Final Study Report

Study Title: Hyperalgesia, Persistent Pain, and Fentanyl Dosing in On-Pump Coronary Artery Bypass Grafting

EudraCT number: *2017-003278-15*

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Sponsor: *UZ Ghent*

National Coordinator/ Coordinating Investigator: Prof dr Patrick Wouters

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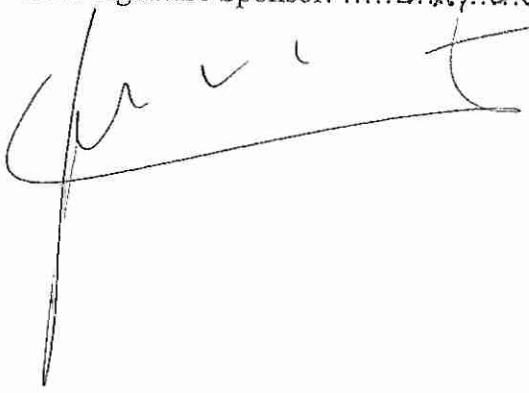

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1. Introduction

The objective of this randomised trial was to assess whether different intraoperative dosing schemes of fentanyl during on-pump CABG surgery influence the area of hyperalgesia as measured by sternal pin-prick testing on the first postoperative days. The trial started in May 2018 and ended in January 2021. A total of 80 patients were included

Secondary wound hyperalgesia has been shown to occur shortly after surgery in virtually all patients. Remifentanil has been shown repeatedly to increase hyperalgesia, leading to the phenomenon of "opioid-induced hyperalgesia". Higher doses are an extra risk factor for hyperalgesia. Postoperative hyperalgesia may be a factor in the development of chronic or persistent pain.

This trial was a prospective, randomised double blinded clinical trial. We included patients older than 18 years undergoing elective on-pump CABG surgery with a midline sternotomy. Patients with chronic pain, opioid use in the last 30 days, morbidly obesity, OSAS or GFR < 30 ml / min were excluded. The patients were randomised in three groups with a high or a low fentanyl dosing scheme, or a Shibutani continuous dosing scheme. The high dose group received 20 µg / kg fentanyl, while the low dose group received 3 µg / kg before sternotomy.

Both groups received a freely chosen induction dose and top-up doses of fentanyl if deemed necessary by the attending anaesthesiologist. Postoperative remifentanil was started according to the ICU sedation protocol. If extubated and responsive, protocolized pin-pricking was performed 24h and 48h after surgery by means of a 256 Nm von Frey monofilament and hyperalgesia surface was measured.

2. Objectives of the study

2.1 Primary objectives

The primary objective of this trial was to assess whether or not different intraoperative dosing schemes of fentanyl during on-pump CABG surgery influence the area of hyperalgesia as measured by sternal pin-prick testing on the first postoperative day.

2.2 Secondary objectives

Secondary endpoints consisted of finding a possible association between fentanyl dosage and pain at 3-6 and 12 months after surgery.

3. Investigational Medicinal Product

Fentanyl is commercialised by Janssen Cilag NV. The first approval of fentanyl, an opioid anesthetic analgesic, was granted to Janssen Cilag NV on 01/08/1980 to be used during general or local anesthesia or as part of neuroleptanalgesia. The approved dose(s) is determined individually and depends on age, body weight, physical condition, underlying pathology, use of other medications, type of surgery and anesthesia.

Fentanyl is authorised for sale worldwide.

