Part I: Trial related part of the protocol

1 Title of the trial

Comparison of pain and comfort in patients following cardiac surgery: Opioid- morphine managed versus multimodal pain-management.

Short title: **M**utimodal versus **O**pioid a**N**algesia in car**D**i**A**c surgery**: MONDAY-study**

2 Trial number

Protocol: AGO/2018/

EudraCT number

Clinical trial number

3 Objective of the study

To compare standard "Fentanyl – Tramadol – Paracetamol – Oxycodon" regimen to a multimodal painmanagement "pregebaline- minimal fentanyl-ketamine-lidocain-dexmedetomedine-paracetamol" to determine which therapy provides the most comfort, the fastest extubation time, the least pain and the least delirium.

4 Primary endpoints

4.1 Primary Endpoint

The primary endpoint of this study is postoperative pain (at rest, when coughing and at movement) at 8-h, 16-h, 24-h, 32-h, 40-h and 48-h after cardiac surgery. Pain is measured by a NRS-scale if the patient is awake, and by the Critical-Care Pain Observation Tool(CPOT) in the sedated patient.

4.2 Secondary Endpoints

Secondary endpoints include delirium in the direct postoperative phase measured by the ICDSC-score. Also included in the secondary endpoints are: time till extubation, length of hospital stay, length of stay at the ICU department and total consumption of pain medication registered in mg/kg.

4 General information

Investigators

Dr. Simon Bogaert

Dr. Harlinde Peperstraete

Dr. Annelies Moerman

Dr. Stefaan Bouchez

Dr. Wim Vandenberghe

Dr. Ingrid Herck

Sponsor

Ghent University Hospital

Departments involved in the study

Department of Anesthesia

Intensive Care Unit

5 Introduction

Cardiac surgery for the adult, performed by sternotomy is associated with moderate to severe acute postoperative pain. Postoperative pain is the primary reason for prolonged convalescence [2] and one of the main concerns of the surgical patient in the ICU department. This pain is multifactorial and multifocal; and can be caused by incision, intraoperative tissue retraction and dissection, surgical manipulation of the parietal pleura, posterior rib dislocation or fracture, possible brachial plexus injury, chest tube insertion and harvesting of the saphenous vein and internal mammarian artery. (1-3)

The most common analgesic schemes for postoperative pain in cardiac surgery are based on intravenous opioids by bolus, with patient- or nurse-controlled delivery systems. Although there is no doubt they have a beneficial effect on pain, opioids are associated with dose-related side effects including “over”sedation, ileus, urinary retention, nausea, vomiting, pruritus, mental confusion and respiratory depression leading to a prolonged extubation time. (1, 3, 4)

In the last decades many has been written about the value of multimodal pain protocols to treat acute postoperative pain in non-cardiac surgery. This is not only to reduce the dose and side effects of opioids. By blocking both the central and peripheral pain mechanisms the aim is to find a holy grale, by which the patient suffers the least, by which central neural hyper-excitability that increases postoperative pain is minimized (3, 5) and by which the transformation of acute into chronic pain is reduced to a minimum.

Pregabalin has his role in treating various neuropathic pain syndromes. It inhibits central neuronal sensitisation and prevents hyperalgesia by decreasing excitatory amino acid neurotransmission in the spinal cord through a direct postsynaptic or presynaptic inhibition of Ca^{2+} influx. It has been shown that gabapentin reduced pain scores and opioid requirements in different surgical settings. (3, 6-8) Literature is not conclusive and because of conflicting results the routine use of gabapentin and pregabalin to reduce opioid consumption in the cardiac surgical patients is not yet recommended.(6, 8)

Dexmedetomedine is an alpha-2 adrenergic receptor agonist that can be directly applied to the peripheral nervous system, causing a dose-dependent inhibition of C-fibers and Aα-fibers(1, 9). It is widely used for sedation and anxiolysis in ICU settings. The clinical efficacy has been proven in non-cardiac surgery by augmenting anesthesia and analgesia, and allowing a reduction in opioid requirements.(1) Additionally, there was a significantly lower incidence of postoperative delirium.(1, 10, 11)

