A randomised clinical trial evaluating the effect of remifentanil vs fentanyl during cardiac surgery on the incidence of chronic thoracic pain.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41643

Source
ToetsingOnline

Brief title
REFLECT

Condition

- Other condition

Synonym
chronic thoracic pain ; chronic pain on chest

Health condition

chronische thoracale pijn

Research involving

Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: chronic thoracic pain, fentanyl, remifentanil, sternotomy

Outcome measures

Primary outcome

Primary endpoints:

- The percentage of patients reporting chronic thoracic pain one year after cardiac surgery.

Secondary outcome

- The percentage of patients reporting chronic thoracic pain three months and six months after cardiac surgery

- The mean NRS score of patients with chronic thoracic pain three months and six months after cardiac surgery.

- The quality of life (QoL) three months, six months and one year after surgery.

- The difference in postoperative pain thresholds three days and one year after cardiac surgery compared to the preoperative pain threshold (baseline)

- The difference in pain variability preoperative, three days postoperative and one year after cardiac surgery.

- The prevalence of increased pain variability in patients with chronic pain one year after cardiac surgery.

- The use of analgesics three months, six months and one year after cardiac

surgery.

- The percentage of patients with at least one NRS-score of >= 4 at rest during ICU and hospital stay

- The mean NRS per patient at rest during ICU stay

- The required amounts of analgesics (morphine/paracetamol) during hospital stay

- Length of ICU and hospital stay

- Total administered amount of remifentanil and fentanyl

- Total medical costs during one year, including costs of hospitalization days (ICU and non-ICU) and costs of medications

- Productivity costs during one year (i.e., foregone paid and unpaid work and reduced productivity while at work)

- Cost-effectiveness, expressed as incremental costs per case of chronic pain at 12 months after cardiac surgery avoided and incremental costs per quality-adjusted life-year (QALY) gained

- Safety parameters of remifentanil; such as nausea, constipation, respiratory depression, duration of ventilation, hallucinations, delirium, Glascow Coma Scale, renal function)

- Genetic variances involved in pain sensitivity (e.g. GCH-1, WDF-4, ZNF, MC1R) and pharmacokinetics and pharmacodynamics of opiates (e.g. UGT, MRP, OPRM1, COMT)

- Biomarkers for chronic pain are investigated, with a special focus on endogenous pain modulation and beta-endorphins.

Study description

Background summary

Chronic thoracic pain after cardiac surgery via sternotomy is a serious condition affecting many patients. Recent studies report incidences one year after surgery varying from 11% to 56%(1-6), depending on the definition and the study population. Patients suffering from chronic thoracic pain experience a significantly lower physical and mental health status compared with patients without chronic thoracic pain.(1,5,7,8) Since 2006, in the Intensive Care Unit (ICU) of the St. Antonius Hospital, efforts were made to improve postoperative pain management in patients after cardiac surgery (9,10). As part of this research, a follow-up study (11) was performed including cardiac ICU patients, in order to identify predictors for the development of chronic thoracic pain one year after cardiac surgery. In this study, intraoperative use of remifentanil appeared to be a major predictor for chronic thoracic pain.(11) This association appeared to be dose dependent.
The association between the use of remifentanil and the development of chronic pain was also suggested in a prospective, non-randomised study (12) designed to evaluate allodynie after thoracotomy. Furthermore, it is suggested that higher intraoperative remifentanil consumption correlates with an increase in early postoperative hyperalgesia(13-15), which may eventually lead to the development of chronic thoracic pain. It is unknown whether this development of postoperative hyperalgesia is related to changes in pain thresholds.
Nowadays, in the St. Antonius Hospital the use of remifentanil or fentanyl depends on the attending anaesthetist. No randomised controlled trials are yet available evaluating the influence of intraoperative remifentanil during cardiac surgery on the incidence of chronic thoracic pain. In this clinical trial, the effect of the intra-operative use of remifentanil versus fentanyl during cardiac surgery on the development of chronic thoracic pain will be investigated. Within this context, it is of interest to investigate pain thresholds pre- and postoperatively using quantitative sensory testing, in order to evaluate changes in pain sensitivity of the patient due to cardiac surgery or intraoperative use of remifentanil. Also, the role of pain biomarkers measured with metabolomics will be investiged as well as the influence of genetic variances involved in pain sensitivity and in pharmacokinetics and pharmacodynamics of opiates. The results of this randomised trial may be used to optimise perioperative options and thereby improve the quality of life of patients after cardiac surgery.
Bearing in mind the increasing pressure on health care budgets and the growing interest in cost-effective and evidence-based health care, this study will analyze the cost-effectiveness of remifentanil versus fentanyl. The cost-effectiveness of remifentanil in cardiac surgery patients has hardly been studied before, so it can only be speculated upon whether it provides good value for money.