4. Investigational Medical Device

Not applicable

5. Study Protocol Summary

As the mechanisms causing opioid-induced analgesia are poorly understood but appear to be dosis-related, we examined 3 clinically used fentanyl application schemes in cardiac surgery: 1) a high-dose bolus group, 2) a low-dose bolus group, and 3) a low-dose continuous infusion group. Each group received an induction dose and were given top-up doses of fentanyl if deemed necessary by the attending anaesthesiologist. The dosing schedules were as follows:

1. High dose fentanyl bolus (20 μgkg-1 BW; e.g. 70 kg 1400 μg or 1.4 mg)
2. Low dose fentanyl bolus (3 μgkg-1 BW; e.g. 70 kg 210 μg or 0.2 mg)
3. Continuous fentanyl infusion according to Shibutani. The Shibutani scheme (including induction) involves a bolus of 2-5 μgkg-1 followed by continuous infusion with hourly step-down rates over a term of 4 hours (0.07, 0.05, 0.03, 0.02 μgkg-1/min) (34, 35).

All patients were administered a standard fentanyl bolus (3 μgkg-1) at induction. This was not included in the study medication but was used as a standard of care. Each patient received pre-incision maintenance analgesia according to one of the three arms as shown above. The anaesthetist was permitted to give a further fentanyl bolus pro re nata (again, not a study medication but standard of care). The three dosing regimens provide significant range in total intraoperative fentanyl dose.

5.1 Inclusion criteria

- Age ≥ 18 jaar
- First elective on-pump CABG with median sternotomy and central cannulation

5.2 Exclusion criteria

- Opioid use in the last 30 days or a history or documented case of opioid abuse
- BMI > 35 kg/m2 or history of OSAS
- Kidney failure and clearance < 30 ml/min
- Neuraxial anaesthesia
- Pregnancy
- Planned wound infiltration with local anaesthetic
- Known allergies or intolerance to fentanyl or other opiates
- Unable to understand the concept of the pin-prick test and answer the associated questionnaires.

5.3 Primary endpoint

The primary aim of this study was to determine whether or not different intraoperative dosing regimens of fentanyl influence the surface area of hyperalgesia. Specifically, the surface area of hyperalgesia was determined by a von Frey 256 mN filament pin-prick test.

5.4 Secondary endpoints

Secondary endpoints consisted of finding a possible association between fentanyl dosage, hyperalgesia and pain at 3-6 and 12 months after surgery. All results took into account individual patient characteristics.

5.5 Procedures

Hyperalgesia was evaluated both by clinical observations and a von Frey filament. 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 (4, 11, 15-17, 22, 29).
Upon consent, participating patients underwent the following steps:

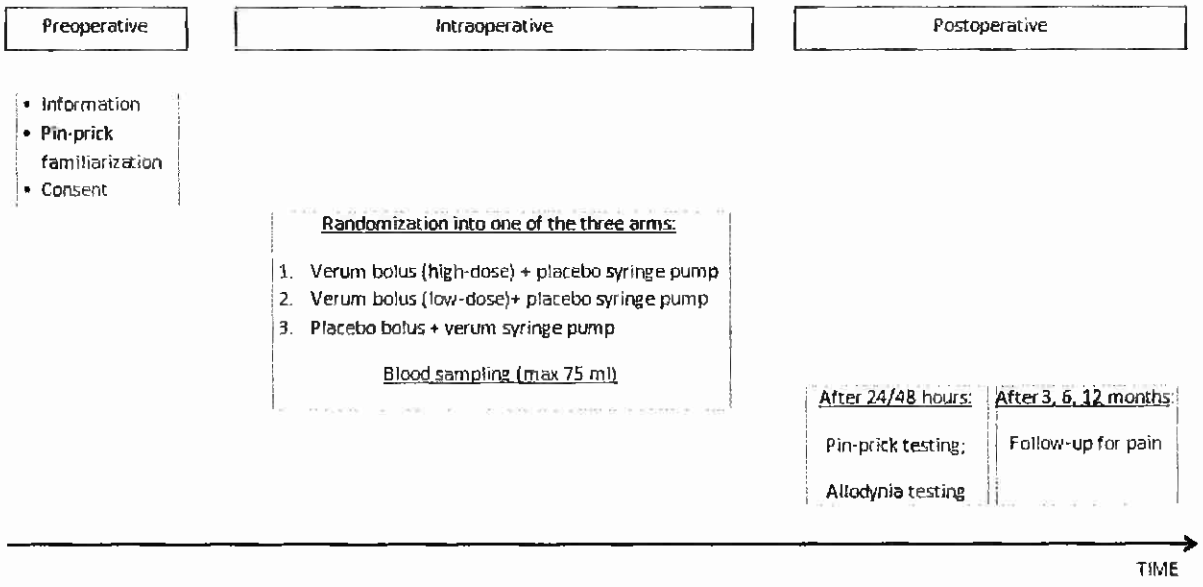
1) Received a preoperative explanation of the course of the study and what the pin-prick test entails.