Ketamine isn't only an anesthetic agent but also has an analgesic effect. The exact mechanism is not yet known but some of the pathways are already identified.(12) It binds to the opioid receptors κ(kappa) δ(delta) μ(mu) and it was proven that ketamine induces phosphorylation of mitogen-activated protein kinases by 2–3 times that of traditional opioid drugs.(10, 13) Another way of producing its analgesic effect is by the muscarinic acetylcholine receptors in the central nervous system.(10) Ketamine also effects other ion channels including sodium channels and voltage sensitive calcium channels leading to local anesthetic and gabapentin like effects.(12) Because of the unique effect of keeping hemodynamic stability during induction, ketamine can be useful in cardiac surgery. The analgesic effect, the absence of respiratory depression and hemodynamic stability make it an excellent drug to use in the ICU. (12)

Intravenous lidocaine during the perioperative period has many beneficial effects in open procedures, such as an earlier return of gastrointestinal tract function, less postoperative opioid consumption, improvement of postoperative cognitive dysfunction and reduced stay in the hospital.(8, 14, 15) The exact working mechanism isn't 100% identified but the anti-inflammatory effects of LA mediated through interactions with polymorphonuclear cells and the inhibition of G protein-coupled receptors may play a crucial role for the observed effects in the perioperative setting.(15)

Magnesiumsulfate's analgesic mechanisms are also not fully identified, but it is thought that the NMDA receptor is blocked by calcium regulation mechanisms. Because the NMDA receptor plays a role in the transmission of pain, magnesium has become a subject of interest as potential use in postoperative painschemes.(16, 17) It was proven that peri-operative intravenous magnesium can reduce opioid consumption especially in the first 24h.(17)

Our goal is to compare standard "Fentanyl – Tramadol – Paracetamol – Oxycodon" regimen to a multimodal painmanagement "pregabalin- magnesiumsulfate - minimal fentanyl-ketamine-lidocain-dexmedetomedine- paracetamol" to determine which therapy provides the most comfort, the fastest extubation time, the least pain and the least delirium.

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6 The present study

Study design

Prospective randomised double-blinded (for participant and study staff) study

Medication, producer administration route and dosing

Classic protocol

Medication	Dose	Route	Time of administration
Fentanyl	Max. 15µg/kg	IV	Per-op
Ultiva (Remifentanyl)	0.02-0.1µg/kg/h	IV	Post-op
	4x1g /24h	IV	Post-op
Tradonal (Tramadol)	100mg IV 4/d	IV	Post-op (Break through pain)
Oxynorm (Oxycodon)	5-10mg 4-6/d	PO	Post-op (Break through pain)
Paracetamol	4x1g /24h	IV	Post-op

Multimodal protocol

Medication	Dose	Route	Time of administration
Lyrica (Pregabalin)	75mg	PO	Pré-op
Dexdor (Dexmedetomidine)	0.8µg/kg/h	IV	Per-op / Post-op
Ketalar (Ketamine)	Bolus (0.5mg/kg) + 0.3mg/kg/h	IV	Per-op until stop propofol
Linisol (Lidocaïne)	Bolus (1.5mg/kg) + 1.3mg/kg/h	IV	Per-op until 12h post-op
Magnesium Sulfate	Induction (25mg/kg) + 25mg/kg weaning ECC	IV	Per-op
Fentanyl	2.5µg/kg	IV	Per-op
Paracetamol	4x1g /24u	IV	Post-op
Tradonal (Tramadol)	100mg IV 4/d	IV	Post-op (Break through pain)
Oxynorm (Oxycodon)	5-10mg 4-6/d	PO	Post-op (Break through pain)

Distributor

Pharmacy department, Ghent University Hospital

Packaging

Commercially available packaging

Labelling

Following the rules of both the department of Anesthesia and Intensive Care Unit. In case of tablets packaging is double: the commercially available monopackage is found in little tear-off plastic bags, produced by the pharmacy department of Ghent University Hospital.

Storage conditions

All medication will be stored by the general recommendations of the pharmacy department of our hospital.

Known side effects of the medication

The frequency of possible side effects , is defined by using the following terminology.

Very common	May affect more than 1 in 10 people
Common	May affect up to 1 in 10 people
Uncommon	May affect up to 1 in 100 people
Rare	May affect up to 1 in 1000 people
Very rare	May affect up to 1 in 10000 people
Not known	Frequency cannot be estimated from available data

1. Fentanyl 50micrograms/ml Solution for Injection/Infusion

Like all medicines, this medicine can cause side-effects, although not everyone gets them. All medicines can cause allergic reactions although serious allergic reactions are rare. Any of the following side effects should be reported to a doctor immediately:

Not known (frequency cannot be estimated from available data):
- any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Other side effects:

Very common (may affect more than 1 in 10 people):
- feeling sick (nausea), being sick (vomiting),
- muscle stiffness (which may involve your chest muscles).

