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Original study

Hyperalgesia and fentanyl dosing in on-pump coronary artery bypass grafting: a prospective, randomised, double-blinded clinical trial

S. Slagmulder[1], E. Mauermann[2], M. Vandenheuvel[3]

[1]Anaesthesiology Trainee, Department of Anesthesiology, University Hospital Ghent, Corneel Heymanslaan 11, 9000 Gent; [2]Department of Anesthesiology, University Hospital Basel, Basel, Switzerland; [3]Department of Anesthesiology, University Hospital Ghent, Corneel Heymanslaan 11, 9000 Gent.

Corresponding author: M. Vandenheuvel, Department of Anesthesiology, University Hospital Ghent, Corneel Heymanslaan 11, 9000 Gent. E-mail: michael.vandenheuvel@uzgent.be

Abstract

Background: **Chronic post-sternotomy pain after coronary artery bypass grafting (CABG) is an underestimated complication. Pain has a major impact on quality of life. Increasingly, low-dose or even opioid-free anesthesia has been shown to be feasible and in some cases beneficial. Different intraoperative analgesic treatment strategies may significantly impact occurrence of hyperalgesia and subsequent pain in cardiac surgery.**
Objective: **To investigate whether different intraoperative dosing regimens of fentanyl during CABG influence the area of hyperalgesia 24 and 48 hours postoperatively. As secondary endpoints, we investigated whether acute postoperative pain measured by the numerical rating scale (NRS) scores at 24 and 48 hours and the occurrence of chronic pain after 3, 6 and 12 months were influenced by perioperative fentanyl dosing.**
Design: **Prospective, randomized double-blind clinical trial.**
Setting: **A preliminary analysis of a randomized multicenter study (University Hospital of Ghent and the University Hospital of Basel), including patients undergoing elective on-pump CABG in University Hospital of Ghent.**
Methods: **We screened 80 patients, of whom 66 were included and randomized into three groups: a high fentanyl regimen (20 µg.kg-1 IBW (Ideal Body Weight)), a low dosing regimen (3 µg.kg-1 IBW), or a Shibutani continuous dosing regimen. When extubated and responsive, protocolized pin-pricking was performed at 24 and 48h to evaluate the surface area of hyperalgesia. Additionally, patients are asked to report the Numeric Rating Scale (NRS) at 24h, 48h, as well as the occurrence of persistent pain at 3, 6, and 12 months. Additional preoperative rescue fentanyl dosing and postoperative remifentanil dosing were taken into account as possible confounders.**
Results: **Primary endpoint: the difference in the measured area of hyperalgesia between the randomization groups was not significantly different. At 24h a mean area of 88 cm2, 90 cm2 and 96 cm2 was found in the low, high and Shibutani groups, respectively. At 48h areas of 91 cm2, 96 cm2 and 103 cm2 were measured in the respective groups. Secondary endpoints: significantly higher NRS scores were recorded at 24 hours in the low-dose group. A higher NRS score was found at 6 months in the Shibutani group compared to the other groups in the longer term. Postoperative administration of remifentanil is was not found to be a confounding cause of hyperalgesia.**
Conclusion: **More short-term pain was reported in patients administered lower doses of fentanyl intraoperatively. Other clinically relevant differences in outcomes were not found. Our findings suggest that the benefits of opioid low anesthesia may not be as relevant to cardiac surgery with median sternotomy. The total postoperative opioid dosing (including remifentanil) could be a possible cause of hyperalgesia.**
Trial registration: **EudraCT (European Union Drug Regulating Authorities Clinical Trials Database), the European database for all interventional clinical trials on medicinal products authorized in the European Union. Eudra CT number: 2017-003278-15, AGO/2017/005.**

Keywords: **Hyperalgesia, chronic pain, fentanyl, CABG, analgesia in cardiac surgery.**

Introduction

Clinical relevance

Chronic post-sternotomy pain after Coronary Artery Bypass Grafting (CABG) is a significant and underestimated clinical complication. It is defined as any non-anginal postoperative pain lasting more than 3 months[1,2]. Furthermore, chronic pain has important effects on quality of life and general well-being. Moreover, the treatment of chronic post sternotomy pain is often difficult and/or inadequate, underscoring the importance of its avoidance. Treatment relies on opioids and other medications which provide minimal benefit to the patient, often in combination with significant adverse effects. Furthermore, little is known regarding chronic pain prevention after sternotomy[3]. Secondary wound hyperalgesia has been shown to occur shortly after surgery in virtually all patients and is a potential cause of chronic postsurgical pain[4]. While most patients with post-sternotomy pain experience this as mild or moderate, 15% report their pain as severe (> 7 VAS, visual analogue scale[7,8,10,11]. Remifentanil, a strong opioid commonly used perioperatively, has been shown to increase hyperalgesia[5,6]. Higher remifentanil doses have been implicated with higher chronic and persistent pain rates[7,8]. Despite the widespread use of opioids in both acute and chronic pain management, evidence implies these molecules may enhance pain when re-administered, especially when used in high doses[9].

