

The Minimum Alveolar Concentration (MAC) of Sevoflurane Required to Prevent Bell's Phenomenon During Examination of the Eye Under Anaesthesia.

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A research report submitted to the Faculty of Health Sciences, University of the Free State, Bloemfontein, in partial fulfillment of the requirements for the degree Masters of Medicine in the branch of Anaesthesia.

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Table of content

DECLARATION	iv
DEDICATION	v
PREFACE	vi
ABSTRACT	vii
ACKNOWLEDGEMENTS	x
List of figures	xi
List of tables	xi
Abbreviations and Definitions	xii
CHAPTER 1	1
1.1 Introduction	1
1.2 Problem statement.....	1
1.3 Aim and Objectives	2
1.4 Location of the Study	2
1.5 Ethical considerations	2
1.6 Research methodology	3
1.6.1 Research design	3
1.6.2 Study population and sample	3
1.6.3 Inclusion and exclusion criteria.....	3
1.6.4 Schedule of dates.....	4
1.6.5 Data analysis	5
1.7 Significance of the Study.....	5
CHAPTER 2	6
2. LITERATURE REVIEW	6
2.1 Introduction	6
CHAPTER 3	11
3. METHODOLOGY	11
3.1 Introduction	11
3.2 Study Design	11
3.3 Study Site.....	11
3.4 Study Population.....	11
3.5 Ethical Considerations.....	12
3.5.1 Authorization	12
3.5.2 Participation and Informed Consent	12
3.5.3 Confidentiality	13
3.6 Inclusion and exclusion criteria	14
3.6.1 Inclusion criteria	14
3.6.2 Exclusion criteria	14
3.7 Construction of the Instrument.....	14
Flowchart:	18
3.8 Technical challenges	19
3.9 Data Management/Analysis.....	20
CHAPTER 4	21
4. RESULTS	21
4.1 Introduction	21
4.2 Sample and Exclusions	21
4.3 Results	21
4.4 Summary of Results.....	26

CHAPTER 5	28
5. DISCUSSION	28
5.1 Interpretation of findings.....	28
5.2 Comparison with published work.....	28
5.3 Discussion of potential limitations and shortcomings of the study.....	29
CHAPTER 6	33
6. CONCLUSION AND RECOMMENDATIONS	33
6.1 Conclusion	33
6.2 Suggestions for practice and further research.....	33
CHAPTER 7	35
7. References	35
APPENDICES	38
Appendix A: Ethics approval certificate	38
Appendix B: Ethics approval of amendment to protocol.....	40
Appendix C: Permission from department of Anaesthesiology	41
Appendix D: Permission from department of Ophthalmology.....	42
Appendix E: Permission from hospital	43
Appendix F: Patient information	44
Appendix G: Consent forms	48
Appendix I: Data collection sheet.....	51

DECLARATION

I, Johann de Beer, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia at the Faculty of Health Sciences, University of the Free State, Bloemfontein. It has not been submitted before for any degree or examination at this or any other University.

J de Beer
16 February 2016

For my father, who would have been proud.

PREFACE

Ophthalmologists often need to closely examine the eyes of children to determine the cause of a presenting problem or to measure the intraocular pressures. Young children cannot keep still during this examination of the eye and therefore anaesthesia is required to perform this examination. As registrar I did my Ophthalmology rotation from 1 February to 30 March in 2012. During this time I noted that some of the children had specific eye movements during periods of stimulation of the eye during the examination although they were anaesthetized.

Normally the eyes are in a central position during anaesthesia, however if the eye is stimulated, the eyeball may move upwards; this is usually a sign of being too light under anaesthesia, although the child is not awake or aware.

In order to return the eye to the central position, the anaesthesia has to be deepened until the eye is central again.

This eye movement is known as Bell's phenomenon, and is a natural defense mechanism that also occurs during blinking or forced eye opening when awake.

I found these eye movements very interesting and wondered how deep the anaesthetic should be to prevent these reflex eye movements. Prof G. Lamacraft suggested that I do this as a research project. I started doing a literature search and to my surprise I could not find any research done on this specific topic. I therefore decided to study the depth of anaesthesia required to prevent these eye movements.

