The influence of electroencephalographic density spectral array guidance of sevoflurane administration on recovery from general anaesthesia in children between 6 months and 12 years.
A randomised controlled trial.

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PROTOCOL TITLE

"The influence of electroencephalographic density spectral array guidance of sevoflurane administration on recovery from general anaesthesia in children between 6 months and 12 years".

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EudraCT number	Not applicable	
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Sponsor (in Dutch: verrichter/opdrachtgever)	***Dept. of Anaesthesia, Erasmus MC***	
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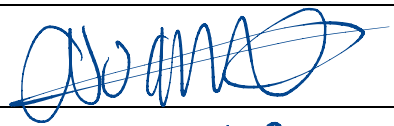
PROTOCOL SIGNATURE SHEE

Name	**Signature**	**Date**
Head of Department: ***Dr. C.D. van der Marel***		14/07/22
Coordinating Investigator/Project leader/Principal Investigator: ***Prof. Dr. F. Weber***		14-07 2022

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
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**
DoH	**Depth of hypnosis**
DSA	**Density Spectral Array**
DSMB	**Data Safety Monitoring Board**
EEG	**Electroencephalogram**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GA	**General anaesthesia**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
MAC	**Minimal Alveolar Concentration**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie 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**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Electroencephalographic density spectral array (DSA) is a three dimensional method to display electroencephalogram (EEG) signals consisting of the EEG frequency (y-axis), the power of the EEG signal (colour-coded to be integrated into a two dimensional plot) and the development of the EEG power spectrum over time (x-axis). DSA is routinely used to measure depth of hypnosis (DoH) by a part of the staff members in our department. When DSA is used, dose adjustments of sevoflurane will be made based on monitoring depth of anaesthesia. However, most of our colleague do not use DSA. Dose adjustment is then based on (subjective) clinical surrogate parameters, or in general mostly based on a minimal alveolar concentration of the anaesthetic gas that is used.

Electroencephalographic DSA monitoring provides continuous objective information on DoH and should result in a faster speed of emergence and recovery from general anaesthesia (GA). This will be addressed in a randomised controlled trial.

Objective:

To evaluate the influence of DSA monitoring, provided by the Narcotrend™ monitor, on the speed of emergence and recovery from GA.

Study design:

Single centre, prospective randomised, double-blind, controlled trial.

Study population:

Paediatric patients, aged ≥ 6 months and ≤ 12 years, scheduled for surgical procedure requiring general anaesthesia supplemented with caudal analgesia.

Intervention:

In patients randomised to the intervention group of the trial, the anaesthetic agent sevoflurane will be titrated according to the typical DSA pattern for GA with sevoflurane, provided by the Narcotrend™.[1] In patients randomised to the control group, sevoflurane will be titrated according to a Minimal Alveolar Concentration (MAC) of 0.9 respectively an end tidal sevoflurane concentration of 2.3% based on standard practice in our paediatric anaesthesia department.

Main study parameters/endpoints:

The speed of emergence from GA (time interval from discontinuation of hypnotic agent until criteria for transfer from the operation theatre to the recovery room are met) is the primary

objective of this trial. Secondary objectives of this trial are the time until discharge criteria from the recovery room are met, the incidence of postoperative delirium, the difference in intra-operative blood pressure between the intervention group and the control group, the incidence of recall of intraoperative events, adverse events and DoH during GA (as measured by the Narcotrend monitor™).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

In patients randomised to the intervention group, the anaesthetic agent sevoflurane will be administered on the basis of objective measures of anaesthetic depth, the typical DSA pattern for GA. We expect a significantly faster speed of emergence and recovery based on clinical experiences with the use of DSA. The Narcotrend™ monitor is validated for use in paediatric patients. There are thus no additional risk factors apart from those, which are inherent with general anaesthesia. Patient randomised to the control group will receive standard treatment, that is delivery of sevoflurane based on a MAC of 0.9 respectively an end tidal sevoflurane concentration of 2.3%.

