INFORMATION NOTE FOR PATIENTS PARTICIPATING IN THE RESEARCH

Title of the research involving a human being**: Opioid Free Anesthesia in cardiac surgery – OFACS study**

N° EUDRACT: 2020-002126-90

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Authorization from the ethics committee CPP OUEST II – ANGERS on the 5th February 2021

Authorization from the national agency for security of drugs and medical products (ANSM) on the 9th march 2021.

Madam, Miss, Sir,

Your physician, Professor/Doctor _____, is inviting you to take part in a research protocol entitled “Opioid-free anesthesia in cardiac surgery - OFACS study”, sponsored by Rouen University Hospital.

The aim of this information note is to explain as openly and clearly as possible all the different aspects of this clinical trial, so that you can decide whether or not to take part.

Rational for this trial

Your physician has asked you to take part in this study because you are about to undergo cardiac surgery involving coronary artery bypass grafting.
General anesthesia is essential for cardiac surgery, and for several decades has been based on a combination of hypnotics, major opioids and muscle blockers. Among these, opioids help to limit the pain signal during surgery, so as to limit reactions on the cardiovascular system. Although you are not conscious during the procedure, and therefore cannot feel the pain directly, over-stimulation of the nerve fibers conveying pain can lead to damaging cardiac and vascular reactions during the operation. Despite the beneficial effects of opioids on pain control, these drugs have potentially harmful post-operative side-effects: respiratory depression, which can lead to oxygenation failure, slowed digestive transit, cognitive disorders and even increased pain after surgery (hyperalgesia).
The use of a strategy aimed at reducing the need for opioids, or even doing without it, could therefore be beneficial after major cardiac surgery. To this end, several drugs exist and are commonly used in anesthesia:

- intravenous lidocaine, used to reduce pain after certain types of painful surgery

- dexmedetomidine, which controls the cardiovascular effects of the pain signal and has already been shown to have a beneficial effect on cognition after cardiac surgery.

Thus, the use of a general anesthesia without opioids could be beneficial in cardiac surgery patients on complications attributable to these drugs.

Objective of the trial

The aim of this trial is to evaluate the impact of an opioid-free anesthesia strategy on certain major complications after cardiac surgery, compared with a traditional strategy involving opioids
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Design of the trial

The trial is taking place in four hospitals in France, and we plan to include 268 patients over a total period of 3 years. Inclusion will take place during the pre-anesthetic visit. Each patient will then be medically monitored for 7 days, including follow-up visits with a physician. Information on the patient's state of health at discharge, or at a maximum of 45 days after inclusion, will be collected from the medical record. A telephone call will be made at 90 days post-inclusion to ask about your post-operative state of health.

Patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass are eligible to participate in this trial. Affiliation to a social and health insurance plan is required to participate in this trial.

Patients with contraindications to drugs used in this trial, chronic treatment with opioids, morbid obesity, cardiac conduction disorders, severe heart failure, prior oxygen therapy or respiratory pressure support, recent coronary suffering or shock cannot take part in this trial. Pregnant or breast-feeding women, or persons deprived of their liberty, are also ineligible. If you have just taken part in a clinical trial involving an innovative drug or procedure, you will not be able to take part in this new clinical trial within 1 month of the end of your participation in the previous trial. You will also not be able to participate in another trial at the same time.

This trial randomly selects the type of anesthetic strategy prior to surgery:
- opioid free anesthesia combining dexmedetomidine and lidocaine,
or
- opioid based anesthesia using remifentanil and morphine.

You will not be informed of the strategy chosen for your care, but your physician will be, to ensure the safety of your care. The rest of the treatment is carried out in the usual way, including other anasthetic treatments and post-operative pain management, in accordance with current guidelines. Morphine can be used in the event of severe pain after surgery, whatever the anesthetic strategy chosen.

Physicians will collect and record some of your health data for the purpose of the trial: post-operative cardiac, respiratory and digestive complications, pain, use of certain medications, duration of respiratory support, length of stay, routine laboratory tests, etc. …

A functional blood test will also be carried out outside the usual care to check for adrenal gland function. This involves checking the adrenal glands' ability to produce cortisol in response to a low-dose of the natural hormone adrenocorticotropin). To this end, 3 additional blood samples (12 mL total) will be taken at 30-minute intervals after the administration of 250 µg of adrenocorticotropin,

using the same sampling catheter used for the usual care. This test will be performed 24 hours after the end of your surgery.

Each patient in the study will be followed up until discharge from hospital, and by telephone at 90 days after inclusion.