ABSTRACT

BACKGROUND

In children, sevoflurane is the most commonly used volatile anaesthetic. Its excellent hemodynamic tolerance gives it a wide therapeutic index. This halogenated agent can abolish movement or hemodynamic responses to noxious stimuli in children and in adults. In order to investigate the effect of sevoflurane on Bell's response, we determined the minimum alveolar concentration (MAC) of sevoflurane inhibiting Bell's reflex in 50% of the subjects in response to an eye examination (MACBell). Bell's phenomenon can be seen at any time during anesthesia when the patient's depth of anesthesia has changed. It is a natural protective reflex in which the globe turns cephalic in response to stimuli such as pressure on the eye by a lid speculum. This occurs both in the awake state and with light planes of anesthesia. It is usually a sign of light anaesthesia although the patient is not awake or aware. In contrast, the reflex is extinguished with deep planes of anesthesia such that the eye remains in neutral gaze, which is the position required by the ophthalmologist when performing an examination of the eyes under anaesthesia.

OBJECTIVES

The aim of this study was to determine the effective minimum alveolar concentration of sevoflurane that is necessary to prevent Bell's phenomenon in children undergoing an eye examination under anesthesia. The question we aimed to answer with this study was the following: What is the minimum alveolar end tidal concentration of sevoflurane that is required to prevent reflex movement of the eyeball during an eye examination under anesthesia (EUA) in children?

This study aimed to give anesthesia providers, involved in ophthalmology examinations, an indication of the dose of sevoflurane that is necessary during anesthesia to prevent the eyeball turning upward and thus safely guide the child through the EUA. A secondary aim of the study was to determine what the main stimuli were for eliciting Bell's reflex during the EUA.

METHODS

A prospective, experimental study was designed. Children aged 2 months to 10 years having an EUA between 19/05/2015 and 23/07/2015 were included in the study. UFS Ethics Committee approval of the study protocol and parental consent were obtained. A dose finding study using up-and-down methodology was used to determine the effective dose in 50% of the population (ED50) of sevoflurane that was required to prevent Bell's phenomenon under anaesthesia. Patients received sevoflurane at preselected concentrations according to the 'up-and-down' study design, and after a steady-state period an examination under anaesthesia was performed. Bell's reflex was graded as either minimal, when the center of the cornea was still visible or as a full response when the center of the cornea was not visible anymore. The stimulus that elicited the response was also recorded.

RESULTS

Forty-three children were studied. In a sub analysis of 32 patients the ED50 of sevoflurane was determined. The ED50 of sevoflurane needed to prevent Bell's phenomenon was found to be a MAC of 1.8. The main stimuli responsible for eliciting the reflex were forced abduction, adduction or traction on the eye muscles.

CONCLUSION

MACbell(1.8) was higher than surgicalMAC(1.0). The most potent stimulus that was responsible for eliciting Bell's reflex was during traction on the eye muscles, adduction and abduction.

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I am grateful to the following people:

Prof G Lamacraft; my mentor, supervisor and study leader, for her advice, encouragement and support during the supervision of this project.

The Department of Anaesthesia, Universitas Hospital complex, for the countless hours of research time given for data collection and for the costs of the consent and data collection forms.

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Mr. Cornel van Rooyen, Department Biostatistics for the data analysis.

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List of figures

Figure 1: Sequential eye responses of patients with corresponding MAC values (n=43)	21
Figure 2: Sub-analysis of equally paired sequential eye responses with corresponding MAC values (n=32)	22

List of tables

Table 1: Frequency of eye responses (n = 32)	23
Table 2: Frequency of MAC values of participants (n=32)	23
Table 3: Age distribution of participants	24
Table 4: Gender distribution of participants	25
Table 5: Age, temperature, weight and MAC of patients (n=32)	25
Table 6: Qualification level of ophthalmology doctor performing the eye examination	25
Table 7: Grading of positive eye responses	26
Table 8: Stimulus responsible for eliciting a positive eye response ...	26

Abbreviations and Definitions

MAC – Minimum Alveolar Concentration

The MAC is the concentration of the vapour (measured as a percentage at 1 atmosphere, i.e. the partial pressure) that prevents patient movement in response to a supramaximal stimulus (traditionally a set depth and width of skin incisions) in 50% of subjects. This measurement is done at steady state, under the assumption that this allows for an equilibration between the gasses in the alveoli, the blood and the brain. MAC is accepted as a valid measure of potency of inhalational general anaesthetics because it remains fairly constant for a given species even under varying conditions.

ED50 – Effective Dose in 50% of the population

The "median effective dose" is the dose that produces a quantal effect (all or nothing) in 50% of the population that takes it (median referring to the 50% population base). It is also sometimes abbreviated as the ED50, meaning "effective dose, for 50% of people receiving the drug". The ED50 is commonly used as a measure of the reasonable expectancy of a drug effect, but does not necessarily represent the dose that a clinician might use. This depends on the need for the effect, and also the toxicity. The toxicity and even the lethality of a drug can be quantified by the TD50 and LD50 respectively. Ideally, the effective dose would be substantially less than either the toxic or lethal dose for a drug to be therapeutically relevant.