Recently, a model of pain in healthy volunteers showed that opioid-induced hyperalgesia is not specific to remifentanil, but may also be caused by fentanyl, arguably the most commonly used opioid in anesthesia[11]. Traditionally, opioid dosing – especially in cardiac surgery – has been very liberal, most likely due to hemodynamic considerations. Furthermore, it has been suggested that wound hyperalgesia may be a factor in the development of chronic or persistent pain. Given the unchanged and high incidence of persisting post sternotomy pain of 15 to 50%, a study examining the effect of fentanyl dosing, hyperalgesia, and persistent post sternotomy pain seems appropriate[1,12].

Objective

This is a preliminary analysis of a multicenter study (Ghent University and the University of Basel). It handles only the results achieved at the Ghent University Hospital. The trial started in May 2018 and ended in January 2021. We investigated whether a higher intraoperative dose of fentanyl in CABG patients causes a greater post-surgical area of secondary wound hyperalgesia (as measured by 24 and 48-hour-postsurgical pin-prick test) compared to a lower dose. Additionally, persistent post-sternotomy pain was examined at 3, 6 and 12 months by a standardized questionnaire.

Methods

Study design

This trial was a prospective, randomized double-blind clinical trial. The study was approved by the ethics committee of the University Hospital of Ghent (prof. Dr. D. Matthys Eudract Nr. 2017-003278-15, Nov. 23, 2017). All participants gave written informed consent prior to participation.
The subjects were randomized into three groups: a high fentanyl bolus regimen, a low fentanyl bolus regimen or a Shibutani continuous dosing regimen. The dosing schedules were as follows:

1. High dose fentanyl bolus: 20 µg.kg-1 IBW (Ideal Body Weight)
2. Low dose fentanyl bolus; 3 µg.kg-1 IBW
3. Continuous fentanyl infusion according to Shibutani scheme. This involves a bolus of 2-5 µg.kg-1 followed by continuous infusion with hourly step-down rates over a term of 4 hours (0.07, 0.05, 0.03, 0.02 µg.kg-1min-1)[13,14].

An example for a typical patient is presented in Table I. Each group received a standardized induction dose of 3 µg.kg-1 IBW and was given top-up doses of fentanyl if deemed necessary by the blinded attending anesthesiologist. There was no defined protocol for additional fentanyl whichw as simply administered at the discretion of the attending anesthesiologist. The three dosing regimens provide a significant range in total intraoperative fentanyl dose (Figure 1).

All three dosing regimens were prepared by a study nurse, according to normal clinical practice, in a blinded fashion. The method of administration (intravenous bolus or continuous infusion) did not deviate from standard guidelines. The general anesthesia technique provided is standardized for all patients (using propofol and rocuronium, maintenance with sevoflurane). Remifentanil – propofol infusion was used as a postoperative analgesic as is standard on the ICU. Dosing regimen varied between 0,05 to 0,2µg.kg-1min-1 according to the Richmond Agitation-Sedation Scale (RASS). Following extubation, morphine, dipidolor and/or tramadol were administered as rescue analgesics as per ICU standards.

Endpoints

The primary aim of this study was to determine whether or not different intraoperative dosing regimens of fentanyl influence the surface area of