2) Randomisation according to one of three fentanyl dosing regimens.

3) Postoperative evaluation for hyperalgesia by way of a pin-prick test using a von Frey 256mN filament. We predicted an ellipse-like surface area of hyperalgesia around the sternum. Use of standard pins or needles is often hindered due to the presence of wound dressings or drains. Pin-pricks were performed along 3 horizontal, parallel lines: 1 line through the centre of the sternotomy, 1 line 5 cm cranial to the centre, 1 line 5 cm caudal to the centre. The pin-prick test started at a point 12 cm lateral to the sternum and proceeded medially in 1 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 centre was recorded and the pin-prick test ended on 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 "painful" pin-pricks.

4) Persistent postoperative pain at 3 – 6 and 12 months post-surgery was evaluated by way of a structured telephone interview. Questions asked were:
- NRS value at rest and during exertion/coughing
- whether medication was being taken
- if they were experiencing itching, burning or numb sensations
- the presence of other pain symptoms related to the surgery and, if so, related NRS and analgesic use

The highest pain rating was also determined for the last 24 and 48 hours. Pain was quantified according to a numeric rating scale as this enabled simpler measurement and outcome (7). Attention was also given to the possibility of mobilisation, as well as patient feedback in relation to a preference for more pain relief in view of the risk of potential side effects.



5.6 Randomisation and blinding

Randomisation was achieved by way of a sealed envelope selected by an anesthesiologist involved neither with the patient nor outcome. Based upon randomisation, the study nurse prepared the pain medication as described above. The patient, anaesthetist and assessor were not aware of the randomly allocated regimen. A sealed list of all patients with the allocated randomised regimen was made available in case of emergency.

6. Study analysis

The primary endpoint of the study was the surface area of hyperalgesia determined by a von Frey 256 mN filament pin-prick test, which was performed by the investigator. The highest pain rating was also determined for the last 24 and 48 hours. Pain was quantified according to a numeric rating scale as this enabled simpler measurement and outcome. Study data was collected by treating anesthesiologist, intensivist and nursing staff, and managed using REDCap (Research Electronic Data Capture) tools hosted by UZ Gent. Collected data was exported to RStudio, a statistical analysis software package that includes a statistics calculator.

Sample size was calculated on a power analysis for the primary endpoint - a decrease in hyperalgesia of 15 cm2 st. dev +/- 15 cm2 with alpha 0.05 and a power 0.9. This gave us a sample size of 66 patients.

Statistical analysis involved 264 variables from 80 patients, this data was sorted and organized by the blinded analyser. With regard to the research question on fentanyl dosage and hyperalgesia, an analysis of variance was performed on that data. The same was done with NRS

scores at 24 and 48 hours. A subsequent chi-square test investigated association between fentanyl dosage and the presence of long-term pain.

7. Independent Ethics Committee and Competent Authority

For this study, institutional board review was obtained (Ghent Ethical Committee, EC/2017/1295).