Common (may affect up to 1 in 10 people):
- involuntary, repetitive body movements
- drowsiness
- dizziness
- problems with vision
- rapid or slow heartbeats
- low or high blood pressure
- pain in your veins
- choking caused by cramping (spasm) of the muscles in your throat
- difficulty in breathing or wheezing
- stop breathing for a short period of time (apnoea).
- skin rash
- confusion after the operation.

Uncommon (may affect up to 1 in 100 people):
- changes in blood pressure
- breathing complications
- breathing faster than normal
- fall in body temperature below normal or chills
- headache
- swelling and clotting in a vein
- hiccups
- mood elevation
- agitation after operation.

Not known (frequency cannot be estimated from the available data):
- convulsions (fits or seizures)
- loss of consciousness
- muscle twitching
- stopping of the heart (cardiac arrest)
- slow or shallow breathing
- itching of the skin
- unusual increase in sense of smell, taste, touch, feel (e.g. feel of pain) or hearing
- cough
- constipation.

If you received Fentanyl Injection/Infusion with a tranquiliser (such as droperidol) and you notice any of the following effects, tell your doctor:
- shivering and restlessness
- seeing or hearing things that aren't there (hallucinations)
- unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, shuffling walk and stiffness of the arms and legs.

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine

2. Remifentanyl (ULTIVA® 2g) for Injection:

Like all medicines, Ultiva can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Some people can be allergic to Ultiva. **You must tell your doctor or nurse immediately if you have**:
Rare (may affect up to 1 in 1,000 people)
- sudden wheeziness and chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- a lumpy skin rash or 'hives' anywhere on the body
- collapse.

Tell your doctor **as soon as possible** if you notice any of the following:
Very common (may affect more than 1 in 10 people)
- muscle stiffness
- low blood pressure
- feeling sick or being sick

Common (may affect up to 1 in 10 people)
- slow heartbeat
- shallow breathing or temporarily stop breathing
- itching

Uncommon (may affect up to 1 in 100 people)
- problems breathing (hypoxia)
- constipation

Rare (may affect up to 1 in 1,000 people)
- allergic reactions
- heart stops beating

Not known (frequency cannot be estimated from the available data)
- physical need for Ultiva *(drug dependency)* or the need for increasing doses over time to get the same effect *(drug tolerance)*
- fits (seizures)
- a type of irregular heartbeat *(atrioventricular block)*

Other side effects that can happen when you wake up after having an anaesthetic include:
Common (may affect up to 1 in 10 people)
- shivering
- increases in blood pressure

Uncommon (may affect up to 1 in 100 people)
- aches

Rare (may affect up to 1 in 1,000 people)
- feeling very calm or drowsy (sedation)

Other side effects which occurred particularly upon abrupt cessation of Ultiva after prolonged administration of more than 3 days
- heart beating faster *(tachycardia)*
- high blood pressure *(hypertension)*
- restlessness *(agitation)*

3. Paracetamol 10mg/ml Solution for Infusion

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following may occur:

Rare side effects, may affect up to 1 in 1,000 people
- a drop in blood pressure
- abnormally high levels of liver enzymes found during blood checks. Regular blood checks may be required.
- feeling generally unwell and run down.

Very rare side effects, may affect up to 1 in 10,000 people
- a serious skin rash or allergic reaction. **Stop the treatment immediately and inform your doctor**. Signs of allergic reactions may be skin redness, flushing, itching and abnormally rapid heart rate, sudden difficulty in breathing, speaking or swallowing, feeling dizzy, sick or faint, or experiencing dizziness when standing up.
- abnormally low levels of some types of blood cells (platelets, white blood cells), possibly leading to bleeding from the nose or gums. Your doctor may have to check your blood regularly.
- local reactions (such as pain and burning sensation) at the injection site.

Very rare cases of serious skin reactions have been reported.

4. TRAMADOL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

Like all medicines, Tramadol Injection can cause side effects. However, do not be alarmed, as most patients do not have problems with this medicine.

Tell your doctor or a nurse immediately if you experience any of the following:

- swelling around the throat, tightness in your chest or difficulty in breathing.

You may have had an allergic reaction, these are rare but, if severe, can be serious and you may need urgent medical attention.