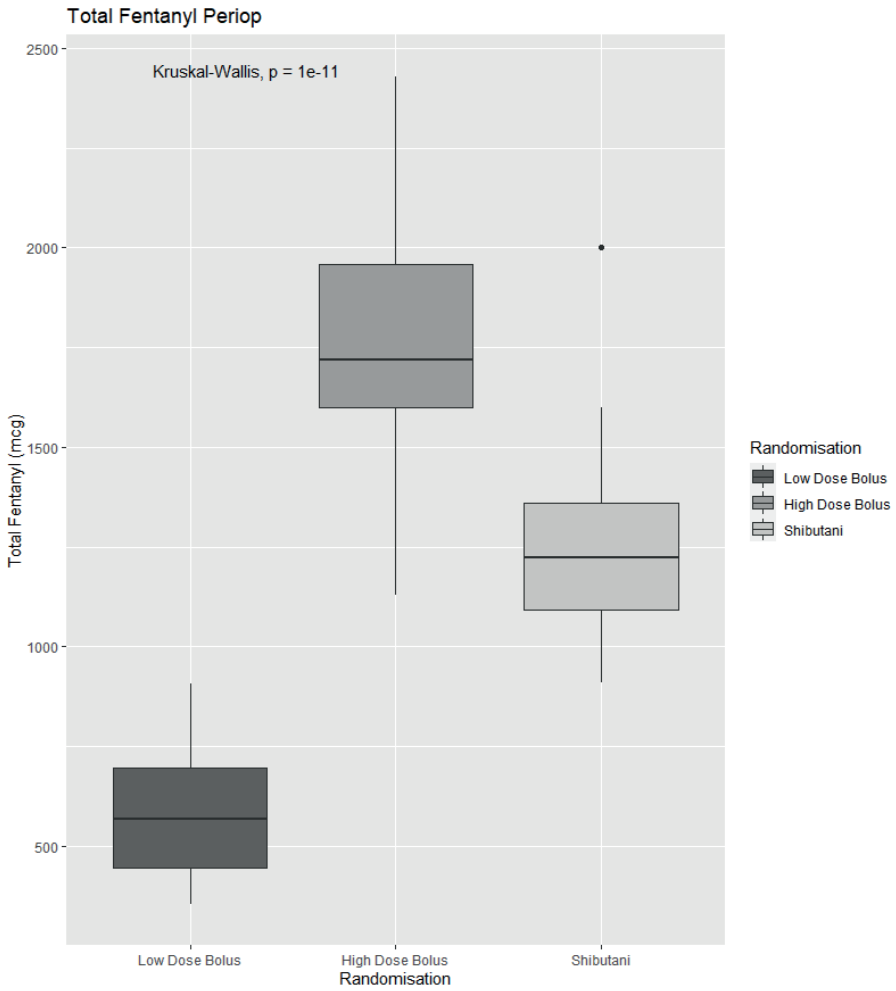


Fig. 1

hyperalgesia at 24h and 48h postoperative. The surface area of hyperalgesia was determined by a pin-prick test. Secondary endpoints included the NRS score at 24h and 48h post-surgery. Additionally the highest level of pain (i.e. worst pain) was asked at 24 and 48 hours (both at rest, at movement/upon coughing). We also noted the morphine-equivalent opioid consumption at 24 and 48 hours. Finally, a study team member performed a telephone follow-up at 3, 6, and 12 months. Other pertinent data was recorded from the patient's electronic record.

Table I. — Three intervention groups.

Study arm	Induction µgkg^{-1}IBW	Maintenance (5 min prior to sternotomy)	As needed µgkg^{-1}IBW
High-dose bolus	3	Bolus 20 µgkg^{-1}BW fentanyl in 2x20ml syringes [e.g. 70 kg – 1400µg fentanyl + 12 ml NaCl 0.9%] Syringe pump 20 ml (NaCl 0.9%); Shibutani scheme [e.g. 70 kg - 5.9 ml/h, 4.2 ml/h, 2.5 ml/h, 1.7 ml/h]	1-2
Low-dose bolus	3	Bolus 3 µgkg^{-1}BW fentanyl in 2x20ml syringes [e.g. 70 kg – 210µg fentanyl + 35.8 ml NaCl 0.9%] Syringe pump 20 ml (NaCl 0.9%); Shibutani scheme [e.g. 70 kg - 5.9 ml/h, 4.2 ml/h, 2.5 ml/h, 1.7 ml/h]	1-2
Continuous (Shibutani)	3	Bolus 0 µgkg^{-1}BW fentanyl in 2x20ml syringes [e.g. 70 kg 0µg fentanyl + 40 ml NaCl 0.9%] Syringe pump 20ml (fentanyl); Shibutani scheme [e.g. 70 kg – 295µg/h, 210µg/h, 125µg/h, 85µg/h]	1-2

Participants

Inclusion criteria:

- Age ≥ 18 years old.
- First elective on-pump CABG with median sternotomy and central cannulation.

Exclusion criteria:

- Documented existing chronic pain.
- Opioid use in the last 30 days or documented case of opioid abuse.
- BMI > 35 kg/m2 or history of OSAS (Obstructive Sleep Apnea Syndrome).
- Kidney failure and clearance < 30 ml/min.
- Neuraxial anesthesia.
- Pregnancy.
- Planned wound infiltration with local anesthetic.
- Known allergies or intolerance to fentanyl or other opiates.
- Unable to understand the concept of the pin-prick test and answer the associated questionnaires.
- Refusal, no informed consent.