A non-invasive therapeutical intervention (DSA based conduct of GA) should result in the advantage of faster recovery, without any additional risk factor.

1. INTRODUCTION AND RATIONALE

1.1 General introduction

EEG-based depth of hypnosis (DoH) could result in a faster recovery after the procedure, compared to a standard anaesthesia regimen. A faster recovery could result in advantages for the patient, advantages for the health care providers (enhanced workflow) and an advantage on the environmental impact (less volatile anaesthetic exposure).[2]
Earlier performed studies with a processed EEG device as the Narcotrend index monitor showed this effect of DoH monitoring in a faster recovery after the procedure.[3]
However the use of processed EEG monitoring in infants or young children is limited, because of the limitations of the monitors with the variability in age related EEG expression and the anaesthesia specific EEG features.[4]
In density spectral array, these limitations are less relevant due to age and anaesthesia specific EEG expression of the density spectral array pattern.[1,5,6] Therefore, we think density spectral array would be a more reliable way of monitoring depth of hypnosis in children.
To investigate the additional value of density spectral array in children we have to perform this randomized controlled trial that will investigate the influence of DSA monitoring during general anaesthesia (GA) on the speed of recovery after the procedure, compared to standard general anaesthesia management.

1.2 Density spectral array monitoring

Electroencephalographic density spectral array (DSA) is a three dimensional method to display electroencephalogram (EEG) signals consisting of the EEG frequency (y-axis), the power of the EEG signal (colour-coded to be integrated into a two dimensional plot) and the development of the EEG power spectrum over time (x-axis) (see figure 1).[7]

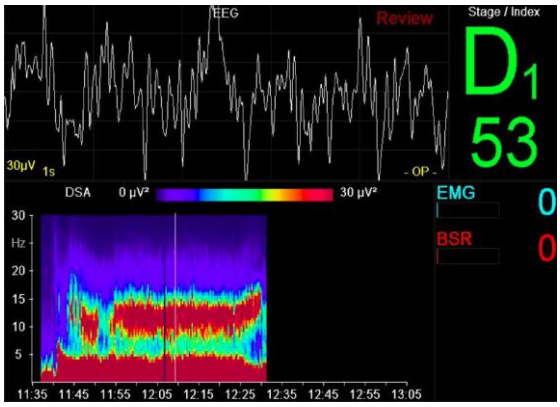


Figure 1 density spectral array (DSA)

Density spectral array has been developed to facilitate the interpretation of unprocessed electroencephalogram signals. It has multiple advantages compared to the widely used electroencephalogram-based indices, or processed EEG monitors.

Electroencephalographic density spectral array shows age-dependent changes in EEG effects of general anaesthetics in children. These age-related changes likely reflect ongoing development within the brain.[5,6,8]
Furthermore, we know that different anaesthetics act at different molecular targets and neural circuits. This results in anaesthetic drug specific EEG signatures that are readily visible in DSA.[7] The index-based indices, or processed EEG monitors assume the same index value defines the same level of unconsciousness for all anaesthetics.
Because of the limitations of processed EEG monitors, recently published articles emphasize the use of raw or “unprocessed” EEG monitoring as DSA in the measurement of depth of hypnosis.[4,9]
We previously performed some observational studies to investigate the specific anaesthetic drug and age-dependent DSA signatures in children.[1,10] A specific DSA pattern of general anaesthesia with sevoflurane in children aged 6 months to 12 years exists of the appearance of high delta and alpha power on the spectrogram.[1]

1.3 General anaesthesia supplemented with caudal analgesia

According to standard care, at Erasmus MC Sophia Children’s Hospital many surgical procedures are performed under general anaesthesia supplement with caudal analgesia. To exclude the impact of opioids on speed of recovery, we choose to include patients undergoing a surgical procedure requiring general anaesthesia supplemented with caudal analgesia.