Tell a doctor or nurse if you get any of the following other side effects:

Very common side effects (occurring in more than 1 in 10 patients):

- nausea, dizziness.

Common side effects (occurring in less than 1 in 10 patients):

- headache, drowsiness, fatigue
- vomiting, constipation, dry mouth, sweating.

Uncommon side effects (occurring in less than 1 in 100 patients):

- changes in heart beat or rhythm which may make you feeling faint or dizzy especially if you stand up quickly
- retching, stomach irritation or feeling bloated
- diarrhoea
- rash.

Rare side effects (occurring in less than 1 in 1000 patients):

- changes in appetite, abnormal touch sensations, trembling, difficulty breathing, fits, fainting, speech disorders
- slowing of the heart rate, increased blood pressure
- nightmares, disturbed sleep patterns, hallucinations (seeing things), feeling confused, changes in mood, activity or awareness, anxiety, delirium
- blurred vision, excessive dilation or constriction of the pupils
- muscle weakness or twitching, abnormal coordination
- increase in liver enzymes
- difficulty or pain passing water (urine)
- worsening of asthma, shortness of breath
- Rarely when some people stop taking tramadol they get withdrawal symptoms. These symptoms include agitation, nervousness, shaking, hyperactivity and difficulty in sleeping. Very rarely panic attacks, severe anxiety, hallucinations, tinnitus or abnormal skin sensations, as well as confusion, delusions, personalisation, derealisation and paranoia, have occurred.

Other side effects (frequency unknown):

- low blood sugar levels.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.
By reporting side effects you can help provide more information on the safety of this medicine.

5. Oxycodon (OxyNorm®) 5 mg, 10 mg and 20 mg capsules

Like all medicines, these capsules can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions, although serious allergic reactions are rare. **Tell your doctor immediately** if you get any sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching especially those covering your whole body.

The most serious side effect is a condition where you breathe more slowly or weakly than expected (respiratory depression). **Tell your doctor immediately** if this happens to you.

As with all strong painkillers, there is a risk that you may become addicted or reliant on these capsules.

Very common side effects
(May affect more than 1 in 10 people)

- Constipation (your doctor can prescribe a laxative to overcome this problem).
- Feeling or being sick (this should normally wear off after a few days, however your doctor can prescribe an anti-sickness medicine if it continues to be a problem).
- Drowsiness (this is most likely when you start taking your capsules or when your dose is increased, but it should wear off after a few days).
- Dizziness.
- Headache.
- Itchy skin.

Common side effects

(May affect up to 1 in 10 people)
- Dry mouth, loss of appetite, indigestion, abdominal pain or discomfort, diarrhoea.
- Confusion, depression, a feeling of unusual weakness, shaking, lack of energy, tiredness, anxiety, nervousness, difficulty in sleeping, abnormal thoughts or dreams.
- Difficulty in breathing or wheezing, shortness of breath, decreased cough reflex.
- Rash.
- Sweating.

Uncommon side effects
(May affect up to 1 in 100 people)
- Difficulty in swallowing, belching, hiccups, wind, a condition where the bowel does not work properly (ileus), inflammation of the stomach, changes in taste.
- A feeling of dizziness or 'spinning', hallucinations, mood changes, unpleasant or uncomfortable mood, a feeling of extreme happiness, restlessness, agitation, generally feeling unwell, loss of memory, difficulty in speaking, reduced sensitivity to pain or touch, tingling or numbness, seizures, fits or convulsions, blurred vision, fainting, unusual muscle stiffness or slackness, involuntary muscle contractions.
- Difficulty in passing urine, impotence, decreased sexual drive, low levels of sex hormones in the blood ('hypogonadism', seen in a blood test).
- Fast, irregular heart beat, flushing of the skin.
- Dehydration, thirst, chills, swelling of the hands, ankles or feet.
- Dry skin, severe flaking or peeling of the skin.
- Redness of the face, reduction in size of the pupils in the eye, muscle spasm, high temperature.
- A need to take increasingly higher doses of the capsules to obtain the same level of pain relief (tolerance).
- Colicky abdominal pain or discomfort.
- A worsening of liver function tests (seen in a blood test).

Rare side effects
(May affect up to 1 in 1,000 people)
- Low blood pressure.
- A feeling of 'faintness' especially on standing up.
- Hives (nettle rash).