	Anesthesia medical consultation	D0 (pre-anesthesia visit) Inclusion V1	D1 (day of surgery) V2	D2 (24 hours after surgery) V3	D3 (48 after surgery) V4	D7 V5	D45 * (or day of the hospital discharge)	D90 +/- 5 days Phone call
Patient information	✓							
Obtaining of consent		✓						
Blood tests	✓			✓	✓			
Blood pregnancy test		✓						
Validation of inclusion and non-inclusion criteria		✓						
Randomization			✓					
Adrenocorticotropin stimulation test				✓				
Pain evaluation			✓	✓	✓	✓		✓
Troponin				✓	✓			
Cognition evaluation				✓	✓	✓		
Duration of respiratory support			✓	✓	✓	✓	✓*	
Duration of vasopressor support			✓	✓	✓	✓	✓*	
Digestive transit				✓	✓			
Acute kidney failure				✓	✓			
Pulmonary complications				✓	✓		✓*	
Total length of hospital stays							✓*	
Mortality							✓*	

Expected beneficial effects

The expected benefits are a reduction in the major complications associated with the use of opioids: less respiratory failure, digestive ileus and cognitive impairment.

Expected risks

The foreseeable risks are complications specific to the study drugs.

- Dexmedetomidine exposes the patient to the risk of decreased or accelerated heart rate, which is resolved in the vast majority of cases by dose reduction or administration of a heart rate stimulating drug (atropine). Exceptionally, cases of transient blockade of electrical activity at high doses have been described, which resolved spontaneously. Intraoperative hypertension may occur, treatable by dose reduction and antihypertensive medication. These effects are short-lived and resolve by the end

of surgery at the latest. Similarly, dexmedetomidine may cause variations in blood glucose levels, diabetes insipidus (excessive production of urine while blood glucose levels remain unchanged), hallucinations, reduced respiratory rate and nausea or vomiting. These effects disappear when treatment is stopped, which will be the case in this study before you wake up in the intensive care unit. It is therefore unlikely that you will experience these effects. Dexmedetomidine is also widely used in anesthesia and intensive care for patient comfort.

- Lidocaine is not associated with any expected excess risk at the doses used in this study. Side effects have been described in the event of overdosage (nervousness, agitation, headaches and other neurological signs; acceleration or reduction of respiratory and cardiac rhythm, cardiac rhythm disorders). Lidocaine at the doses proposed in this study is commonly used in anesthesia for digestive surgery and has not been associated with overdose.

- Remifentanil is a powerful opioid used daily in anesthesia. Its side effects are those typical of opioids: irregular heartbeat, decrease in heart rate, resolvable in the vast majority of cases by dose reduction or administration of atropine, even transient block of electrical activity at high doses, arterial hypotension and decrease in respiratory rate, cough, nausea and vomiting after surgery. These effects are rapidly reversible when treatment is stopped before you wake up. It is therefore unlikely that you will experience these effects.

Medical alternatives

If you decide not to take part in this trial, or if you voluntarily or on the decision of the physician interrupt your participation, you will be offered the reference treatment usual in your case corresponding to the anesthetic strategy with opioids (remifentanil + morphine or sufentanil).

You are free to interrupt your participation at any time. You will then be able to discuss the most appropriate treatment for your personal situation with your physician.

What are your rights?

Your physician must provide you with all the necessary explanations concerning this trial. If you wish to withdraw your consent at any time, for whatever reason, you will continue to benefit from medical monitoring and care.

In accordance with the provisions of the French Data Protection Act and the European General Data Protection Regulation Act of May 25, 2018, you have the following rights at any times:

- **A right of access**
You have a right to information about your personal data collected, processed or, where applicable, transmitted to third parties (Article 15 of the general data protection regulation European law).
- **A right of rectification**
You have the right to request the correction of incorrect personal data concerning you (Articles 16 and 19).
- **A right to deletion**
You have the right to request the deletion of personal data concerning you. For example, if this data is no longer necessary for the purposes for which it was collected (Articles 17 and 19).
- **A right to restrict processing**
Under certain conditions, you have the right to request a processing limitation. In this case, your data may only be stored but not used for the processing, except with your consent (Articles 18 and 19).
- **A right to oppose processing**

You have the right to oppose to the processing of your personal data at any time (Article 21). Processing will then be stopped by the sponsor on the date on which you notify.
However, all data previously collected to the opposition, erasure request or limitation request may be processed if necessary.

These rights may be obtained from the physician who is treating you as part of the trial, and who is aware of your identity.

Your medical data collected for the study will be pseudonymized, i.e. you will be identified by a code number for the purposes of the research, with no mention of your full name. This data will be kept for 25 years by the trial sponsor.