The sample size was calculated based on the primary outcome (area of hyperalgesia). Assumptions on the area of hyperalgesia (effect size, standard deviation) were made based on a trial in healthy volunteers, as no clinical data is available for fentanyl and the proposed method of measuring hyperalgesia. As a result, we assumed a 30% difference in hyperalgesia with a 7% standard deviation at 4.5 to 6.5 hours. We conservatively halved the effect to 15% while doubling the standard deviation to 15% due to differences in study populations. This left the required 66 patients, which is consistent with earlier trials assessing differences in hyperalgesia comparing ketamine with placebo and clonidine and placebo in laparotomy patients (both n=20 per arm)[7,8].

According to the approved study protocol, 80 subjects were enrolled. In total, fourteen dropouts were registered. Four patients withdrew consent before randomization, 2 patients had their surgery postponed, and in 2 cases the investigator was not available. In two subjects, the study was aborted by the attending anesthesiologist citing safety concerns. Both patients were deemed hemodynamically unstable after induction, at which point the attending anesthesiologist decided against administering the study medication. One of these patients died. They had both been randomized (in the high dose bolus group) but did not receive study medication. Two patients were replaced. Four patients refused to continue the study on a 3-month evaluation. Thus, inclusion ended at 66 patients, with 21 patients in the low dose and Shibutani group and 24 patients in the high dosage group (see consort flow chart).

Randomizations

Patients were randomized by a sealed envelope technique. Based on this randomization, dedicated study personnel not involved in patient management prepared medication kits. Treating physicians were blinded by receiving a perfusion syringe with either fentanyl or placebo to be administered along the Shibutani rates as well as with a syringe of fentanyl or placebo to be administered as a bolus. The strength of the study is a triple-blinded protocol: the patient, anesthetist and assessors were not aware of the randomly allocated regimen.

Process

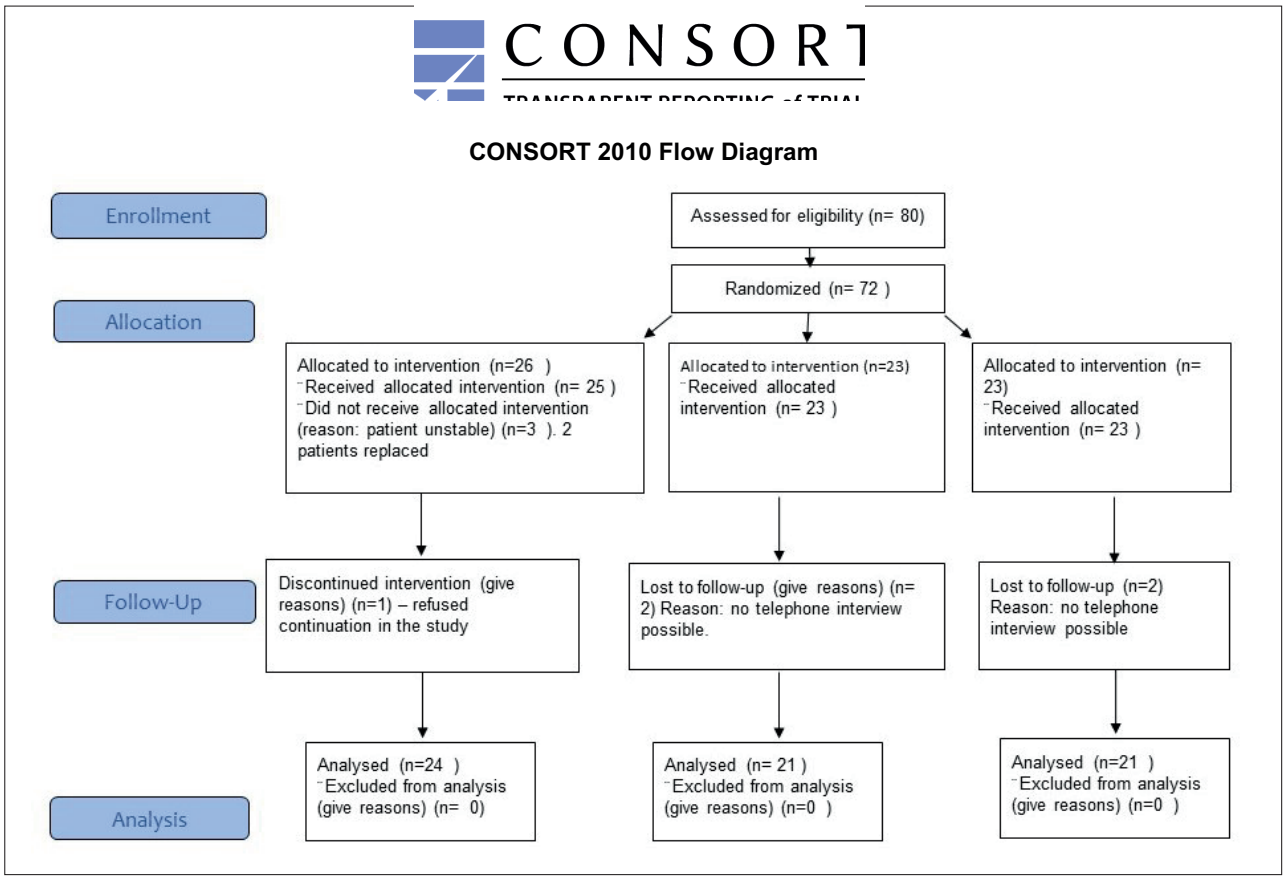
Hyperalgesia was evaluated both by clinical observations and a von Frey filament. The surface area of hyperalgesia was determined by moving from the wound to peripheral skin while exerting constant pressure (256mN). Similar methods have been applied in several other experimental models [5–7,17].