ED95 – Effective dose in 95% of the population

The ED95 is the dose required for desired effect in 95% of the population exposed to it.

Et sevo

The end tidal concentration of sevoflurane (Etsevo) is the percentage sevoflurane that the patient exhales.

Bell's phenomenon

Bell's phenomenon (also known as the palpebral oculogyric reflex) is an upward and outward movement of the eye, when an attempt is made to close the eyes. The upward movement of the eye is present in the majority of the population, and is a defense mechanism. The phenomenon is named after the Scottish anatomist, surgeon, and physiologist Charles Bell. Bell's phenomenon is a normal defense reflex present in about 75% of the population, resulting in elevation of the globes when blinking or when threatened (e.g. when an attempt is made to touch a patient's cornea).

EUA

Examination under anaesthesia

SIMV

Synchronous Intermittent Mechanical Ventilation (SIMV). A ventilation mode in which the ventilator breaths are synchronized with patient inspiratory effort. In SIMV mode of mechanical ventilation, a regular series of breaths are scheduled but the ventilator senses patient effort and reschedules mandatory breaths based on the calculated need of the patient.

CHAPTER 1

1.1 Introduction

Ophthalmologists often need to closely examine the eyes of children to determine the cause of a presenting problem or to measure intra ocular pressures. Young children cannot keep still during this examination of the eye and anaesthesia is required to perform this examination.

1.2 Problem statement

Normally the eyes are in a central position during the surgical plane of anaesthesia, however if the eye is stimulated, the eyeball may rotate upwards due to a protective reflex known as Bell's reflex; this is a sign of light anaesthesia, although the child is not awake or aware.

Any noxious stimuli to the eye during an examination under anaesthesia (EUA) can elicit Bell's reflex, these include insertion of a speculum to keep the eye open, pulling on the eye muscles (transduction) or pushing on the eyeball (scleral indentation). This reflex makes the eye rotate upwards and makes it difficult or impossible for the ophthalmologist to examine the eye and to make measurements during the EUA. Subsequently the anaesthetic has to be deepened until the eye is central again. This eye movement, known as Bell's phenomenon, is a natural defense mechanism that also occurs during blinking or forced eye opening when awake. In this study the researchers aimed to determine the effective dose of sevoflurane that is necessary to prevent Bell's phenomenon in children undergoing an eye examination under anesthesia.

1.3 Aim and Objectives

The aim of this study was to determine the effective minimum alveolar concentration (MAC) of sevoflurane that is necessary to prevent Bell's phenomenon in children undergoing an eye examination under anesthesia.

The question the researcher aimed to answer with this study was:

What is the minimum alveolar end tidal concentration of sevoflurane that is needed to prevent reflex movement of the eyeball during an eye examination under anesthesia (EUA) in children?

This study can give anaesthesiologists, involved in providing anaesthesia for paediatric ophthalmology examinations, an indication of the dose of sevoflurane that is necessary during anesthesia to prevent the eyeball turning upward or outward and thus safely guide the child through the EUA.

A secondary aim the study was to determine what the main stimuli are for eliciting the Bell's reflex during the EUA.

1.4 Location of the Study

The study was conducted at Universitas Annex Hospital Ophthalmology Theatre, Bloemfontein.

1.5 Ethical considerations

Due to the fact that the study was conducted in children undergoing examination of their eyes under anaesthesia, special accent forms were designed to explain the procedure to the children while consent was obtained from the child's parents or legal guardian. A protocol amendment was submitted to the ethics committee to include the data of children that were between the ages of 2 months and 1 year. This was approved on 26 January 2016.

1.6 Research methodology

1.6.1 Research design

This was an experimental study. A sequential design method was used in this dose finding study to determine the concentration or dose associated with the 50% point along the dose-response curve. This study design would give the researcher the ED50 (Effective dose in 50% of the population). This up-and-down method of Dixon and Mood is commonly used in dose finding studies in anesthesia research. Details of the method used are given in Chapter 3.7 Construction of the instrument.

1.6.2 Study population and sample

The study included 43 children that were booked for an eye examination under general anaesthesia at Universitas Annex ophthalmology theatre between 19/05/2015 and 23/07/2015 on Fridays after exclusion criteria were applied. A sub analysis of these 43 children included 32 children that were used to calculate the minimum alveolar concentration of sevoflurane that was needed to prevent Bell's reflex in 50% of the population.

