DEXMEDETOMIDINE VERSUS PROPOFOL IN AWAKE IMPLANTATION OF NEUROMODULATIVE SYSTEMS

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DCS	**Dorsal Column Spinal Cord stimulation**
DRG	**Dorsal Root Ganglion Stimulation**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
OR	**Operation Room**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: We want to observe the usefulness of dexmedetomidine in the awake implantation of a neuromodulative system. This is a painful procedure, which can be uncomfortable due to the long-term prone position. Deep sedation is undesirable because the patients have to be cooperative during the procedure. Dexmedetomidine has proven to be a good sedative in several diagnostic and therapeutic “awake” procedures.
Compared to commonly used sedatives and analgesics, such as remifentanil and propofol, Dexmedetomidine appears to be hemodynamically and respiratory safer, more comfortable for the patient while at the same time it is possible for the patient to be fully cooperative.
Objective: The objective of this study is to assess the patient satisfaction with the awake implantation of a neuromodulative system comparing dexmedetomidine with propofol as a sedative.
Study design: This is a randomized controlled trial with an intervention.
Study population: 72 patients (18 - 65 years) with an indication for implantation of a neuromodulative system.
Intervention: One group of patients will receive dexmedetomidine in a titrated dose and remifentanil in a set dose during the procedure. Dexmedetomidine will be titrated on effect using the Ramsey sedation score. The other group will receive propofol in a titrated dose and remifentanil in a set dose during the procedure. Propofol will be titrated on effect using the Ramsey sedation score. Sedation will be performed under responsibility of an anaesthesiologist not involved in the interventional procedure.
Main study parameters/endpoints: The primary endpoint of the study is the assessment of the satisfaction of the patient with dexmedetomidine or propofol as a sedative. Secondary endpoint is the estimation of the clinical usefulness of dexmedetomidine or propofol in terms of hemodynamics, respiration, sedation, pain relief, complications, patient’s comfort and operator’s comfort and the number of adjustments of dexmedetomidine or propofol titration. All the measurements will be performed by an independent observer not involved in the sedation and/or interventional procedure.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The potential benefits of the use of dexmedetomidine during procedure include no blur of consciousness; no decline of cognitive skills; the patient is less alert, is sleeping but still arousable, cooperative and instructable without any agitation. dexmedetomidine has a good anxiolytic effect, a light analgesic effect and causes no respiratory depression. It makes a lower dose of propofol and remifentanil possible. Side effects are the possibility of hypotension and bradycardia. A disadvantage is that is has no amnesic effects.

1. INTRODUCTION AND RATIONALE

Neuromodulation.
Neuromodulation is an acknowledged method for the treatment for chronic neuropathic pain. In the Netherlands neuromodulation is used when other more conventional therapies for chronic neuropathic pain have failed. The most important indications are “failed back surgery syndrome”, “complex regional pain syndrome” and peripheral nerve damage. At this moment Dorsal Column Spinal cord (DSC) stimulation is the most commonly used therapy, but more recently there is a possibility for the use of Dorsal Root Ganglion (DRG) stimulation. The advantage of DRG stimulation is the potential of stimulating the more difficult to reach areas such as the feet and torso. [1, 2]

The placement of the electrodes for stimulation is carried out in an awake patient under local anesthesia. The patient needs to be awake to find the right position for the electrodes with respect to the spinal cord and nerve roots. These procedures can be uncomfortable for the patient because it is performed in prone position, can last for over three hours and has a limited possibility for local anesthetics because the deeper structures are not allowed to be anaesthetized. In daily practice an intravenous short-lasting opiate, remifentanil and/or an low dosed sedation medication (like propofol) is used under supervision of an anesthesiologist not involved in the interventional procedure. The problem with these medications is the risk of respiratory depression while at the same time the prone position causes a difficult control of the air way. Another problem is the blur of consciousness.[3]

The clinical experience with the use of dexmedetomidine in Erasmus MC during awake craniotomy is good, especially with regards to comfort, hemodynamic and respiratory control. Until recently, in awake craniotomy, the same analgo-sedative regimen, with remifentanil and propofol was used, with similar disadvantages as earlier described. Both procedures are long-term interventions, with an uncomfortable position and the patient must remain instructable while it can be a painful and stressful experience. During both procedures airway management is difficult, due to the position of the patient. In the literature there are many good experiences written of the use of dexmedetomidine in diagnostic and interventional procedures.[4]

Dexmedetomidine is an α2- agonist. In the USA it is registered for the use at the ICU since 1999, under the brand name Precedex, for use duration for a maximum of 24 hours. Recently in the USA, dexmedetomidine has been registered for the use at procedures in the OR with non-intubated patients.