Upon consent, participating patients underwent the following steps:

1) Preoperative explanation of the course of the study and demonstration of the pin-prick test.
2) Randomization according to one of three fentanyl dosing regimens.
3) Postoperative evaluation of the area of hyperalgesia by a pin-prick test using a von Frey 256mN filament. We assumed an ellipse-like surface area of hyperalgesia around the sternum. Pin-pricks were performed along 3 horizontal, parallel lines: a line through the center of the sternotomy, a line 5 cm cranial to the center, and a line 5 cm caudal to the center. The pin-prick test started at a point 12 cm lateral to the sternum and proceeded medially in one cm increments. The patient had been instructed to let the tester know the moment a pin-prick produced more pain or was sharper than its predecessor. The distance of this sensation from the center was recorded and the pin-prick test ended in this section. The same happened along the other two lines, at both sides of the sternum. By deviating cranially or caudally by 1 cm, the nipples were avoided. The total surface area of hyperalgesia was determined as the medial surface of the six points that registered "more pointy" pin-pricks. There was no pre-examination NRS determined.

Statistical analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted by UZ Gent. REDCap is a secure, web-based software platform designed to support data



capture for research-based studies. Collected data was exported to RStudio (version 4.0.3, Boston), a statistical analysis software package[18,19].

The calculation involved 264 variables from 66 patients, this data was sorted and organized. Concerning the relationship between fentanyl dosage and hyperalgesia, a one-way analysis of variance (ANOVA) was applied to the data alongside a Tukey test. All NRS and area results were normally distributed according to Shapiro-Wilks testing. The one-way ANOVA test can show significant differences in group means without indicating which pairs are different. Specific pairs must be compared using a Tukey test. The same was done with NRS scores.

Results

Population definition

Patient characteristics were balances between the three groups. Overall, we noted a higher proportion of men (84.9%) than women (15.1%) as is common in cardiac surgery; no difference in the gender distribution could be found in the three randomization groups.

Surface area of hyperalgesia and fentanyl

No difference in the area of hyperalgesia between the randomization groups was found. At 24h mean areas of 87cm^2; 90cm^2 and 96 cm^2 were found in the low, high and Shibutani groups. At 48h 91cm^2; 96 cm^2 and 103 cm^2 were measured in the respective groups (Figure 2, overall p-values 0.87 and 0.78 respectively).

Numeric rating scale and fentanyl

Patients were asked to report according to the NRS scale at 24 and 48 hours. One-way ANOVA showed a significant difference between the low and high bolus group at 24 hours (p= 0.048). The mean NRS score of the low bolus group was 5.7 compared to the other NRS scores of 4.0 (high bolus group) and 4.7 (Shibutani) (Table II, Figure 2). A difference of 1 NRS point is generally considered to be clinically relevant. At 48h postoperative, no statistically significant difference was found.

Postoperatibe pain score at 3, 6 and 12 moths ans fentanyl

We found a statistically significant – but clinically irrelevant – difference in NRS at 6 months. (NRS 0,17 in the high dose group, 0,21 in the low dose group, and 1,17 in the Shibutani dosing regimen, Table III). No difference whatsoever were found at 3 and 12 months.