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - Protocol v.1 dd.30-Aug-2017 - Protocol Summary v.1 dd.30-Aug-2017 - ICF v.1 dd. 30-Aug-2017 - Questionnaires pain v.2 dd. 02-Oct-2017 - Summary of product characteristics Fentanyl dd. Sep-2016 - Crf v1. dd.19-Sep-2017 - Label fentanyl v.2 dd.31-Aug-2017	**Approval Central EC:** 23-Nov-2017	**Approval FAGG:** 07-Dec-2017
Non-substantial amendment 1: - Protocol v.1.1 dd.29-Jun-2018 - ICF v.1.1 dd. 29-Jun-2018 ***Note: As changes were non-substantial for CEC or FAGG, ICF and protocol have not been submitted. Implementation on 29-Jun-2018.***	**Approval Central EC:** NA	**Approval FAGG :** NA
Non-substantial amendment 2: - ICF v.2 dd. 10-Dec-2018 - Prolongation recruitment until 28-Feb-2020, follow-up until 28-Feb-2021	**Approval Central EC:** 13-Jan-2019	**Approval FAGG :** NA
Notification 1: - Progress & Safety Report #1: Reporting period 13-May-2018 until 31-Dec-2018	**Approval Central EC:** N.A. **Submission:** 22-Jan-2019 **AoR CEC:** 23-Jan-2019	**Approval FAGG :** NA **Submission:** 22-Jan-2019 **AoR FAGG:** 23-Jan-2019
Notification 2: - Development Safety Update Report #1 (DSUR): Reporting period 01-Jan-2019 until 31-Dec-2019	**Approval Central EC:** N.A. **Submission:** 30-Jan-2020 **AoR CEC:** 18-Mar-2020	**Approval FAGG :** N.A. **Submission:** 30-Jan-2020 **AoR FAGG:** 30-Jan-2020

Notification 3: - DSUR #2: Reporting period 01-Jan-2020 until 31-Dec-2020	**Approval Central EC:** N.A. **Submission**: 25-Jan-2021 **AoR CEC:** 01-Feb-2021	**Approval FAGG :** NA **Submission**: 25-Jan-2021 **AoR FAGG:** 25-Jan-2021
Notification 4: - EOT (End of Trial) with LPLV 09-Jan-2021	**Approval Central EC:** N.A. **Submission**: 04-Jun-2021 **AoR CEC:** 08-Jun-2021	**Approval FAGG :** NA **Submission**: 04-Jun-2021 **AoR FAGG:** 04-Jun-2021
Notification 5: - DSUR #3: Reporting period 13-May-2018 until 09-Jan-2021	**Approval Central EC:** N.A. **Submission**: 02-Jul-2021 **AoR CEC:** 04-Jul-2021	**Approval FAGG :** NA **Submission**: 02-Jul-2021 **AoR FAGG:** 02-Jul-2021

8. Results

8.1 Subject enrollment and demographics

After an initial inclusion of 80 patients, 14 dropouts were registered due to various, previously mentioned reasons. This brought the total study population to 66 patients. As has already been mentioned, the implementation of power analysis showed that this number met the minimum sample size.

We noted a higher proportion of men (84.9%) compared to women (15.1%). Gender distribution appeared to be more or less equal across the three randomisation groups. Chi-square analysis gave a P-value of 0.53. This value translates to no significant difference in the male-female ratio between the three groups.

The three randomisation groups were also equally distributed with regard to weight and height.

8.2 Study specific results

Preliminary results are reported, as analysis is still ongoing.

The zone of hyperalgesia was calculated according to the defined pin-prick area at 24h and 48h postoperatively. A one-way analysis of variance (ANOVA) was applied to the data alongside an additional Tukey test. The one-way ANOVA test can show significant differences in group means without indicating which pairs are different. Specific pairs must be compared by means of a Tukey test. For the research question "Is there a difference in surface area of hyperalgesia at 24 and 48 hours between the three randomised groups?", we can conclude there is no significant difference in surface area of hyperalgesia at either 24 hours or 48 hours postoperatively. P-values were 0.87 and 0.78 respectively. Results are shown in the table and box and whisker plots below.

