concerning the limitations of our study. First, patients receiving 7.5 mg were more often exposed to the intervention 'drain removal', which may be more painful than the intervention 'turning' and thus may have reduced the difference in effect of pain relief between the patients receiving 2.5 mg and 7.5 mg. However, there was no significant difference in pain intensity between turning and drain removal. Secondly, the low procedural pain levels may theoretically have contributed to the reported lack of difference in pain levels between the morphine 2.5 and 7.5 mg group. I.e. as a result of the low overall pain scores which the patients reported within the context of the pain titration protocol, further decrease of pain intensity is more difficult to detect. In the ideal study design, we compared morphine 7.5 mg with placebo in combination with the pain titration protocol. However, for ethical considerations we preferred to treat these patients with a low dose of morphine. In this context, morphine may be dosed on kg bodyweight instead of a fixed dose. Finally, it cannot be excluded that the low overall pain scores in a context of studying the clinical trial itself. During a clinical trial with relation to pain management, all health workers in the ICU will be "affected" in their approach to pain treatment.

Conclusions

In intensive care patients after cardiothoracic surgery with low pain levels for pain at rest, there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

Acknowledgements

The authors thank the staff and nurses of the Department of Anaesthesiology and intensive care and the staff of the Department of Clinical Pharmacy of the St. Antonius Hospital for their contribution to this study.

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