In the Netherlands dexmedetomidine is registered for the use at the ICU, under the brand name Dexdor, for unlimited duration of use. It is available for off-label use at the OR during certain procedures. [5]

Dexmedetomidine
Dexmedetomidine doesn’t act on GABA-receptors, like propofol and benzodiazepines, but acts on mainly presynaptic α2-receptors. There is no blur of consciousness and no decline of cognitive skills. The patient is sleeping but still arousable, cooperative and instruct able without any agitation. Dexmedetomidine has a good anxiolytic effect, a light analgesic effect and causes no respiratory depression. It makes a lower dose of propofol and remifentanil possible. Side effects are the possibility of hypotension and bradycardia. [4, 6]

Dexmedetomidine versus Clonidine
Clonidine is the classical α2- agonist. Dexmedetomidine has clear advantages in comparison with clonidine. There is an eight fold higher affinity for the α2-2A receptors, which are predominantly located in the locus coeruleus. This gives a much better sedation and less hemodynamic effects. Dexmedetomidine is known as a sedative

agent, whereas clonidine as a antihypertensive agent. Dexmedetomidine has less influence on the imadazoline receptor, which participates in hypotension – caused by centrally acting α2-agonists. There is a shorter elimination half-life time (two hours against eight to twelve hours). Dexmedetomidine doesn't show any rebound effect after stopping prolonged dispense.[7]

Propofol
Standard care in the Erasmus MC during the implantation of a neuromodulative system involves the use of propofol in combination with remifentanil. Propofol belongs to standard care because there is much knowledge and experience about propofol and it is a cheap anaestheticum. It is suitable for general anesthesia as well as for sedation.[8] On the other hand there are also side effects on the cardiovascular system (low bloodpressure) and the respiratory system (respiratory depression or arrest).[9] Furthermore propofol creates a somnolent state of the patient, also during sedation. This is not desired during the implantation of a neuromodulative system because we want the patient to be able to tell us exactly where to place the electrodes. That is why we want to compare dexmedetomidine with propofol.

Rationale
Dexmedetomidine has proven to be a good working sedative and is registered for the use in ICU's in the Netherlands since 2011 under the brand name Dexdor. In our study we want to observe the usefulness of dexmedetomidine and propofol in patients during awake implantation of a neuromodulative system.

2. OBJECTIVES

Primary objective:
The primary objective will be the patient satisfaction with sedation instrument.

Secondary objective:
Secondary objectives is to assess usefulness of dexmedetomidine or propofol by measuring:

- Hemodynamics
- Respiration
- Ramsey sedation scores
- Pain relief
- Complications
- Cost-effectivity analysis
- Patients comfort and operators comfort
- The number of adjustments of dexmedetomidine or propofol titration

3. STUDY DESIGN

This is a randomized controlled trial in patients with an indication for an implantation of a neuromodulative system. In September 2014 we started a proof of concept study whether or not dexmedetomidine is useful for the implantation of a neuromodulative system since there was no data available about the use of dexmedetomidine during this procedure. Therefore we have chosen for this study design. This study is finished end of february 2015 and therefore we want to perform a randomized controlled trial comparing the effect of dexmedetomidine with standard care, which involves the use of propofol.

The study will be performed in an estimated compact period of 24 months. The inclusion period is 1-2 weeks before the planned procedure. The demographic parameters of the patients are preoperatively documented in the anesthesia record. Other measurements will be performed before, during and after procedure.

All eligible patients will be asked to participate in this randomized controlled trial. The inclusion procedure including the signing of the informed consent forms will be performed according to the guidelines for Good Clinical Practice.

The sedation will be performed under responsibility of an anesthesiologist not involved in the interventional procedure.
The implantation of the neuromodulative system will be performed by an anesthesiologist pain specialist not involved in the sedation.
An independent observer not involved in the sedation or the interventional procedure will perform all measurements.
The administrative processing will be performed by the principal investigator.

The study coordination will take place by the research group of the Erasmus MC Center for Pain Medicine. Implantations will be performed, as usual, in the surgical day care center of Erasmus MC, Rotterdam.

4. STUDY POPULATION

4.1 Population (base)

The study population consists of patients with an indication for a neuromodulative system.

Feasibility of recruitment:
The study will include 72 patients from the Erasmus MC in Rotterdam. The pain specialist sees enough patients with an indication for a neuromodulative system to expect an inclusion of 72 patients in 24 months.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- Patients need to be between 18 and 65 years.
- Patients have an indication for implantation of a neuromodulative system.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Hypersensitivity of active part of one of any of the excipients
- AV-blok (II or III)
- Acute cerebrovascular disease
- Pregnancy
- Acute epilepsy
- Severe liver dysfunction
- Use of a beta blocker
- Use of medications causing hypotension or bradycardia.
- Psychologically unstable
- Communication problem
- Heart rate <60bpm
- Allergy for soya or peanuts
- Heart failure
- Severe heart disease
- Electroconvulsive therapy (ECT)
- ASA III, IV, V

4.4 Sample size calculation

Data will be analyzed by means of an Independent Samples T-Test. Dependent primary outcome parameter is the total score on the Patient Satisfaction with Sedation Instrument (PSSI). As no results with this instrument of previous studies are available, a statistically detectable and clinically relevant effect size (d) of 0.67 is chosen based on reference [10]. The power of the study (1 - β) is chosen to be 0.8, an allocation ratio of 1:1 and the two-sided

level of significance (α) to be 0.05. The required a priori total sample size computed by this method is 72.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

To cover the pain associated with propofol insertion we will give all patients 1 cc lidocaine intravenous before starting dexmedetomidine or propofol infusion.