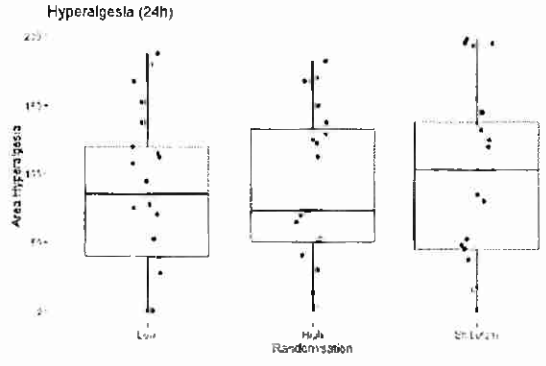


Figure 7: Hyperalgesia 24h

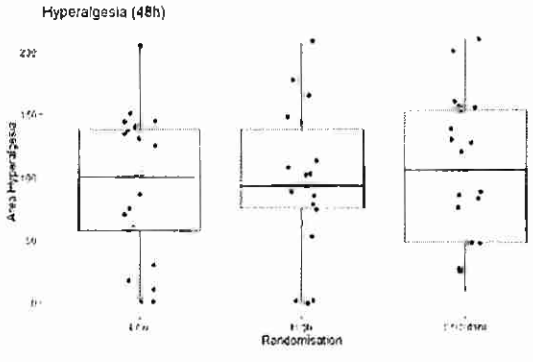


Figure 8: Hyperalgesia 48h

Patients were asked to report according to the NRS scale at 24 and 48 hours, The NRS is a standardised tool used to evaluate pain (in this case, sternum pain). A one-way ANOVA test was applied to these results. A significant difference was reported between the high and low bolus group at 24 hours with a P value of 0.048. We can conclude a significant difference in pain scale at24 hours postoperatively exists between these two dosing regimens. Notably, higher pain scores were reported in the low dose group. This result was unexpected.

We evaluated patients according to the NRS scale (for sternum pain) at 3, 6 and 12 months postoperatively to seek an association between fentanyl dosage and long-term pain. More specifically, we asked the patients to report at-rest pain scores. Results were obtained through a telephone interview. Results showed a statistically significant difference in NRS score between Shibutani and the other dosing regimens at 6 months; more pain is experienced in patients administered fentanyl according to the Shibutani regimen.

All the above results give reason to conclude there is a significant difference between the 24-hour NRS scores of high and low dose regimens. A significant outcome also exists for 6-month pain scores between the Shibutani group and both of the other groups; this showed less favourable results for the Shibutani regimen. Patients administered the lowest total intraoperative dose of fentanyl reported higher pain scores at 24 hours. However, the Shibutani group appeared to once again experience the most discomfort further down the line.

When we convert postoperative analgesics to the equipotent dose of morphine (via a predetermined conversion factor) and add these up per randomisation group, patients in the Shibutani group received the highest total dose of opiates (remifentanil, oxynorm, dipidolor and tradonal) (38). This group also reported the highest long-term pain score.

9. Safety

SAE Overview				
Subject ID	*Study Arm (if applicable)*	*SUSAR (Y/N)*	*SAE Description*	*Outcome (ongoing, resolved, death, ...)*
25		*N*	*Sudden onset ventricular fibrilation and epilepsy. Negative coronaro and CT brain. No further events. Probably unrelated to study protocol.*	*resolved*
40	*High Dose*	*N*	Postoperative bleeding after CABG	*resolved*
40	*High Dose*	*N*	Postoperative cardiogenic shock	*death*

All SAE's were reported within the timelines as mentioned in the latest approved protocol to the sponsor.

10. Device deficiencies

Not applicable.

11. Protocol deviations

To the best of my knowledge (M Vandenheuvel), no protocol deviations occurred. This has to be checked with the study nurse, which is currently not available.