1.4 Sevoflurane anaesthesia

At ErasmusMC Sophia Children’s Hospital many surgical procedures are perfomed under general anaesthesia with the volatile anaesthetic sevoflurane. This anaesthetic drug is used for induction and maintenance of general anaesthesia. The concentration sevoflurane is titrated according to age and clinical status of the patient. The minimum alveolar concentration (MAC) is a widely used tool in titrating the surgical level of anaesthesia when DoH monitoring is not used. The MAC value changes with age, where MAC decreases with increasing age. The average MAC concentration of sevoflurane used in the ErasmusMC Sophia Children’s Hospital is 0.9 respectively an end tidal sevoflurane of 2.3%.[11,12]

1.5 Post-anaesthesia discharge criteria – The Steward Post-Anaesthetic Recovery Score

The 'Simplified Post-Anaesthetic Recovery Score', published by Steward[13], is the golden standard for assessment of recovery from Anaesthesia:

Consciousness	**Score**
Awake	**2**
Responds to stimuli	**1**
Not responding	**0**
Airway	
Cough on command or cry	**2**
Maintaining good airway	**1**
Requires airway assistance	**0**
Motor	
Moves limbs purposefully	**2**
Non-purposeful movement	**1**
Not moving	**0**

1.5.1 Discharge criteria from the operating room

The patient is ready to be transferred from the operating room (OR) to the recovery room when the following criteria are met:

- Responding to stimuli (domain Consciousness) **Score ≥ 1**
- Maintaining good airway (domain Airway) **Score ≥ 1**
- Non-purposeful movements (domain Movement) **Score ≥ 1**

That corresponds with a total Steward Score of ≥ 3.

1.5.2 Discharge criteria from the recovery room

Complete recovery from general anaesthesia is the prerequisite for discharge from the recovery room. It is achieved when the patient meets the following criteria:

- Awake (domain Consciousness) **Score 2**
- Coughing on command or crying (domain Airway) **Score 2**
- Moving limbs purposefully (domain Movement) **Score 2**

That corresponds with a total Steward Score of 6.

1.6 Previous research related to this topic and significance of the project

By now only a limited number of paediatric trials have been published about DSA guidance during general anaesthesia. None of them focused on the speed of recovery after general anaesthesia with DSA.

Based on clinical experience with DSA guided anaesthesia, we expect the use of DSA will result in a faster recovery after general anaesthesia. However, the speed of emergence has never been investigated in previous trials demonstrating the use of DSA in children.

2. OBJECTIVES

Primary Objective: the influence of density spectral array monitoring with the Narcotrend™ monitor on the speed of emergence from general anaesthesia with sevoflurane. The speed of emergence is defined as the time interval between the end of hypnotic drug application and the moment when discharge criteria from the operating room are met (defined as a Steward score ≥ 3).

Secondary Objectives:

- Total time from discontinuation of anaesthetic drug delivery until discharge from the post anaesthesia care unit.
- The incidence of postoperative delirium by the Cornell Assessment of Postoperative Delirium (CAPD) score.[14,15]
- The difference in intra-operative blood pressure between the intervention group and the control group.
- Differences of depth of hypnosis during the procedure, as measured by the Narcotrend monitor™.
- Incidence of recall of events during the procedure (awareness)
- Adverse events

3. STUDY DESIGN

Single centre, prospective, randomized, double blind trial.

In paediatric patients, aged 6 months until 12 years, scheduled for a surgical procedure which requires general anaesthesia supplemented with caudal analgesia. General anaesthesia is either guided by density spectral array or by a minimal alveolar sevoflurane concentration of 0.9 respectively an end tidal sevoflurane concentration of 2.3%.

The two study groups are compared with respect to the speed of recovery (primary objective). Secondary objectives of this trial are total time from discontinuation of anaesthetic drug delivery until discharge from the post anaesthesia care unit, the incidence of postoperative delirium, the difference in intra-operative blood pressure between the intervention group and the control group, ddifferences of depth of hypnosis during the procedure, as measured by the Narcotrend monitor™, the incidence of recall of events during the procedure (awareness) and adverse events.