Dexmedetomidine.

Dexmedetomidine is a registered sedative medicine at the ICU in the Netherlands. It is available for off-label use at the OR during certain procedures.
Because of the potential hemodynamic effects (hypotension, hypertension and bradycardia) it is undesirable to administer Dexmedetomidine by bolus, and therefore it is advised to administer a loading infusion of 6 mcg/kg/hr during ten minutes. The needed dose of Dexmedetomidine depends on the desired sedation level of the patient. When the patient has to be cooperative (Ramsey 2-3) we will lower the dose of Dexmedetomidine. When the patient has to be more sedated (Ramsey 3 – 4) we will raise the dose. We start the the maintenance dose of Dexmedetomidine at 0,6 mcg/kg/hr.
The maintenance dose of Dexmedetomidine to keep the patient in Ramsey 3 is 0,6 – 1,4 mcg/kg/hr.

We will titrate the dose of Dexmedetomidine to a Ramsey score 2 or 3 during procedures. Every two minutes there will be an evaluation of the Ramsey score. We won't expect the patient to be in Ramsey 1 but if this happens we will raise the dose of Dexmedetomidine with 0,2 mcg/kg/hour. If the patient reaches Ramsey 4 we will lower the dose of Dexmedetomidine with 0,2 mcg/kg/hour.

We will start the loading infusion of Dexmedetomidine at the moment that the patient will be transferred from back position to prone position during the procedure in the OR.

During procedure we will measure the number of adjustments of Dexmedetomidine titration.

We will give a dose of remifentanil of 3 mcg/kg/hr as a set dose. In case of high pain we will give a bolus of 25-50 mcg/kg/hr remifentanil.

Propofol

Propofol is a registered medicine at the operation room in the Netherlands.

Because of its potential hemodynamic and respiratory effects (hypotension or respiratory depression / arrest) it is advised to administer first a loading infusion of 0,5 mg/kg for 10 minutes. The needed dose of propofol depends on the desired sedation level of the patient. When the patients has to be cooperative (Ramsey 2-3) we will lower the dose of propofol and when the patient has to be more sedated (Ramsey 3-4) we will raise the dose.
The maintenance dose of propofol to keep the patient in Ramsey 3 is 2,0 mg/kg/hr. [9]

We will titrate the dose of propofol to a Ramsey score 2 or 3 during procedures. Every two minutes there will be an evaluation of the Ramsey score. We will start loading infusion of propofol at the moment the patient will be transferred from back to prone position during the procedure in the OR. During the procedure we will measure the number of adjustments of propofol titration.

We will give a dose of remifentanil of 3 mcg/kg/hr as a set dose. In case of high pain we will give a bolus of 25-50 mcg/kg/hr remifentanil.

5.2 Use of co-intervention (if applicable)

Not applicable.

5.3 Escape medication

A higher dose of remifentanil than the set dose (3 mcg/kg/hr) is allowed if needed depending on the evaluation of the anaesthesiologist. This is part of standard anaesthesia care. We will mention this in our report.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Dexdor.

Dexdor is a medicine that contains the active substance Dexmedetomidine. It is available as a concentrate to be made up into a solution for intravenous infusion. Dexdor is used to sedate adult patients in hospital intensive care units. Dexdor is used to cause a relatively light level of sedation in which the patient can still respond to verbal stimulation (corresponding to the Ramsey score).
Dexmedetomidine can only be obtained with a docters prescription.
The active substance in Dexdor, Dexmedetomidine, is a selective alpha-2 receptor agonist. It works by binding alpha-2 receptors primaly located in the central nervous system and causes a reduction in the activity of the sympathetic nervous system which is involved in controlling people's anxiety, arousal and sleep as well as the blood pressure and heart rate. By reducing the activity of the sympathetic nervous system, Dexmedetomidine helps to make patients calm or sleepy.[5, 10]

Propofol

Propofol is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia in adults.
Propofol may also be used for sedation of ventilated adult patients in intensive care and for anaesthesia in pediatric surgery (for children of 3 years of age or older) for surgical procedures which do not exceed 1 hour in duration.
Propofol may also be used for conscious sedation for surgical and diagnostic procedures.[9]

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 - 1 mg propofol/kg bodyweight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol Fresenius infusion to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg bodyweight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg propofol (1 – 2 ml Propofol 1% (10 mg/1 ml) Fresenius) if a rapid increase of the depth of sedation is required.
In patients older than 55 years and in patients of ASA grades III and IV lower doses of Propofol Fresenius may be required and the rate of administration may need to be reduced.

6.2 Summary of findings from non-clinical studies

Dexdor.

The effects of Dexdor were first tested in experimental models before being studied in humans. [5, 10]

Propofol.