Study objective

The primary objective of this study is to determine the influence of intra-operative use of remifentanil versus fentanyl on the percentage of patients with chronic thoracic pain one year after cardiac surgery.

The secondary objectives are to evaluate the influence of intra-operative use of remifentanil versus fentanyl on the percentage of patients with chronic thoracic pain and their mean NRS scores (pain score 0-10 using the Numeric Rating Scale) three months and six months after cardiac surgery. Also, the effect on the quality of life (QoL) and the use of analgesics three months, six months and one year after surgery will be evaluated. Moreover, total administered amount of remifentanil and fentanyl will be taken into account. Furthermore, pain thresholds and variability in pain scoring will be measured, evaluating the difference in postoperative pain threshold (three days and one year after surgery) compared to preoperative pain threshold (baseline), using quantitative sensory testing.
Also other aspects in the postoperative period will be investigated, such as postoperative NRS scores, postoperative analgesics consumption (e.g. paracetamol, morphine), length of ICU- and hospital stay, and safety parameters of remifentanil, such as nausea, rigidity of skeletal muscles, hypotension, constipation, respiratory depression, duration of ventilation, hallucinations, delirium and Glascow Coma Scale. In addition, the influence of different genetic variances (e.g. COMT, UGT, GCH-1, MC1R) involved in pain sensitivity and involved in pharmacokinetics and pharmacodynamics of remifentanil, fentanyl and morphine are evaluated. In addition to genetic research, biomarkers for chronic pain are also investigated with the help of metabolomics. Metabolomics is an emerging approach and used as a novel approach do research in the field of biomarkers. Finally, with the aim of demonstrating whether the effects of remifentanil are worth the costs, a cost-effectiveness analysis alongside the randomised controlled trial (RCT) with a 12 month follow-up will be performed.

Study design

Prospective, randomised, single-blind clinical trial

Intervention

126 patients will be randomised into two groups before cardiac surgery.
During cardiac surgery, group A will be given remifentanil, starting with 0.15 ug/IBW(kg)/min, next to fentanyl bolus (200 - 500 ug) injections on predetermined times; before incision, at sternotomy, at aorta canulation and at opening of the pericard.
Group B will be given fentanyl bolus injections on an *as needed* base, next to the fentanyl bolus injections on predetermined times. Both interventions are

daily practice in the St. Antonius Hospital.

Study burden and risks

Participation in this study has minimal burden and risks for the patient as both treatment options (remifentanil or fentanyl) are considered daily practice in our hospital. Nowadays the choice between these two treatment options depends on the attending anaesthetist.
The questionnaire considering chronic pain and quality of life (appendices I and J) may be a burden to the patient, because they are time-consuming.
The amount of blood taken from the patient during hospitalization for this study is eight millilitres once after induction of the cardiac surgery. These amounts are not expected to influence the recovery of the patient. This blood sample is taken from an existing arterial line, so no invasive interventions are therefore needed. The second blood sample, also eight millilitres is taken one year after surgery when patients are fully recovered. All the other procedures are part of the standard care.

Pain thresholds will be measured one day before surgery, three days and one year after the surgery. This may be a burden to these patients. Although the measurements are non-invasive and are also successfully used in children(16), they are time-consuming.(17,18) Analyzing pain thresholds (cold detection limit, warm detection limit, cold pain threshold, hot pain threshold) and measuring pain variability using quantitative sensory testing takes about 40 minutes per patient.(19)The third pain threshold measurement will be done one year after surgery. Most patients will be visiting the St. Antonius Hospital one year after surgery for routine check. So only for few patients an extra hospital visit one year after surgery is required for measuring pain thresholds. Therefore, only patients from region Utrecht and surroundings will be asked to participate the REFLECT-trial; in case an extra hospital visit is required for measuring pain thresholds one year after surgery, the time needed to travel to the hospital will be acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All patients living in Utrecht and surroundings undergoing cardiac surgery via sternotomy, including a CABG and/or valve replacement, admitted to the ICU or PACU in the St. Antonius hospital, between 18 and 85 years old, weighing between 45 and 140 kg, written informed consent.

Exclusion criteria

- Pregnancy/ breastfeeding
- Language barrier
- History of drug abuse
- Neurologic condition such as peripheral neuropathy
- Known morphine or paracetamol allergy
- BMI groter dan 35 kg/m2
-Prior cardiac surgery (sternotomy)
-Chronic pain conditions

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-02-2014
Enrollment:	126
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fentanyl 100 ug = 2 ml
Generic name:	Fentanyl 100 ug = 2 ml
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fentanyl 500 ug = 10 ml
Generic name:	Fentanyl 500 ug = 10 ml
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remifentanil 2 mg
Generic name:	Remifentanil 2 mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	30-05-2013

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-000201-23-NL
ClinicalTrials.gov	NCT02031016
CCMO	NL43076.100.13