4. STUDY POPULATION

4.1 Population (base)

Paediatric patients, aged 6 months until 12 years, scheduled for a surgical procedure which requires general anaesthesia supplemented with caudal analgesia. The average annual caseload of 400 surgical procedure requiring general anaesthesia supplemented with caudal analgesia at Sophia Children's Hospital indicates that it should be possible to recruit enough patients for this study in a reasonable period of time (approximately 18 months).

4.2 Inclusion criteria

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

- Written informed consent of the parents/legal representatives
- Age > 6 months and < 12 years
- Surgical procedure requiring GA supplemented with caudal analgesia
- Ability of the parents or legal guardians to communicate in Dutch

4.3 Exclusion criteria

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

4.3.1 primary exclusion criteria

- Withdrawal of informed consent
- (Chronic) use of drugs influencing the electroencephalogram
- Use of premedication
- Known intolerance for sevoflurane
- Parents/legal guardians unable to communicate in Dutch

4.3.2 secondary exclusion criteria

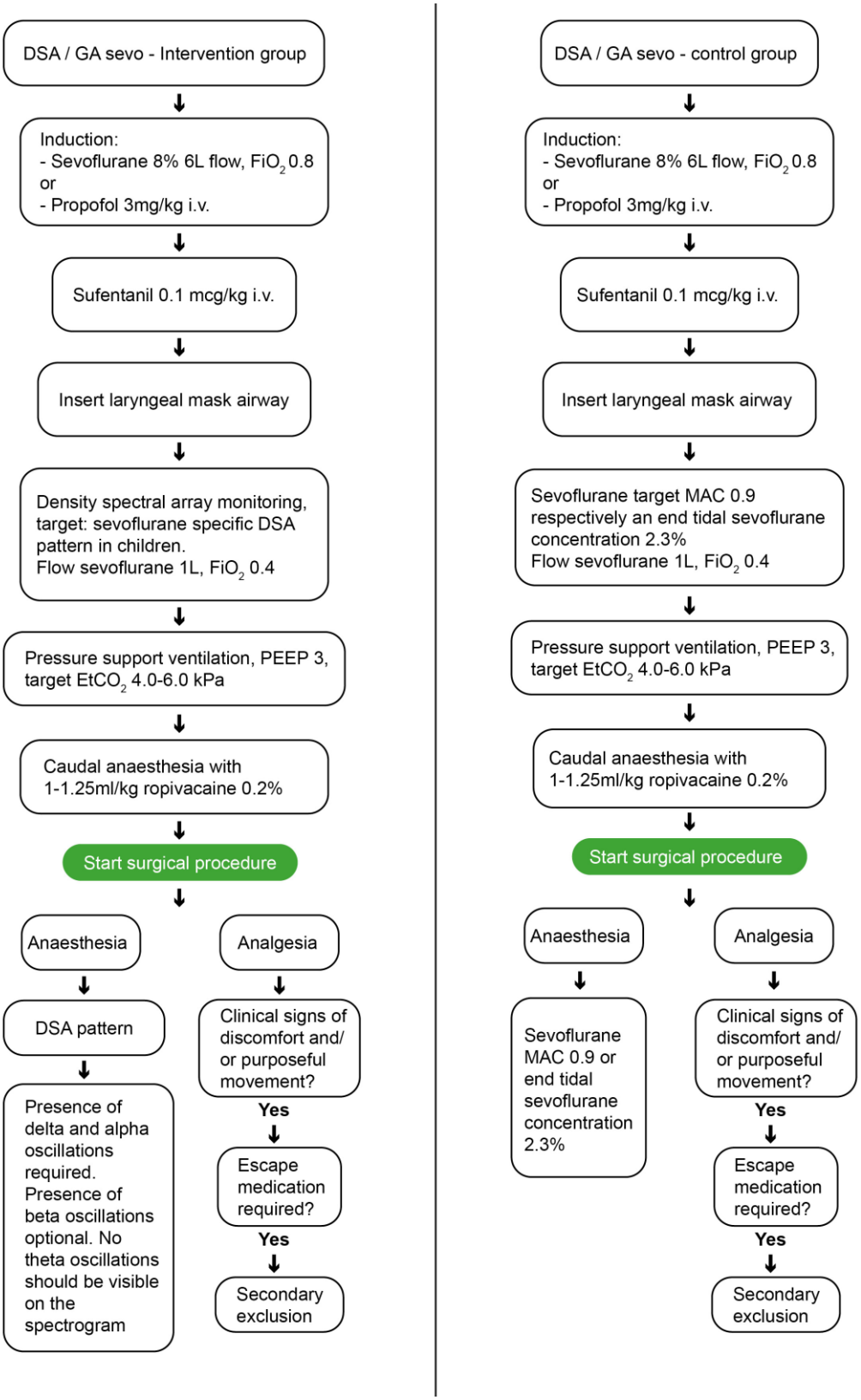
- protocol violation
- data registration failure