Frequency not known
(Frequency cannot be estimated from the available data)
- An increased sensitivity to pain.
- Aggression.
- Tooth decay.
- Absence of menstrual periods.
- A blockage in the flow of bile from the liver (cholestasis). This can cause itchy skin, yellow skin, very dark urine and very pale stools.
- Long term use of ***OxyNorm*** capsules during pregnancy may cause life-threatening withdrawal symptoms in the newborn. Symptoms to look for in the baby include irritability, hyperactivity and abnormal sleep pattern, high pitched cry, shaking, being sick, diarrhoea and not putting on weight.

6. Pregabaline (Lyrica) 75 mg hard capsules:

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people

Dizziness, drowsiness, headache.

Common: may affect up to 1 in 10 people

- Increased appetite.
- Feeling of elation, confusion, disorientation, decrease in sexual interest, irritability.
- Disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal.
- Blurred vision, double vision.
- Vertigo, problems with balance, fall.
- Dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen.
- Difficulties with erection.
- Swelling of the body including extremities.
- Feeling drunk, abnormal style of walking.
- Weight gain.
- Muscle cramp, joint pain, back pain, pain in limb.
- Sore throat.

Uncommon: may affect up to 1 in 100 people

- Loss of appetite, weight loss, low blood sugar, high blood sugar.
- Change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attack, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation.
- Changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell.
- Dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.
- Heart rhythm disturbances, increased heart rate, low blood pressure, high blood pressure, changes in heart beat, heart failure.
- Flushing, hot flushes.
- Difficulty breathing, dry nose, nasal congestion.
- Increased saliva production, heartburn, numb around mouth.
- Sweating, rash, chills, fever.
- Muscle twitching, joint swelling, muscle stiffness, pain including muscle pain, neck pain.
- Breast pain.
- Difficulty with or painful urination, incontinence.
- Weakness, thirst, chest tightness.
- Changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate aminotransferase increased, platelet count decreased, neutropaenia, increase in blood creatinine, decrease in blood potassium).
- Hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring.
- Painful menstrual periods.
- Coldness of hands and feet.

Rare: may affect up to 1 in 1,000 people

- Abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss.
- Dilated pupils, cross eyes.
- Cold sweat, tightness of the throat, swollen tongue.
- Inflammation of the pancreas.
- Difficulty in swallowing.
- Slow or reduced movement of the body.
- Difficulty with writing properly.
- Increased fluid in the abdomen.
- Fluid in the lungs.
- Convulsions.
- Changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances.
- Muscle damage.
- Breast discharge, abnormal breast growth, breast growth in males.
- Interrupted menstrual periods.
- Kidney failure, reduced urine volume, urinary retention.
- Decrease in white blood cell count.
- Inappropriate behaviour.
- Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain).
- Jaundice (yellowing of the skin and eyes).

Very rare: may affect up to 1 in 10,000 people

- Liver failure.
- Hepatitis (inflammation of the liver).

If you experience swollen face or tongue or if your skin turns red and starts to blister or peel, you should seek immediate medical advice.

Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

7. Dexmedetomidine (Dexdor) 100 micrograms/ml concentrate for solution for infusion:

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (*affects more than 1 user in 10*)
- slow heart rate
- low or high blood pressure.

Common (*affects 1 to 10 users in 100*)
- chest pain or heart attack
- fast heart rate
- low or high blood sugar
- change in breathing pattern or stopping breathing
- nausea, vomiting or dry mouth
- restlessness
- high temperature
- symptoms after stopping the medicine

Uncommon (*affects 1 to 10 users in 1,000*)
- reduced heart function
- swelling of the stomach
- thirst
- a condition where there is too much acid in the body
- low albumin level in blood
- shortness of breath
- hallucinations
- the medicine is not effective enough.

8. Ketamine (Ketalar®) 50 mg/ml INJECTION:

Like all medicines, this medicine can cause side effects although not everyone gets them.

Tell your doctor **immediately** if you notice pain, inflammation of the skin or rash at the injection site. Ketalar can sometimes cause allergic symptoms ('anaphylaxis') such as breathing problems, swelling and rash. Some people have hallucinations, vivid dreams, nightmares, feel ill at ease, confused, anxious or behave irrationally while recovering from anaesthesia with Ketalar. These side effects are collectively known as an 'emergence reaction'. You will be allowed to recover from the anaesthetic in a quiet place and this helps to prevent the reaction (see Section 3 under 'How Ketalar Injection is given').