Aditional analysis

Further analyses were made to determine a possible effect of additional fentanyl boli administered by the treating physician, postoperative remifentanil and other postoperative analgesics.

Table II. — NRS and P values for multiple comparisons.

NRS	Randomization	Mean	P-value	Comparison	Lower (95% CI)	Upper (95% CI)	Adjusted P-value
24 h	Low	5,71	0,06	High - Low	-3,69	-0,01	0,048
	High	4,00		Shibutani - Low	-2,81	0,91	0,44
	Shibutani	4,76		Shibutani - High	-0,94	2,74	0,47
48 h	Low	3,80	0,79	High - Low	-2,25	5,08	0,55
	High	3,86		Shibutani - Low	-3,44	3,57	0,10
	Shibutani	4,35		Shibutani – High	-4,57	1,87	0,50

a. Perioperative additional fentanyl

The total dose of fentanyl added as a supplementary bolus (deemed necessary by the anesthesiologist) differs significantly between the three randomization groups (P=0.033). The Shibutani group received the highest total dose of added fentanyl (mean=188 mg).

b. Postoperative remifentanil

Up until extubation, remifentanil was standard of care postoperative analgesic in the postoperative ICU. There were some patients receiving more remifentanil than others. E.g. in the Shibutani group, one patient needed longer sedation in intensive care, which explains the outlier. As such, total remifentanil dosage was calculated for each group. An additional Kruskal-Wallis test showed no statistically significant difference in remifentanil consumption between the three groups (P=0,59) (see figure 3 A).

c. Other postoperative analgesics

Postoperatively, we lacked of a standardized protocol for postoperative pain management using other postoperative opioid analgesics (tramadol, dipidolor, remifentanil and oxynorm). Therefore, all were converted to an equipotent dose of morphine. No significant difference in perioperative equipotent morphine doasges could be found among the three treatment groups (p=0,60).

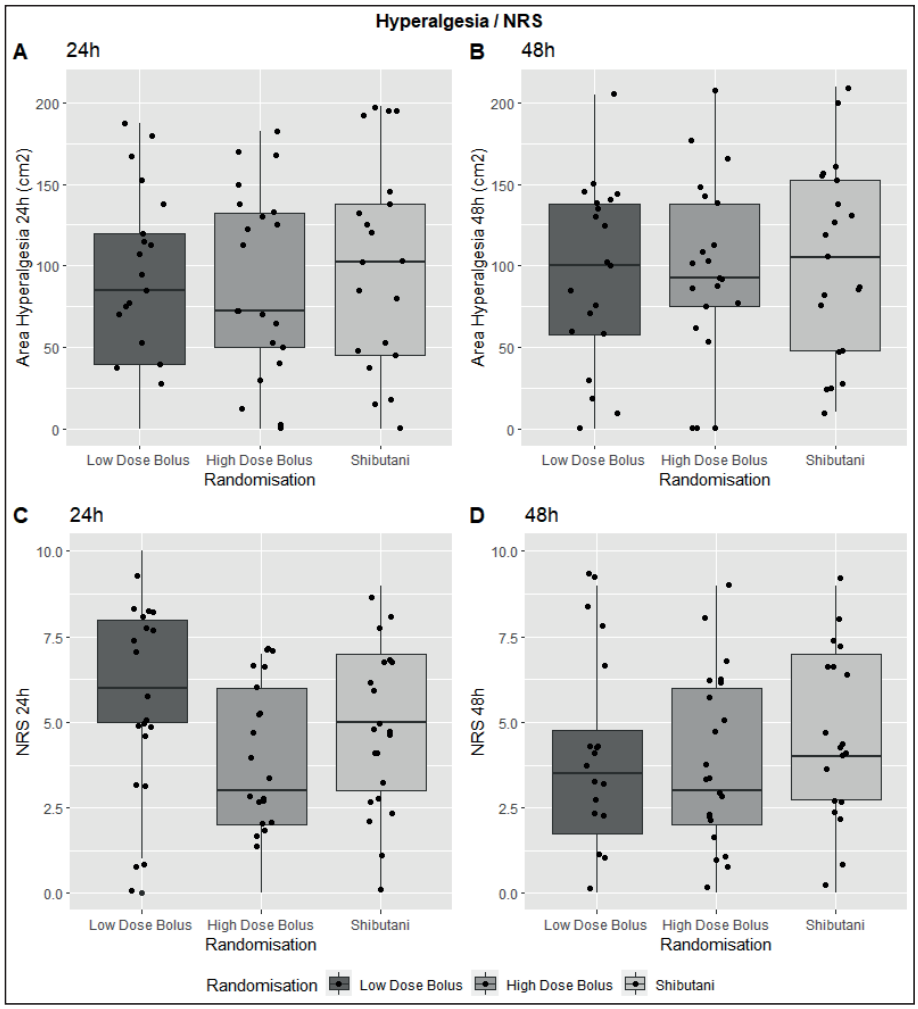


Fig. 2

Table III. — NRS at 3, 6 en 12 months - Multiple comparisons.