4.4 Sample size calculation

There are no previous studies about DSA and the speed of recovery after general anaesthesia.
Based on clinical experience we expect a medium to large effect size so we performed a power analysis using G* power software package with an effect size d of 0.6. The Wilcoxon-Mann-Whitney test was used as statistical test. A sample size of 51 patients per study group is required to achieve a power of 0.9 with an alpha error probability of 0.05.[16]
In order to compensate for possible dropouts due to protocol violation or data registration failure a total of 56 patients will have to be included in either group (+10%).

5. TREATMENT OF SUBJECTS

The effect of DSA on recovery of anaesthesia in children protocol



Standard anaesthesia monitoring is used during the procedure, ECG, pulse-oxymetry, capnometry an non-invasive measurement of blood-pressure.

Patients randomized to the control group are also attached to the Narcotrend monitor, but with the screen of the monitor obscured. The electroencephalographic data will later be compared to the data of the intervention group in order to assess for differences of depth of hypnosis during the procedure.
After complete recovery from GA, the day thereafter and two weeks later, parents or legal guardians will be contacted via telephone for a systematic interview with the patient if aged > 6 years. This systematic interview is the “Modified Brice-interview”, which is the golden standard for the detection of recall of intraoperative events.[17,18] Brice interviews will only be performed in patients of at least 6 years of age, because it is known that interviews taken in children of younger ages are likely not to provide the interviewer with reliable information.
At the end of the procedure, sevoflurane will be stopped and washed out with 10L flow, FiO_2 0.5. The patients will be otherwise left undisturbed on the operation table. The sound level in the operation theatre will be reduced to a minimum.
The speed of emergence and recovery will be assessed with the Steward Recovery Score from Anaesthesia.[13]
The incidence of postoperative delirium will be assessed with the Cornell Assessment of Postoperative Delirium (CAPD).[14,15]

5.1 Investigational product/treatment

This trial is designed to investigate the additional value of Density Spectral Array monitoring, provided by the Narcotrend™ monitor in the “speed of emergence” after general anaesthesia. compare traditional general anaesthesia with sevoflurane using a MAC value and subjective clinical parameters to the objective and continuous approach to depth of hypnosis by DSA monitoring with the primary outcome parameter “speed of emergence”. The investigational product is the validated Narcotrend™ monitor, an electroencephalographic monitor, that is regularly used in anaesthesia practice in the Sophia children’s hospital and will be used according to intended purpose. The extended version as used in the operating room in the Sophia Children’s hospital offers a diversity of diagrams including Density Spectral Array.
The electroencephalographic Narcotrend™ monitor records frontal EEG-activity. Standard paediatric ECG electrodes are used for EEG registration.