12. Discussion and overall conclusions

Results are not entirely consistent with what was expected from previous studies. We predicted higher postoperative pain scores in the groups that received the high bolus of fentanyl but this result could not be reproduced. Yildrim et al. demonstrated a significant difference in postoperative pain between a high and low dose group, specifically on days 1 and 3. The doses in Yildrim's study differed significantly from those used in this study. Yildrim's high dose group received 40-70 µg/kg fentanyl; the low dose group, 2 µg/kg. In both cases, the initial bolus was followed by continuous fentanyl infusion. Our study concerned lower doses of fentanyl in accordance with current clinical practice. Even so, our study is one of the few (besides Yildrim et al.) to look for an association between fentanyl and hyperalgesia. Remifentanil is not the only opiate linked to hyperalgesia. Fechner et al. similarly studied the effect of low and high dose intraoperative opiates, in their case sufentanil, on pain and hyperalgesia in patients after CABG. Primary endpoints were cumulative postoperative morphine consumption, pain score during deep inspiration, primary hyperalgesia and mechanical hyperalgesia via pin-prick test. A significant disparity was found between the two dosing regimens and postoperative morphine use. Increased morphine consumption was recorded in the high dose group. Pain scores on the day of surgery were lower in the low dose group. Hyperalgesia was measured in all patients on the second and third postoperative day; no significant difference between the two groups was found. This study illustrates how objectifying hyperalgesia or differentiating between acute and chronic pain is far from evident.

The mechanism of chronic poststernotomy pain is complex and has not, to date, been described in detail. We also know pain and hyperalgesia correlate poorly and require different lines of treatment. As has already been described, hyperalgesia leads to an increase in pre-existing pain and pain sensitivity, as well as the onset of chronic pain in the long term. This has implications for treatment, as pain is often managed with opioids. However, in the case of opioid-induced hyperalgesia, opioids can make the pain worse. This is illustrated by the increasing focus on drugs that affect the central nervous system postoperatively (e.g. ketamine, pregabalin and gabapentin). It is often difficult to distinguish between hyperalgesia and pain. Mauermann et al. were able to differentiate the two forms of pain during their research. This research implemented intradermal electrical stimulation and cold application to the skin.

It should also be noted that during the first hours in intensive care, our patients received a propofol-remifentanil infusion as postoperative sedation. The quantity of remifentanil varied from patient to patient and was titrated to effect. Longer periods of sedation are sometimes necessary; these patients receive a higher total dose of remifentanil. The results might indicate the postoperative administration of remifentanil alone could be a cause of hyperalgesia rather than intraoperative fentanyl.

It is also important to mention that data obtained via telephone interview was not conclusive. Communication by telephone could produce unreliable results; many patients seemed to find the reporting of a specific pain score difficult, or the pain scale itself was misinterpreted. Pain is an extremely subjective sensation and remains difficult to objectify despite the development of validated tools (NRS score). Registering patient requests for pain relief can act as an important indicator and help to create a more objective picture.

Our results cannot demonstrate a statistically significant difference in hyperalgesia between the different dosing regimens at 24 and 48 hours postoperatively. Perhaps our technique lacked finesse in its measurement of hyperalgesia. This was often complicated by the presence of dressings and drains, etcetera. Analysis also failed to take sufficient account of the additional need for pain relief (oxynorm, dipidolor or tradonal) in the intensive care unit and on the ward. We can consider these factors to be weaknesses.

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. 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.

This is one of a small handful of studies that investigates the link between fentanyl and hyperalgesia, with the added attraction of a study population of 64 patients selected in advance via well-defined inclusion and exclusion criteria. All patients underwent the same standardised procedure and, on the whole, followed the same postoperative clinical pathway. Our study emphasised the importance of an anaesthesia protocol for cardiac surgical procedures. Selection bias was avoided through sealed envelope randomisation. This was in effect a triple-blind study; patients, treating physicians and researchers were unaware of the allocated intervention.

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