NRS	Randomization	Mean	P-value	Comparison	Lower (95% CI)	Upper (95% CI)	Adjusted P-value
3 mo	High	0,39	0,46	High – Low	- 0,78	1,36	0,79
	Low	0,68		Shibutani - Low	-0,84	1,39	0,82
	Shibutani	0,67		Shibutani - High	-1,08	1,05	0,99
6 mo	High	0,17	**0,01**	High - Low	-1,26	1,35	1,00
	Low	0,21		**Shibutani - Low**	0,20	2,88	**0,02**
	Shibutani	1,71		**Shibutani – High**	0,17	2,82	**0,02**
12 mo	High	0,11	0,10	High – Low	-0,83	1,67	0,70
	Low	0,53		Shibutani - Low	- 0,78	2,28	0,09
	Shibutani	1,18		Shibutani – High	-0,84	1,86	0,40

No difference in postoperative opioid dosing, NRS, or hyperalgesia at 48h and NRS at 3,6, or 12 months (see figure 3B and 3C) were found.

Discussion

All the above results give reason to conclude there is a statistically significant difference between the 24-hour NRS scores of high and low dosing regimens. Patients administered the lowest total intraoperative dose of fentanyl reported higher pain scores at 24 hours. No clinically relevant difference in postoperative outcomes at 3, 6, or 12 months was found.

These results are not entirely consistent with what was expected from previous studies, particularly considering the trend in opioid free and opioid low anesthesia. We had predicted a higher postoperative area of hyperalgesia in the groups that received the high bolus of fentanyl. Our results did not