5.2 Use of co-intervention (if applicable)

Not applicable.

5.3 Escape medication (if applicable)

The investigator can use every medication that is needed for good clinical practice. Each opioid or anaesthetic that is used outside the protocol will be considered as escape medication. The subject will be secondary excluded from analysis when escape medication is used.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Narcotrend™ monitor or Narcotrend compact M is an electroencephalographic monitor recording frontal EEG-activity. Multiple diagrams to interpret the EEG are available on this monitor. The extended version as used in the operating room in the Sophia Children's hospital offers a diversity of diagrams; the cerebrogram, the relative Band activities/Power, the Quantiles, the Power Spectrum, the Amplitude-Integrated EEG/Burst-Suppression-Ratio and Density Spectral Array.

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

The Narcotrend has been validated for use in children undergoing both surgical procedures under general anaesthesia and gastrointestinal endoscopy under procedural sedation in the Sophia Children's Hostpital.[19-21]

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

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

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint of the study is the time interval between the termination of anaesthetic drug delivery and discharge from the operating theatre according to predefined discharge criteria.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary end points are:

- Total time from discontinuation of anaesthetic drug delivery until discharge from the post anaesthesia care unit.
- The incidence of post-operative delirium
- Differences of depth of hypnosis during the procedure.
- Incidence of recall of events during the procedure (awareness)
- Adverse events

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Patients will be allocated to either the intervention group or the control group by a computer-generated block randomisation. A paediatric anaesthetist who is not otherwise involved in this trial will perform the randomisation procedure, including the preparation of sealed envelopes with the randomisation codes per patient and the randomisation schedule.

The investigator who determines the hypnotic state of the patient after discontinuation of delivery of anaesthetic drugs is not present at the operating theatre during the surgical procedure. He enters the theatre at the moment of discontinuation of drug delivery, which equals the start of the emergence period. That enables us to blind the investigator as to the study-group assignment of the patient.
The member of the research team that provides general anaesthesia cannot be blinded with respect to group allocation. In patients allocated to the control group the screen of the Narcotrend monitor is obscured.

8.3 Study procedures

See flowchart under “study design (page 15).

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)

In case of unexpected events requiring opioids or anaesthetics outside the protocol during the procedure, the patient will be withdrawn from the study.

8.5 Replacement of individual subjects after withdrawal

In order to compete with possible dropouts, due to withdrawal for whatever reason or due to protocol violation, the sample size of the study is about 10% in excess of the results of the sample size calculation. In paediatric depth of anaesthesia studies dropout rates are usually within the range of +/- 5% and mostly due to equipment failure. As a consequence of secondary exclusion due to protocol violation or data registration failure, we choose to increase the number of subjects with 10% on forehand. There is no need to replace individual subject after withdrawal.

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 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. 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 [the investigational product / trial procedure/ the experimental 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

- 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; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. .

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

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

Participants of this study receive general anaesthesia and caudal analgesia for a planned surgical procedure. Both the intervention-group and the control-group receive the same anaesthetics. The only risk in this study is the risk that is inherent with general anaesthesia, which will be applied regardless whether or not the patients agree to participate in the study. General anaesthesia with sevoflurane supplemented with caudal anaesthesia is considered appropriate and safe for many surgical procedures and is frequently used in general practice in the ErasmusMC Sophia children's hospital.

As a result of a risk assessment using the guideline "kwaliteitsborging van mensgebonden onderzoek", provided by the Dutch Federation of University Medical Centres (NFU), we conclude that this study has a negligible risk level.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The time interval between the end of anaesthetic drug application and the moment when discharge criteria from the operating room are met (Steward score ≥ 3) is compared between the study groups. Therefore datasets will first be tested for normality by means of the Shapiro-Wilk normality test. As appropriate, either a Mann-Whitney-U-test or a t-test will be performed.