The effects of Propofol were first tested in experimental models before being studied in humans. [11]

6.3 Summary of findings from clinical studies

Dexdor

Dexdor was compared with other sedative treatments (propofol or midazolam) in two main studies of 1,000 patients in intensive care units requiring sedation. The main measures of

effectiveness were based on how well the medicines maintained the required sedation level and the time patients needed to spend on a mechanical ventilator.
In comparison to already used medications showed similar effects on maintaining sedation. In one main study, 65% of patients given Dexdor maintained the required level of sedation compared with 65% of those receiving propofol. In the second study, 61% of patients given Dexdor maintained the required level of sedation compared with 57% of those receiving midazolam. In addition the studies showed a benefit of Dexdor in reducing the duration of mechanical ventilation. [5, 10]
The distribution half-life from Dexmedetomidine is 6-8 minutes. After steady state IV infusion the elimination half-life is 2 hours. Peak effect is reached in 45-60 minutes. [7]

Propofol

Propofol was studied in clinical trials which included pediatric surgery or sedation as well as adult surgery or sedation. The clinical trials were about neuroanesthesia (brain tumors) or to evaluate its effect on cerebrospinal fluid pressure (CSFP). Furthermore they studied the effect of propofol in the Intensive Care Unit (ICU) sedation. They compared propofol with benzodiazepines and opioids in clinical trials involving ICU patients. Adequate sedation was maintained with propofol in hemodynamically stable head trauma patients ranging in age from 19 to 43 years. Propofol was found to be effective in status epilepticus which was refractory to the standard anticonvulsant therapies. Clinical trials also evaluated propofol involving patients undergoing coronary artery bypass graft (CABG). [11]

6.4 Summary of known and potential risks and benefits

Dexdor

Dexdor showed similar potency as the comparator medicines in maintaining sedation. In one main study, 65% of patients given Dexdor maintained the required level of sedation compared with 65% of those receiving propofol. In the second study, 61% of patients given Dexdor maintained the required level of sedation compared with 57% of those receiving midazolam. The studies also showed a benefit of Dexdor in reducing the duration of mechanical ventilation.

The most frequently reported side effects with Dexdor are hypotension (low blood pressure), hypertension (high blood pressure) and bradycardia (slow heart rate), occurring in approximately 25%, 15% and 13% of patients respectively. Dexdor reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension. For the full list of all side effects reported with Dexdor, see the summary of product characteristics (SPC) of Dexdor. [12]
Dexdor must not be used in people who are hypersensitive (allergic) to dexmedetomidine or any of the other ingredients. It must also not be used in patients with advanced heart block (a type of heart rhythm disorder), patients with uncontrolled hypotension and in patients with conditions such as stroke that affect the blood supply to the brain. [5]

Dexmedetomidine has also been used during awake craniotomy in our hospital. We also expect Dexmedetomidine to be safer compared to propofol because the prone position makes a good control of the airway difficult. We expect the same side effects in our study as described above.

Propofol

The most frequently reported side effects with propofol are local pain during the injection or high fat percentages in the blood (hypertriglyceridemia). Furthermore one should be attentive to the cardiovascular and respiratory effects like low bloodpressure and respiratory depression. For the full list of all side effects reported with propofol, see the summary of product characteristics (SPC) of propofol. [9, 13]

Propofol must not be used in people who are hypersensitive (allergic) to propofol or any of the other ingredients. It must also not be used in patients with allergy for soya and peanuts. One should be extra careful with the use of propofol when there is advanced heart failure, severe heart disease or when a patient is getting electroconvulsive therapy (ECT). [9]

6.5 Description and justification of route of administration and dosage

Dexdor

Dexdor is for in hospital use only and should be given by a healthcare professional skilled in managing patients requiring intensive care.
Dexdor is given by infusion into a vein using a controlled infusion device. The doses are adjusted until the required level of sedation is attained. If adequate sedation is not achieved with the maximum dose, the patient should be switched to an alternative sedative agent.
For more information on the use of Dexdor, including doses and dose adjustments, see the summary of product characteristics (also part of the EPAR).[5, 10]

Propofol

For intravenous use. Propofol 1% (10 mg/1 ml) Fresenius can be used for infusion undiluted or diluted with 5% w/v glucose intravenous infusion solution or 0.9% w/v sodium chloride intravenous infusion solution only, in glass infusion bottles.
When Propofol 1% (10 mg/1 ml) Fresenius is infused undiluted, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. [9, 13]

6.6 Dosages, dosage modifications and method of administration

Dexdor

Dexmedetomidine is a registered sedative medicine at the ICU in the Netherlands. It is available for off-label use at the OR during certain procedures.
Because of the potential hemodynamic effects (hypotension, hypertension and bradycardia) it is undesirable to administer Dexmedetomidine by bolus, and therefore it is advised to administer a loading infusion of 6 mcg/kg/hr during ten minutes. The needed dose of Dexmedetomidine depends on the desired sedation level of the patient. When the patient has to be cooperative (Ramsey 2-3) we will lower the dose of Dexmedetomidine. When the patient has to be more sedated (Ramsey 3 – 4) we will raise the dose. We start the the maintenance dose of Dexmedetomidine at 0,6 mcg/kg/hr.
The maintenance dose of Dexmedetomidine to keep the patient in Ramsey 3 is 0,6 – 1,4 mcg/kg/hr.