1.6.3 Inclusion and exclusion criteria

Screening of the patients in terms of inclusion criteria was performed during the preoperative visit by the anaesthesia registrar responsible for the ophthalmology theatre list. A thorough history was taken during the preoperative examination by the principal researcher Dr J de Beer, whereby it was determined if a patient qualified for the trial (fulfilled inclusion criteria) and if any exclusion criteria existed, which would exclude the patient from the trial. Screening was performed during the pre operative visit on the day before the planned examination. Informed consent for the study was then obtained from

the patients and parents who fulfilled the inclusion criteria and in whom no exclusion criteria were present.

1.6.3.1 Inclusion criteria

Inclusion criteria consisted of the following: Children aged 2 months to 10 years, scheduled for an eye examination under anesthesia (EUA) at Universitas Annex Theatre Complex. For these procedures, it is standard practice at this institution for the parent of the child to accompany the child into theatre and remain with them until anaesthesia is induced; hence anxiolytic medication to reduce the anxiety of parent separation is not usually required. If anxiolytic premedication was required the child was excluded from the study.

1.6.3.2 Exclusion criteria

The following were exclusion criteria: Children under the age of 2 months and over 10 years old, if premedication was required. Patients who received any other sedative or analgesic drug during the anesthesia except for the Sevoflurane as described and the eye drops which are routinely given for this procedure to produce ocular mydriasis.

1.6.4 Schedule of dates

Ethics committee approval was obtained on 9 April 2015.

Enrollment of patients and conduct of study was initially set so start on June 2014 to August 2014. Due to unforeseen circumstances the above dates expired and an amendment to the original protocol was made. Ethics approval for the change in time schedule was obtained to extend the study period until December 2016

The clinical phase of data collection commenced after final ethics committee approval on 19 May 2015.

1.6.5 Data analysis

The analysis was done by the Department of Biostatistics.

Descriptive statistics, namely means and standard deviations or medians and percentiles were calculated for continuous data. Frequencies and percentages were calculated for categorical data.

1.7 Significance of the Study

This study aims to give anesthesia providers, involved in ophthalmology examinations, an indication of the dose of sevoflurane that is necessary during anesthesia to prevent the eyeball turning upward and thus safely guide the child through the EUA.

A secondary aim of the study was to determine what the main stimuli are for eliciting the Bell's reflex during the EUA.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

The concept of minimal alveolar concentration (MAC) was first described at the beginning of the 1960s, in order to be able to compare inhalation anaesthetic agents in terms of anaesthetic potency.¹ The MAC is a complex index based on the assessment of a motor response to a nociceptive stimulus such as skin incision, integrating the concepts of hypnosis, immobility, and analgesia. The amount of anaesthesia required to block autonomic responses (eg increased heart rate or arterial pressure) to nociceptive stimuli in 50% of the subjects is called 'MACBAR' (blocking autonomic responses).²

Inhalational agents are known to cause a dose dependent suppression of reflexes and movements.¹ Purposeful movement of a body part in response to noxious stimuli has been extensively used as a clinical sign of depth of anaesthesia. Using this movement to quantitate anaesthetic response induced by potent inhaled anaesthetics, Eger et al defined MAC as the minimum alveolar concentration of inhaled anaesthetic required to prevent 50% of subjects from moving in response to a skin incision.²

MAC is a useful measure because it mirrors brain partial pressure, allows comparisons of potency between agents, and provides a standard for experimental evaluations.^{1,2}

Zbinden et al undertook a comprehensive examination of the effects of different noxious stimuli on the purposeful movement response with isoflurane.³ This study demonstrated that varying clinical stimuli required different isoflurane concentrations to prevent a clinical

response and can be used to define a concentration-versus-response relationship for the hypnotic effects of isoflurane.

In children, sevoflurane is the most commonly used agent today for anaesthesia by inhalation. Its inhibitory effects on hemodynamic (MACBAR) and motor (surgical MAC) response to nociceptive stimulation have been widely investigated.⁴ However, its inhibitory effects on Bell's reflex is unknown.

Therefore, the aim of this study was to determine (MACBell) the MAC of sevoflurane inhibiting Bell's reflex in 50% of the subjects after a standardized surgical stimulus, namely an eye examination in children.

In 1823 Sir Charles Bell, a British anatomist, reported the oculogyric phenomenon which accompanies forceful closure of the eyelids. He first noted this palpebral-oculogyric reflex as an upward deviation of the eye during attempted eyelid closure in the presence of a lower motor neuron facial palsy (Bell's palsy)^{5,6} The usual finding of Bell's phenomenon is that the eyes roll upward and outward on attempted bilateral voluntary eyelid closure against resistance. The exact neural mechanism is unknown, but involves brainstem pathways between the seventh cranial nerve nucleus in the pons and the third cranial nerve nuclear complex in the rostral midbrain.