Common: may affect up to 1 in 10 people
- the following, while recovering from anaesthesia (these are collectively known as an 'emergence reaction'): hallucinations (which may include flashbacks or floating sensation), vivid dreams, nightmares, feeling ill at ease, confused, anxious and irrational behaviour.
- unusual eye movements, increased muscle tone and muscle twitches (which may resemble 'fits' or convulsions).
- double vision.
- increased blood pressure and increased pulse rate.
- breathing more quickly.
- nausea, vomiting.
- skin inflammation/rash.

Uncommon: may affect up to 1 in 100 people
- loss of appetite, feeling anxious.
- slowing of heart rate, changes in heart rhythm.
- lowering of blood pressure.
- breathing more slowly, narrowing of the voice-box leading to difficulty in breathing.
- pain, inflammation of the skin or rash at the injection site.

Rare: may affect up to 1 in 1000 people
- allergic symptoms ('anaphylaxis') such as breathing problems, swelling and rash.
- drifting in and out of consciousness (with feeling of confusion and hallucinations), flashbacks, feeling ill at ease, sleeplessness, feeling disorientated.
- effect on the reflexes which keep your airways clear, resulting in temporary inability to breathe.
- increase in salivation.
- inflammation of the bladder and/or pain when urinating ('cystitis'). The appearance of blood in the urine may also occur.

Not known: frequency cannot be estimated from the available data
- raised pressure in the eyes.
- abnormal results to liver function tests.
- drug-induced liver injury (when taken for more than 3 days).

9. Lidocaine 1% solution for injection (Lidocaine Hydrochloride):

Like all medicines, this medicine can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are rare. Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips,

rash or itching (especially affecting your whole body) should be reported to a doctor immediately.
Lidocaine may result in abnormal amount of methemoglobin (a form of hemoglobin in blood) which may cause bluish discoloration of skin, headache, shortness of breath, malaise and fatigue.
Other serious side effects are also rare, but may occur if too much Lidocaine Hydrochloride is given or if the drug is unintentionally injected into a blood vessel.
Such reactions may include:

- changes in the rhythm and speed of the heart
- low blood pressure
- slow heart rate (less than 60 beats/minute)
- cessation of normal circulation of blood due to heart attack.
- pain at the injection site, or numbness or weakness of the muscle of the lower legs after the effects of the injection should have worn off
- temporary pain sensation at the lower back, buttocks, legs which resolves within a few days.
- numbness or tingling/paralysis of legs after administration of lidocaine in the spine.
- difficulty in passing water, problems with the frequency, consistency and/or ability to control your bowel movements (bowel dysfunction).
- loss of balance, pins and needles around the mouth, numbness of the tongue, difficulty tolerating everyday sounds (hyperacusis), ringing in the ears (tinnitus), dizziness or lightheadedness, confusion, nervousness, restless or twitching, changes in your normal mood or behavior, involuntary rhythmic muscular contractions, fits or seizures, profound state of unconsciousness (coma).
- allergic reaction to local anaesthetic e.g. a skin rash or breathlessness or collapse
- feelings of anxiety or fear
- blurred vision, double vision or temporary loss of vision
- feeling sick (nausea) or sick (vomiting)
- difficulty in breathing
- decreased rate of breathing or breathing may stop
- feeling drowsy or faint

Note: If you are having a blood test, tell your doctor, as injection of lidocaine into a muscle can increase the blood levels of an enzyme marker for muscle damage. If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

10. Magnesium sulfate 10% w/v Solution for injection or infusion:

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Seek immediate medical help if you have an allergic reaction. This includes any of the following symptoms:
- Difficulty in breathing - slow and/or shallow breathing.
- Swelling of your eyelids, face or lips.
- Rash or itching especially those covering your whole body.

The frequency of side effects is not known (cannot be estimated from the available data).

Nervous System disorders
- Feeling sick (nausea)
- Vomiting
- Drowsiness
- Feeling confused
- Coma
- Slurred speech
- Double vision

Heart problems
- Drop in blood pressure
- Flushing of the skin
- Irregular heart beats
- Heart attack
- Other effects
- Loss of the knee jerk reflex
- Muscle weakness
- Feeling thirsty
- Low blood calcium levels in pregnant women and their developing babies have been reported extremely rarely
- Low levels of calcium in your blood. (This may cause you to have pins and needles or twitching muscles)
- Vein irritation
- Tissue damage due to extravasation (medication injected or leaked outside the vein into the surrounding tissue)
- Dilatation of blood vessels

Drug accountability

Drug accountability will be documented. The batch number and expiry date of the used vials will be documented in the CRF which will be available in the trial cell of ICU.