We will titrate the dose of Dexmedetomidine to a Ramsey score 2 or 3 during procedures. Every two minutes there will be an evaluation of the Ramsey score. We won't expect the patient to be in Ramsey 1 but if this happens we will raise the dose of Dexmedetomidine with 0,2 mcg/kg/hour. If the patient reaches Ramsey 4 we will lower the dose of Dexmedetomidine with 0,2 mcg/kg/hour.

We will start the loading infusion of Dexmedetomidine at the moment that the patient will be transferred from back position to prone position during the procedure in the OR.

During procedure we will measure the number of adjustments of Dexmedetomidine titration.

We will give a dose of remifentanil of 3 mcg/kg/hr as a set dose. In case of high pain we will give a bolus of 25-50 mcg/kg/hr remifentanil.

Propofol
Propofol is a registered medicine at the operation room in the Netherlands.

Because of its potential hemodynamic and respiratory effects (hypotension or respiratory depression / arrest) it is advised to administer first a loading infusion of 0,5 mg/kg for 10 minutes. The needed dose of propofol depends on the desired sedation level of the patient. When the patients has to be cooperative (Ramsey 2-3) we will lower the dose of propofol and when the patient has to be more sedated (Ramsey 3-4) we will raise the dose.
The maintenance dose of propofol to keep the patient in Ramsey 3 is 2,0 mg/kg/hr. [9]

We will titrate the dose of propofol to a Ramsey score 2 or 3 during procedures. Every two minutes there will be an evaluation of the Ramsey score. We will start loading infusion of propofol at the moment the patient will be transferred from back to prone position during the procedure in the OR. During the procedure we will measure the number of adjustments of propofol titration.

We will give a dose of remifentanil of 3 mcg/kg/hr as a set dose. In case of high pain we will give a bolus of 25-50 mcg/kg/hr remifentanil.

6.7 Preparation and labelling of Investigational Medicinal Product

Dexdor
Will be delivered by the hospital pharmacy (Erasmus MC).

Propofol
Will be delivered by the hospital pharmacy (Erasmus MC).

6.8 Drug accountability

Dexdor

Will be delivered by the hospital pharmaxy (Erasmus MC).

Propofol
Will be delivered by the hospital pharmacy (Erasmus MC).

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Remifentanil.
Lidocaine.

7.2 Summary of findings from non-clinical studies

We will refer to the SPC from remifentanil. [14]
We will refer to the SPC from lidocaine. [15]

7.3 Summary of findings from clinical studies

We will refer to the SPC from remifentanil. [14]
We will refer to the SPC from lidocaine. [15]

7.4 Summary of known and potential risks and benefits

We will refer to the SPC from remifentanil. [14]
We will refer to the SPC from lidocaine. [15]

7.5 Description and justification of route of administration and dosage

We will refer to the SPC from remifentanil. [14]
We will refer to the SPC from lidocaine. [15]

7.6 Dosages, dosage modifications and method of administration

Remifentanil:
Standard care involves the use of remifentanil. Remifentanil will be added to dexmedetomidine or propofol at a set dose (3 mcg/kg/hour) to accomplish a high analgetic effect. We will start the remifentanil infusion 10 minutes after the start of the dexmedetomidine loading infusion or propofol loading infusion.[14]

Lidocaine:
Standard care involves the use of 1 % lidocaine in combination with adrenaline (1 op 200.000) at start of procedure, median incision and the end of procedure.[15]

7.7 Preparation and labelling of Non Investigational Medicinal Product

Will be delivered by the hospital pharmacy (Erasmus MC)

7.8 Drug accountability

Will be delivered by the hospital pharmacy (Erasmus MC)

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study parameter is patient satisfaction (using the satisfaction with sedation instrument (PSSI) [16] *)*

8.1.2 Secondary study parameters/endpoints

Secondary objectives are to assess usefulness of dexmedetomidine or propofol by measuring:

- Hemodynamics (blood pressure and heart rate)
- Respiration (capnography and pulse oximetry)
- Ramsey sedation scores
- Pain relief by NRS measurements
- Complications
- Cost-effectivity analysis
- Patient comfort score and operator comfort score
- The measurements of the number of adjustments of dexmedetomidine and propofol titration

8.1.3 Other study parameters (if applicable)

Not applicable.

8.2 Randomisation, blinding and treatment allocation

The medication the patient will receive will be randomised by the hospital pharmacy using a randomization list made by a statistician. An unblinded nurse will get the medication from the pharmacy and will bring it to the operation room. The hospital pharmacy will deliver (ondoorzichtige infuuslijnen). There will be double-blinding during the study. The patient is blinded during procedure. The independent observer is blinded during the procedure. The anesthesiologist performing the sedation (not involved in the interventional procedure) is not blinded. If there is a medical emergency during the procedure or with the patient the blinding will be broken. We will report this.

8.3 Study procedures

We will approach patients sequentially, based on their indication of implantation a neuromodulative system. The eligible patients will be asked to visit our department and will be screened, based on the stated inclusion and exclusion criteria. A medical history will be collect at the screening; Gender, age, hemodynamic measurements (blood pressure and blood rate), in- and expiratory measurements (O2 en CO2) are recorded as well as known relevant diseases and concomitant medication during the last three months.