10.2 Secondary study parameter(s)

Intergroup comparison of total time from discontinuation of hypnotic drug delivery until discharge from the post-anaesthesia care unit will be performed by means of an unpaired t-test or a Mann-Whitney-U-test.

Intergroup comparison of the incidence of postoperative delirium will be performed by means of an chi square test.

Posthoc intergroup comparison of hypnotic depth as measured by DSA is performed as follows: DSA patterns recorded during the procedure are categorised and assigned to three conditions of the specific DSA pattern for GA; appropriate DoH (presence of high power delta and alpha oscillations on the power spectrum), to deep DoH (presence of high power delta, alpha and theta oscillations on the power spectrum), to light DoH (presence of high power delta with the absence of high power alpha oscillations and the presence of high power beta oscillations). Intergroup comparison will be performed by a means of a chi-square test.

10.3 Other study parameters

Descriptive statistics will be applied to demographic variables, continuous variables such as discharge times, incidence of recall of events during the procedure (awareness) and adverse events. All datasets will be tested for normality by means of the Shapiro-Wilk normality test.

10.4 Interim analysis (if applicable)

We will not perform an interim analysis.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (seventh revision 2013) and in accordance the Medical Research Involving Subjects act (WMO).

11.2 Recruitment and consent

According to the procedural steps described in the 2010 version of the CONSORT flow diagram (http://www.consort-statement.org/consort-statement/) patients will be assessed for eligibility to be enrolled in the study as soon as possible after the paediatric surgeon or urologist has made the decision to operate the patient. Preferably patients and/or their legal representatives will be provided with the patient information folder (PIF) during their visit at the pre-anaesthetic assessment clinic. Recruitment of subjects will be done by the clinical investigators (I.H., F.W., G.K. and H.R.). The Dutch PIF's and informed consent forms for both the parents and patients are attached as separate documents.

11.3 Objection by minors or incapacitated subjects (if applicable)

Minors cannot be forced to undergo interventions against his or her will. This study will be conducted according to the Code of Conduct applicable to minors as written by the Pediatric Association of the Netherlands (Nederlandse Vereniging voor Kindergeneeskunde). The parents will be informed about the possibility to withdraw their child at any moment in the study without consequences for the medical care in an information letter they will receive upon inclusion.

11.4 Benefits and risks assessment, group relatedness

Patients randomised to the intervention group might benefit from a better GA technique. Patients randomised to the control group, thus receiving standard treatment, can neither expect any benefit nor any disadvantages from participating in the study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance 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 (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All personal data will be coded by serial numbers. Only the project leader (I.H.) will have access to the key. Statistics will be performed with the coded numbers. Published data from this study cannot be traced to a specific child. All coded data will be stored in a secure place for a minimum of 15 years. We will use Castor EDC as an electronic data capture. All personal data will be handled according to the EU General Data Protection Regulation and the Dutch Act on implementation of the General Data Protection Regulation.

12.2 Monitoring and Quality Assurance

The ‘Monitoringplan’ is constructed in accordance with the least ErasmusMC guidelines. The Clinical trial center will be contacted for the fulfilment of the ‘Monitoringplan’.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

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.

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 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC 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.

12.6 Public disclosure and publication policy

The investigators are responsible for the public disclosure and publication of the research data. No sponsor is involved in the publication of the data.
Parents may request an overview of the study results after completion of the study.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable (see chapter 13.2)

13.2 Synthesis

Only paediatric patients who are scheduled for a surgical of urological procedure requiring general anaesthesia supplemented with caudal analgesia, aged 6 months until 12 years, are eligible to be included in this study. Participants of this study will not be exposed to an increased risk compared to the (negligible) risk of GA.

The aim of this trial is to investigate if there is a significant benefit of DSA guided GA compared to GA guided by MAC and assessment of clinical signs of hypnotic depth. Based on our personal experience we expect that DSA guidance will result in a faster recovery. We do not expect any negative effects of DSA guidance of GA.

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