Study subjects

Number of subjects

Each group will contain 50 subjects; in total there will be 100 subjects.

Inclusion criteria

- Patients undergoing first time cardiac surgery by median sternotomy
- Elective surgery or semi-urgent: there needs to be time to provide 8 hours before surgery the intake of pregabalin
- ≥ 18 years
- Possibility to communicate with the patient to score pain and comfort

- Signed Informed Consent, signed by subject or authorized representative, able and willing to provide written informed consent for study participation

Exclusion criteria

- Urgent surgery
- Pregnancy and lactation
- Hypersensitivity to any of the study medication
- In case of direct postoperative revision the patient is **NOT** excluded.

Replacements of subjects

Subjects, who fall out the study, will be replaced

Restrictions and prohibitions for the subjects

None

Possible advantages and disadvantages for the subjects

A possible advantage can be for the subject that the pain management is done more meticulously.

A possible disadvantage: none.

7 Procedures and flowcharts

Procedures

Postoperative pain (at rest, when coughing and at movement) at 8-h, 16-h, 24-h, 32-h, 40-h and 48-h after cardiac surgery is measured by an NRS-scale if the patient is awake, and by the Critical-Care Pain Observation Tool(CPOT) in the sedated patient.

Secondary endpoints as delirium in the direct postoperative phase is measured by the ICDSC-score. Also included in the secondary endpoints are: time till extubation, length of hospital stay, length of stay at the ICU department and total consumption of painmedication registerd in mg/kg

8 Randomisation and blinding

Patients will be randomised automatically by computer randomization.

Patients and study nurses will be blinded to the pain-management.

9 Adverse event reporting

List of abbreviations

AE	Adverse Event
CA	Competent Authority

EC	Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

Adverse Event (AE)

The following information will be recorded:

- Nature of adverse event
- Date and time of occurrence and disappearance
- Intensity: mild, moderate , severe
- Frequency: once, continuous or intermittent
- Decision regarding study: continuation or withdrawal
- Relation to the study medication (see below)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

AEs will be recorded from the first drug administration until the end of the trial. Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or serious AE.

The term AE is used to include both serious and non-serious AEs.

Serious Adverse Event (SAE)

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening (life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

  Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Medical and scientific

judgment should be exercised in deciding whether other situations should be considered serious adverse event.

Note: medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

Unexpected Adverse event

An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Associated with the use of the drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

Attribution definitions

Not related: An adverse event which is not related to the use of the drug.

Unlikely: An adverse event for which an alternative explanation is more likely- e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible: An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable: An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely e.g. concomitant drug(s), concomitant disease(s).

Definitely: An adverse event which is listed as a possible adverse reaction cannot be reasonably explained by an alternative explanation – e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity. All AE and SAEs will be recorded in the patient's file and in the CRF. All SAEs will be reported as described below.

Medical events that occur between the signing of the informed consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant disease page of the CRF. SAEs occurring within a period of 2 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) and pregnancies occurring during clinical trials must be reported by the local Principal Investigator within 2 working days after becoming aware of the SAE to:

- The EC
- The Trial Bureau of Ghent University Hospital
- The Principle Investigator

This reporting is done by using the appropriate SAE form. For the contact details, see below.

It is the responsibility of the local Principal Investigator (PI) to report the local SAEs to the EC and the CA.

In case the investigator decides the SAE is a Suspected Unexpected Serious Adverse Reaction(SUSAR), the Trial Bureau will report the SUSAR to the EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator reports the SUSAR to all local Principal Investigators.

In case of life-threatening SUSAR the entire reporting process must be completed within 7 calendar days. In case of non-life-threatening SUSAR the reporting process must be completed within 15 calendar days.

The first report of a serious adverse event may be made by telephone, e-mail or fax.

Contact details of the Trial Bureau:

e-mail: trialbureau@uzgent.be

tel 09 332 05 00

fax 09 332 05 20

Contact details of the PI and National Coordinating Investigator:

e-mail: harlinde.peperstraete@ugent.be

tel 09 332 51 85

fax 09 332 4995

The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event and the invesigator's attribution. This report of a serious adverse event by telephone, must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used. Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

If the subjects are not under 12-hour supervision of the investigator or his/her staff (outpatients/volunteers), they (or their designee, if appropriate) must be provided with a "trial card" indicating the name of the trial, the trial number, the medication used, the investigator's name and 24-hour emergency contact number.