We want to include 72 patients. If a patient decides to participate in the study he/she will be asked to sign informed consent (IC) before entering the study. A separate study file will be managed for each patient.

Questionnaire 1 "Patient Satisfaction with Sedation Instrument (PSSI)".
After the procedure the patient will be asked to fill in the PSSI questionnaire which include 20 questions about the patient satisfaction with sedation instrument. The questionnaire is based on reference. [16]

Sedation scale - Ramsey scale
The patients will be evaluated during the sedation. This will be performed by using a score from 1 – 6. The categories from 1 – 6 include:
1. Anxious, agitated or impatient
2. Cooperative, oriented and tranquil
3. Responsive to commands
4. Asleep, but with brisk respons to light glabellar tap or loud auditory stimulus
5. Asleep, sluggish respons to glabellar tap or auditory stimulus
6. Asleep, no respons

Clinical pain relief – NRS score
The patients will be asked to give a pain score. The intensity of pain will be measured with a numeric rating scale, known as NRS. The NRS will be performed on a scale (No pain – most intensive pain ever = 0 – 10).

Complications.
Complications of propofol and dexmedetomidine during the procedure will be noted. Complications involved are desaturation (saturation <90%), jaw trust/manual ventilation, laryngospasm, hypotension (decrease map >20%), bradycardia (decrease heart rate >20% / heart rate <55 bpm), shivering/shaking/unwanted move, vomiting and others.

Questionnaire 2: Patient comfort score – Operator comfort score:
After the procedure the patient will be asked to give a score for comfort. We compare the degree of comfort experienced by patients and the degree of comfort experienced to the operator.
Based on reference [17].

Hemodynamic measuring
The blood pressure and blood rate will be measured.

Respiratory measuring
Respiratory frequency measuring (capnography) and pulse oximetry will be used to give an indication of the respiratory condition of the patient during procedure.

Adjustments of Dexmedetomidine or propofol titration.
We will measure the number of adjustments of dexmedetomidine or propofol titration during the whole procedure.

Cost-effectivity analysis
The costs of the use of dexmedetomidine will be compared with the costs of the use of propofol.

Time schedule (based on reference [18])

We will measure with intervals of 5 – 10 – 20 - 30 minutes after a step (T1, T6, T11, T16, T21, T26). If a step is proceeding fast we will not need the latest interval. If a step is lasting longer because of a complication or another indication we will need the later intervals.

T0	Baseline (before procedure)
T1	Lidocaine 1 cc administration intravenous
T2	**Start Dexdor / Propofol infusion**
T3	5 minutes after start Dexdor / Propofol infusion
T4	10 minutes after start Dexdor / Propofol infusion
T5	20 minutes after start Dexdor / Propofol infusion (if needed)
T6	30 minutes after start Dexdor / Propofol infusion (if needed)
T7	**Start remifentanil infusion** (10 minutes after start Dexdor / Propofol infusion)
T8	5 minutes after start remifentanil infusion
T9	10 minutes after start remifentanil infusion
T10	20 minutes after start remifentanil infusion (if needed)
T11	30 minutes after start remifentanil infusion (if needed)
T12	**Start procedure (operation)**
T13	5 minutes after start procedure
T14	10 minutes after start procedure
T15	20 minutes after start procedure
T16	30 minutes after start procedure
T17	**Time of median incision**
T18	5 minutes after median incision
T19	10 minutes after median incision
T20	20 minutes after median incision
T21	30 minutes after median incision
T22	**End of procedure**
T23	5 minutes after end of procedure
T24	10 minutes after end of procedure
T25	20 minutes after end of procedure (if needed)
T26	30 minutes after end of procedure (if needed)
T27	**1 day after procedure (operation)/sedation**

Measurement schedule.

	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
Patient satisfaction									
Ramsey	X	X	X	X	X	X	X	X	X
NRS	X	X	X	X	X	X	X	X	X
Complications	X	X	X	X	X	X	X	X	X

Comfort									
Hemodynamics	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X	X	X	X	X	X	X

	T10	**T11**	**T12**	**T13**	**T14**	**T15**	**T16**	**T17**	**T18**
Patient satisfaction									
Ramsey	X	X	X	X	X	X	X	X	X
NRS	X	X	X	X	X	X	X	X	X
Complications	X	X	X	X	X	X	X	X	X
Comfort									
Hemodynamics	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X	X	X	X	X	X	X

	T19	**T20**	**T21**	**T22**	**T23**	**T24**	**T25**	**T26**	**T27**
Patient satisfaction									X
Ramsey	X	X	X	X	X	X	X	X	
NRS	X	X	X	X	X	X	X	X	X
Complications	X	X	X	X	X	X	X	X	X
Comfort									X
Hemodynamics	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X	X	X	X	X	X	X

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

If a patient show adverse effect of intolerance for dexmedetomidine like hypotension, hypertension of bradycardia or if a patient show adverse effect of intolerance for propofol like hypotension or respiratory depression.