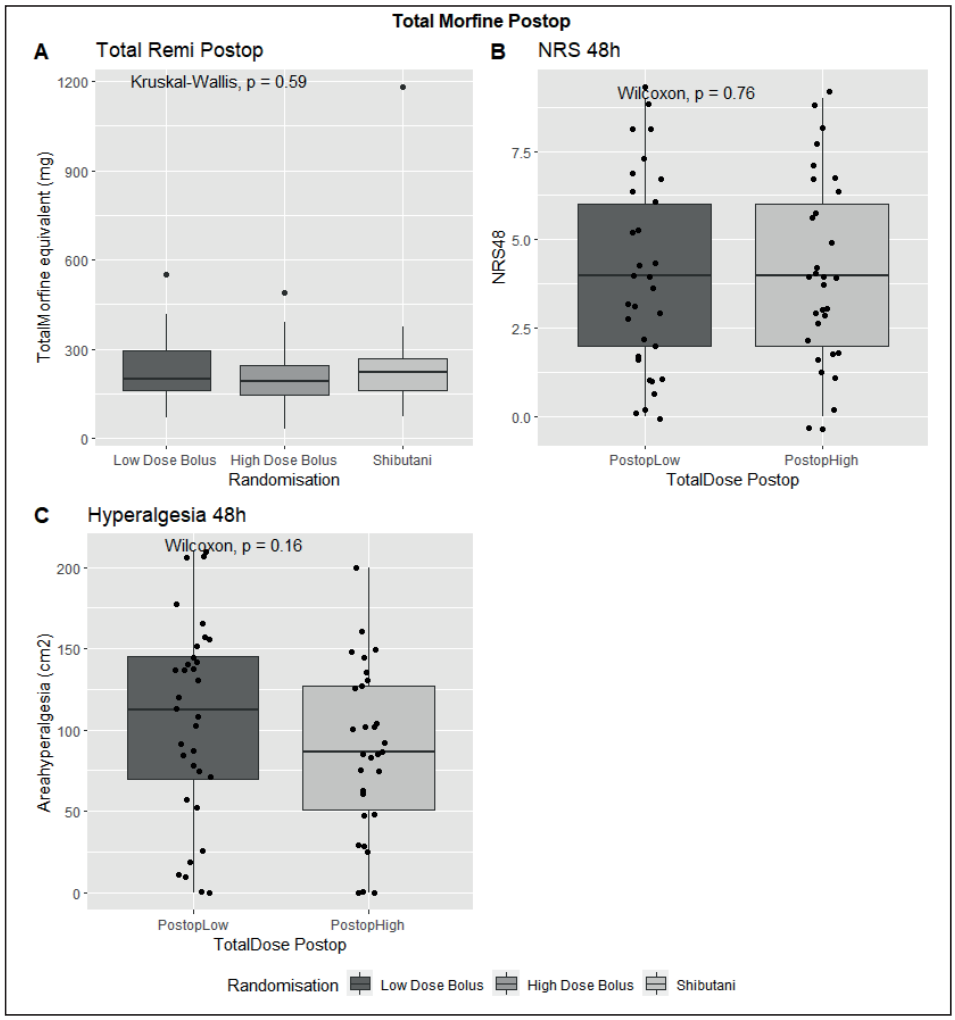


Fig. 3

demonstrate a statistically significant difference in hyperalgesia between the different dosing regimens at 24 and 48 hours postoperatively. However, the mean NRS values at 6 months were very low, between 0 and 1,17. The clinical relevance of this result can be questioned.

Concerning our additional analysis, the Shibutani group received the highest total dose of added fentanyl. This could be explained by the fixed Shibutani scheme and possible lower peaks of fentanyl during painful surgical steps (e.g. sternotomy). Following the scheme, the highest dose was given at induction, with continuous declining doses during surgery.

There was no defined protocol defining the additional fentanyl perioperative. It was important to us for patient safety that the treating anesthesiologist be allowed to administer fentanyl as deemed appropriate on the basis of clinical considerations. The amount of additional fentanyl differs significantly between the three randomization groups. Concerning the postoperative administration of analgesia, a well-defined protocol should be incorporated into future studies. This illustrates how objectifying hyperalgesia or differentiating between hyperalgesia and pain remains difficult[11].

It should also be noted that during the first hours in intensive care, patients received a propofol-remifentanil infusion as postoperative sedation. The dosing of remifentanil varied from patient to patient, but was titrated to effect (RASS). Previous studies indicate that the postoperative administration of higher does of remifentanil alone could be a cause of hyperalgesia. In our study, we aimed to correct for this confounder with an extra analysis for the postoperative remifentanil. It didn't show a significant difference in remifentanil consumption between the randomization groups.

Pain is an extremely subjective sensation and remains difficult to objectify despite the development of validated tools, particularly by phone interview. Registering patient requests for pain relief can act as an important indicator and help to create a more objective picture. In addition, the diagnosis of chronic pain after sternotomy can only be made once it has been reported. Given the considerable anxiety and fear surrounding cardiac surgery, many patients may under-report pain. Some seem to be simply relieved to have survived surgery and do not wish to complain about something they may consider more trivial. Patients perhaps view chronic pain following cardiac surgery as "normal" or "expected" or are more concerned with their cardiac health. Because of this, patients can fail to report symptoms to their surgeon or cardiologist. This leads to delayed or improper diagnosis and treatment[4]. We should also not lose sight of the fact that the study population consisted primarily of males and as described earlier, gender plays an important role in how pain is registered[11]. However, the number of women was evenly distributed between the three groups. The extent of gender as an influencing factor needs to be investigated further.

Despite the limitations of this study, we believe this preliminary analysis may aid in the investigation of this complicated field. In particular and in contrast to the general trend in opioid free or opioid low anesthesia, poststernotomy pain in cardiac surgery may be a more complex entity. Furthermore, remifentanil is not the only opiate linked to hyperalgesia. Even so, our study is one of the few (besides Yildrim et al.) to look for an association between fentanyl and hyperalgesia. It is one of a small handful of studies that investigates this link, with the added attraction of a study population of 66 patients selected in advance via well-defined inclusion and exclusion criteria. All patients underwent the same standardized procedure and similar postoperative clinical pathways. Selection bias was avoided through sealed envelope randomization. This was in effect a triple-blind study. Patients, treating physicians, and researchers were unaware of the allocated intervention.

Conclusion

Hyperalgesia as well as both acute and persistent pain remain a postoperative problem. In this study population, more short-term pain was reported in patients administered lower doses of fentanyl intraoperatively, while no relevant difference was reported at later time points. However, very low NRS scores were recorded in this population. In contrast to the body of emerging literature for other surgical procedures, higher fentanyl dosages for cardiac surgery do not appear to be associated with higher sternotomy pain.

Conflict of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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