Your participation in this research is voluntary and you are under no obligation to take part. This will in no way affect your relationship with the physician treating you or with the medical team. If, during the course of the trial, new information becomes available that could modify the interest of the trial, the physician in charge of the trial will inform you of this and will ensure that you wish to continue to take part.
You may stop participating in this protocol at any time. The investigating physician in charge of this trial may also decide to remove you from the trial if he or she deems it necessary, in particular for your well-being.
Your participation will not entail any additional costs for you.
Moreover, if you wish, you may be informed of the results obtained at the end of the trial.

Once you have read this information note, do not hesitate to ask your physician any questions you may have. After a period of reflection, if you agree to take part, you must complete and sign the consent form. A copy of the complete document will be given to you.

We thank you for your cooperation.

Further information about this clinical trial can be obtained from the physician who suggested you take part,

Dr/Pr _____
Adress _____
_____
_____
Téléphone : _____

Or

Medical coordinator Pr Emmanuel Besnier Département d'Anesthésie-Réanimation Hôpital Charles Nicolle CHU de Rouen 1, rue de Germont, 76031 ROUEN Cedex Tél. : 02 32 88 82 83, Fax : 02 32 88 83 26	**Sponsor** Hôpital Charles Nicolle - CHU de Rouen Direction à la Recherche Clinique et à l'Innovation Maison de la Recherche Clinique 1, rue de Germont, 76031 ROUEN Cedex

CONSENT FORM FOR
TO THE PATIENT TAKING PART IN THE TRIAL
OPIOID FREE ANESTHESIA IN CARDIAC SURGERY
OFACS TRIAL – 2019/0399/HP

Sponsor: CHU de Rouen
Medical coordinator: Pr Emmanuel BESNIER

I the undersigned _____ (Surname, first name) certify that I have read and understood the information note concerning the clinical trial entitled "Opioid-free anesthesia in cardiac surgery - OFACS trial".

I had the opportunity to ask any questions I felt would help me understand the information memorandum, and to receive clear, precise answers from Professor/Doctor _____, who also explained to me the nature, objectives, expected benefits, duration of the clinical trial and its follow-up, potential risks and constraints associated with my participation in this trial.

I understand that I am free to accept or refuse to participate in this trial.

I am aware of the possibility of interrupting my participation at any time without having to justify my decision. Naturally, this will not affect the quality of subsequent care I receive. I will then inform the investigator. I have been assured that the decisions that are necessary for my health will be taken at all times, in accordance with the current state of medical knowledge.

My consent does not relieve the investigator and the sponsor of the trial of their responsibilities towards me and I retain all my rights guaranteed by law.

I have been informed that this trial has been approved by an ethics committee (CPP OUEST II - ANGERS on 05/02/2021) and authorized by the ANSM on 09/03/2021, and has been declared to the National Committee for Information Technologies and Freedom (CNIL).

The sponsor of the trial, Rouen University Hospital, has taken out civil liability insurance in the event of damage.

I have been informed that the pseudonymized data recorded as part of this trial may be processed by or on behalf of the sponsor. I have noted that I have a right of access, information, opposition, rectification of personal data concerning me as well as a right to the limitation of processing as provided for by the CNIL (provisions of the Data Protection Act of January 6, 1978 as amended) and the European General Data Protection Regulation Act

The processing of data concerning me rests on a legal basis of a mission of public interest, so data already collected cannot be deleted. I am aware that my data will be kept for 25 years by the trial sponsor.

I may exercise these rights at any time by contacting the physician investigating my case and/or the trial sponsor, the entity responsible for data processing. I have noted that I have the right to lodge a complaint with the CNIL if I consider that the processing of my personal data has been carried out in violation of my rights. My personal data are confidential.

I am aware that the data recorded in the course of this trial may, under conditions ensuring confidentiality and a sufficient level of security, be transmitted to the French health authorities or to any other partner of the sponsor in France.

My attention has been drawn to the fact that the data recorded in the course of this trial may be used in subsequent research for scientific purposes only.

I have noted that my medical file will be consulted by the promoter's trial staff, who are bound by professional secrecy, and that the persons collaborating in this research or mandated by the sponsor, as well as any representative of the Health Authorities, may have access to the information in strictest confidence.

The overall results of the research will be communicated to me directly, on my request.

I may at any time request further information from the Professor/Doctor _____ (tel.: _____) who suggested that I take part in this trial.

Given sufficient time to consider my decision, I freely and voluntarily agree to take part in the OFACS trial and I do not object to the processing of my personal data.

The |__|__| |__|__| 2 0 |__|__|	The |__|__| |__|__| 2 0 |__|__|
Trial participant	**Physician**
Name and Surname Signature	Name and Surname Signature