8.5 Replacement of individual subjects after withdrawal

When a patient withdraws him/herself (or is withdrawn by the investigator), this patient will be replaced if a next eligible patient is available.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable.

8.7 Premature termination of the study

Not applicable.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All SAEs will be reported by the principal investigator through the web portal *ToetsingOnline* to the accredited METC that approved the study, within 15 days after the principal investigator has first knowledge of the serious adverse events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

<*Please describe also the method of breaking the code for SUSAR reporting*.>

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

10. STATISTICAL ANALYSIS

Descriptive statistics will be used to determine the frequencies of the demographic variables and the outcome parameters and to describe measures of central tendency and of dispersion dependent on the shape of the their distribution. Normality of the distributions will be tested using the Shapiro-Wilk test.

Differences between the two groups will be tested by performing the t-test for independent means in case the parameter is normally distributed or by the Mann-Whitney U test in case it is skewed.

Analyses will be performed using IBM SPSS Statistics 22.

10.1 Primary study parameter(s)

Patient satisfaction (PSSI)

10.2 Secondary study parameter(s)

Secondary parameters are to asses usefulness of dexmedetomidine or propofol by measuring
- Hemodynamics,
- Respiration,
- Ramsey sedation scores,
- Pain relief,
- Cost-effectivity analysis
- Complications,
- Patient’s comfort and operator’s comfort,
- The number of adjustments of dexmedetomidine or propofol titration.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Version 18, October 2013), and in accordance with the Medical Research Involving Human Patients Act (WMO).

11.2 Recruitment and consent

All potential patients will be recruited once the ethics committee has approved the study. The patients with an indication for a neuromodulative system will be selected by the pain specialist.

Potential patients will be informed about the purpose, the nature and the duration of the study. The potential patient will be given two weeks to read the patient information prior to signing the Informed Consent form. If needed, an independent physician will be available to answer questions. After giving informed consent by means of an informed consent patients are enrolled in the study.

11.3 Objection by minors or incapacitated subjects (if applicable)

The study will only include adults (≥18 years old).

11.4 Benefits and risks assessment, group relatedness

Compared to commonly used sedatives and analgesics, such as remifentanil and propofol, Dexmedetomidine appears to be respiratory safer, more comfortable for the patient while at the same time the patient remains cooperative, which is important during this procedure.[17, 19] Use of Dexmedetomidine has been associated with hypotension, bradycardia and hypertension. To prevent strong fluctuations of heart rate and blood pressure, administration of Dexmedetomidine will be started by a loading infusion, and not by a bolus. For the administration a controlled infusion will be used. When used in this way Dexmedetomidine provides a relatively stable hemodynamic state. Blood pressure and heart rate will be monitored continuously. Dosing will be individualized, and titrated to desired clinical respons. As in customary during all procedures with sedation, drugs for immediate intravenous treatment of bradycardia (atropine) and hypotension (ephedrine) are available.

11.5 Compensation for injury

The sponsor/investigator has a liability which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The handling of the personal data conforms with the Dutch Personal Data Protection Act (in Dutch: De wet bescherming Persoonsgegevens (Wbp)).
Every included patient will be coded by a number. The first patient eligible for inclusion and visiting our department will be number 1. The patient's study charts will also be coded with a number. This number will match the number of the patient.

The questionnaires (patient satisfaction with sedation instrument (PSSI) and patient comfort) will be filled in after the procedure. The questionnaires and answers will be added to the patients study charts, using the patients number.

12.2 Monitoring and Quality Assurance

The patients who fully corresponded with the stated inclusion and exclusion criteria will be numbered. Patients who fully comply with the in- and exclusion criteria will be numbered.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.
< Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.>

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The principal investigator is free to publish.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

13.1.1 Dexmedetomidine.

a. Level of knowledge about mechanism of action
Literature / clinical studies.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
Dexmedetomidine is registered in the USA in 2009. (FDA) [19]
Dexmedetomidine is registered in Europe in 2011. (EMA) [5]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Yes, standard care.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Dexmedetomidine has a high affinity for alfa-2 receptors in the locus coeruleus. [7]

e. Analysis of potential effect
Sedative, anxiolytic, sympathicolytic, anti-delirious and analgetic sparing effect with minimal respiratory depression. [7]

f. Pharmacokinetic considerations
Dexmedetomidine distribution half-life is 6-8 minutes. After steady state IV infusion the elimination half-life is 2 hours. [7]

g. Study population
Patients with an indication for implantation of a neuromodulative system.

h. Interaction with other products
Yes. Dexmedetomidine requires a lower dose of remifentanil because of the synergetic interaction. Dexmedetomidine has a strong synergistic effect with other sedatives and opioids.[7]

i. Predictability of effect
Yes.

j. Can effects be managed?
Yes.