Annual Safety reporting

The trial bureau will ask the Principal Investigator for an annual report containing an overview of all SSARs (suspected serious adverse reaction) and a summary regarding the safety of the trials subjects. The trial Bureau will send this report to the EC within the timelines as defined in national legislation.

10 Study analysis

Sample size calculation

We used an online sample size calculator where we used following data : Two independent study groups, continuous endpoints, anticipated incidence of VAS-score 4 (±1,5) vs 3 based on literary study, a probability of type 1 error of 5% and power of 80%. This is all similar to most medical literature. After this calculation we become two groups of 35 patients.

Pain and comfort scales

VAS-Scale.

Delirium

ICDSC-score.

Time to extubation

In hours.

Length of stay in ICU and In hospital

In hours.

Cumulative use of analgetics in the postoperative period

Calculated per kilogram.

Statistical analysis

Parametric data: unpaired t-test, or student t-test

Non-parametric data: Wilcoxon's test

Level of significance (p)= 0.05

11 Quality control and quality assurance

Quality control of data of the CRFs will be done by comparing the data of the original documents with those of the eCRFs by a person who was not associated with filling in the CRFs. All data will be reported in the eCRF files following GCP rules and the internal Trial Bureau Office (Ghent University Hospital) will monitor closely the study. eCRF's will be created by Redcap.

12 Indemnity insurance

No Fault Insurance Ghent University Hospital

13 Publication policy

The results of this study will be published in an A1-journal. The privacy of the subjects will be respected at all times. Results derived from this study will only be published with the permission of the investigators.

Part II: General part of the protocol

14 Independent Ethics Committee / Institutional Review Board

This trial can only be undertaken after full approval of the protocol and addenda has been obtained from the IEC/IRB. This document must be dated and clearly identify the protocol, amendments (if any), the informed consent form and any applicable recruiting materials and subject compensation programs approved.

During the trial, the following documents will be sent to the IEC/IRB for their review:

- reports of adverse events that are serious, unexpected and associated with the investigational drug
- all protocol amendments and revised informed consent form (if any).

Amendments should not be implemented without prior review and documented approval / favorable opinions form the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.

Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the investigator at intervals stipulated in their guidelines.

At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

15 ICH / GCP guidelines

This trial will be conducted in accordance with the protocol, current ICH-GCP guidelines and applicable law(s).

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trialsubjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

16 Subject information and informed consent (IC)

Prior to entry in the trial , the investigator must explain to potential subjects or their legal representatives the trial and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access. After this explanation and before entry to the trial, written, dated and signed IC should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject. In case the subject or the legally acceptable representative is unable to read, an impartial witness must attest the IC. Subjects who are unable to comprehend the information provided can only be enrolled afeter consent of a legally acceptable representative.

17 Case report forms

The source documents are to be completed at the time of the subject's visit. The CRFs are to be completed within reasonable time after the subject's visit. The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is Not Done, Not Available or not Applicable, the investigator must enter "ND"," NAV", "NAP", respectively in the appropriate space.

18 Direct access to source data : documents

The investigator will permit trial-related monitoring, audits, IRB /IEC review, and regulatory inspection(s), providing direct access to source data / documents.

19 Data handling and record keeping

The investigator and sponsor specific essential documents will be retained for at least 20 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirements.

20 Signature page

INVESTIGATOR:

NAME : DR. HARLINDE PEPERSTRAETE

TITLE : PRINCIPLE INVESTIGATOR

DATE:

SIGNATURE :

INVESTIGATOR:

NAME : DR. SIMON BOGAERT

TITLE : INVESTIGATOR

DATE:

SIGNATURE :

INVESTIGATOR:

NAME : DR. ANNELIES MOERMAN

TITLE : INVESTIGATOR

DATE:

SIGNATURE :

INVESTIGATOR:

NAME : DR. STEFAAN BOUCHEZ

TITLE : INVESTIGATOR

DATE:

SIGNATURE :

INVESTIGATOR:

NAME : DR. INGRID HERCK

TITLE : INVESTIGATOR

DATE:

SIGNATURE :

INVESTIGATOR:

NAME : DR. DR. WIM VANDENBERGHE

TITLE : INVESTIGATOR

DATE:

SIGNATURE :