13.1.2 Propofol

a. Level of knowledge about mechanism of action
Literature / clinical studies.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
Propofol is a registered and often used anesthetic and sedative in hospitals in the Netherlands. [9, 13]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Yes, standard care.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Propofol modulates activation and desensitization of GABAa receptors in cultured murine hippocampal neurons.

e. Analysis of potential effect
Analgetic, antihyperalgesic and sedative effect with possibility for respiratory depression.

f. Pharmacokinetic considerations
Propofol distribution half-life is 2-8 minutes, with the slow distribution half-life ranging from 30-70 min and the terminal elimination half-life from 4 to 24h. [20]

g. Study population
Patients with an indication for implantation of a neuromodulative system.

h. Interaction with other products
Yes, the respiratory effects of propofol are potentiated by other respiratory depressants, including benzodiazepines.

i. Predictability of effect
Yes

j. Can effects be managed?
Yes

13.1.3 Remifentanil

a. Level of knowledge about mechanism of action
Literature / clinical studies.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
Remifentanil is registered in the USA in 1996. (FDA) [21]
Remifentanil falls under the opium act and is registered in Europe in 2011. (EMA) [14]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Yes, standard care.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Remifentanil is an analgesic agent.

e. Analysis of potential effect
Remifentanil is indicated for provision of analgesia.

f. Pharmacokinetic considerations
Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes. The average clearance of remifentanil in young healthy adults is 40 ml/min/kg, the central volume of distribution is 100 ml/kg and the steady-state volume of distribution is 350 ml/kg. Blood concentrations of remifentanil are proportional to the dose administered throughout the recommended dose range. For every 0.1 micrograms/kg/min increase in i.v. infusion rate, the blood concentration of remifentanil will rise to 2.5 nanograms/ml. [11]

g. Study population
Patients in need of analgesia during procedure.

h. Interaction with other products
Remifentanil is not metabolized by plasmacholinesterase, therefore, interactions with medicinal products metabolized by this enzyme are not anticipated.
As with other opioids remifentanil, whether given by manually-controlled infusion or TCI, decreases the amounts or doses of inhaled and IV anaesthetics, and benzodiazepines required for anaesthesia. If doses of concomitantly administered CNS depressant medicinal products are not reduced patients may experience an increased incidence of adverse effects associated with these agents.
Information of drug interactions with other opioids in relation to anaesthesia is very limited. The cardiovascular effects of remifentanil (hypotension and bradycardia), may exacerbate in patients receiving concomitant cardiac depressant drugs, such as beta-blockers and calcium channel blocking agents. [11]

i. Predictability of effect
Yes.

j. Can effects be managed?
Yes.

13.1.4 Lidocaine

a. Level of knowledge about mechanism of action
Literature / clinical studies.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
Lidocaine is registered in the USA since 1972 (FDA). [22]
Lidocaine is registered in Europe since 1998. (EMA) [15]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Yes, standard care.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Lidocaine injection is used as a local anesthetic.

e. Analysis of potential effect
Lidocaine injection is used as a local anesthetic.

f. Pharmacokinetic considerations

Lidocaine is absorbed from injection sites including muscle and its rate of absorption is determined by factors such as the site of administration and the tissue vascularity. Except for intravascular administration, the highest blood levels occur following intercostal nerve block and the lowest after subcutaneous administration. Lidocaine is bound to plasma proteins, including alpha-1-acid-glycoprotein. The drug crosses the blood-brain and placental barriers. Lidocaine is metabolised in the liver and about 90 % of a given dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylidide, both of which may contribute to the therapeutic and toxic effects of lidocaine. Further metabolism occurs and metabolites are excreted in the urine with less than 10 % of unchanged lidocaine. The elimination half-life of lidocaine following an intravenous bolus injection is one to two hours, but this may be prolonged in patients with hepatic dysfunction.

g. Study population
Patient in need of local anesthetics.

h. Interaction with other products
The clearance of lidocaine may be reduced by beta-adrenoceptor blocking agents (e.g. propranolol) and by cimetidine, requiring a reduction in the dosage of lidocaine. Increase in serum levels of lidocaine may also occur with anti-viral agents (e.g. amprenavir, atazanavir, darunavir, lopinavir).

Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics (e.g. anti-arrhythmics, such as mexiletine), since the systemic toxic effects are additive. Specific interaction studies with lidocaine and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised. There may be an increased risk of ventricular arrhythmia in patients treated concurrently with antipsychotics which prolong or may prolong the QT interval (e.g. pimozide, sertindole, olanzapine, quetiapine, zotepine), or $5HT_3$ antagonists (e.g. tropisetron, dolasetron).

Concomitant use of quinupristin/dalfopristin should be avoided.
There may be an increased risk of enhanced and prolonged neuromuscular blockade in patients treated concurrently with muscle relaxants (e.g. suxamethonium).

i. Predictability of effect
Yes.

j. Can effects be managed?
Yes.

13.2 Synthesis

There is good experience with Dexdor in the Erasmus MC during awake craniotomy. Awake craniotomy uses the same analgo-sedative regimen, with similar disadvantages. Therefore we think it will be a valuable addition to the existing sedation and analgesia medication used during this procedure. Patients undergoing awake craniotomy don’t possess any of the said exclusion criteria. Furthermore there is experience with dexmedetomidine in the Erasmus MC during the awake implantation of a neuromodulative system based on our experience during the previous proof of concept study.

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