Hiraoka has suggested that the mesencephalic reticular nucleus may play an important role in integrating these two patterns of movement (bilateral lid closure and upward movement of both eyes).⁷ He divided the eye movement in voluntary lid closure into three phases: (i) Initial phase: Eye movement upwards or upwards and inwards;

(ii) Static phase: The eye remains upward and inwards for a few seconds, and is abducted in tight lid closure.

(iii) Final phase: The eye moves down from its upward and inward position.

Hiraoka also determined, using electromyographic (EMG) recording of the orbicularis oculi with simultaneous electro-oculographic (EOG) recording of both vertical and horizontal eye movements, that the amplitude of the movement is proportional to the strength of lid closure. The tighter the blink, the greater the amplitude of movement.⁷

Bell's phenomenon is a normal defense mechanism or reflex present in about 75% of the population. Bell's phenomenon can be seen at any time during anesthesia when the patient's depth of anesthesia has changed. It is a natural protective reflex in which the globe turns cephalic in response to stimuli such as pressure on the eye by a lid speculum.^{8,9} This occurs both in the awake state and with light planes of anesthesia. It is usually a sign of light anaesthesia (although the patient is not awake). In contrast, the reflex is extinguished with deep planes of anesthesia such that the eye remains in neutral gaze.¹⁰

This phenomenon can make eye examinations or corneal measurements under anesthesia difficult or impossible to perform. The anesthetist should be aware of this reflex and be prepared to deepen the anesthesia to facilitate these procedures.¹¹

Although an excessively deep anaesthetic will reliably prevent eye movements, this is not without possible harm. Sevoflurane causes a dose dependent reduction in blood pressure due to vasodilatation

and cardiac suppression. Intra ocular pressures are also reduced by sevoflurane and excessively deep anaesthesia may influence measurements made by the ophthalmologist.¹² Turnover times between cases may be longer after deep anaesthesia due to longer wake up times from patients after high concentrations of sevoflurane have been administered.

By finding the optimal dose of sevoflurane, the adverse cardiovascular effects of an excessively deep anaesthetic will be avoided. There may be a cost sparing effect because of reduced theatre turnover times between cases as well as saving on the amount of sevoflurane used.

Up-and-down method experiments are a simply performed type of sequential design for dose finding at the 50th quantile. The earliest use by the anesthesia research community of one particular sequential design—the up-and-down method (UDM)—seems to have been in studies of the effective concentration for a 50% response (EC50 or minimum alveolar concentration) of inhalation anesthetics.^{13,14}

Because clinical trials are always subject to patient availability and the economic constraints of minimizing the number of subjects, a sequential design is to be preferred. A brief survey of the use of up-and-down methodology in anesthesia research showed that most studies use 20 or more patients in a sequential trial, some studies were smaller. Statistical methods articles using simulation methods recommend that studies have 20 or more patients. Although Dixon proposed a modified up-and-down methodology for very small samples ($n < 6$),¹⁵ anesthesia trials using the up-and-down methodology typically have 20 – 40 patients.

Reports using up-and down methodology usually gives their results in a graphical display. The first report of up-and down methodology by Dixon and Mood¹⁶ included this graphical display. It simultaneously displays the concentrations administered, the sequencing of administered doses, and the positive or negative response for each subject at their assigned concentration.

The dose–response is conceived as a curve with increasing dose represented along the x-axis and the response variable plotted along the y-axis, thus the descriptive term dose–response curve. The points along the curve represent the tolerance distribution of the population exposed to the anesthetic¹⁷; thus the dose at which 50% of the population responds is considered the median effective dose—the effective dose for a response by 50% of patients exposed (ED50)

Columb and Lyons¹⁸ used the same design to report the EC50—labeled by them the minimum local analgesic concentration (MLAC)—of epidural bupivacaine and lidocaine for pain relief during labor.

To the knowledge of the researcher, and after the literature search performed by the researcher, no previous study has been conducted to determine the minimum alveolar concentration of sevoflurane needed to prevent Bell's reflex.

CHAPTER 3

3. METHODOLOGY

3.1 Introduction

Approval from the institutional ethics committee was obtained. Informed written consent for this study was obtained from the parents and assent was obtained from the children if they were able to understand the procedure. Children aged 2 months to 10 years presenting for EUA between 19/05/2015 and 23/7/2015 were prospectively included.

3.2 Study Design

The study design was an experimental study. A sequential design method for binary response variables was used for the determination of the concentration or dose associated with the 50% point along the dose-response curve. This up-and-down method of Dixon and Mood is commonly used in anesthesia research to determine an effective dose of a drug. Thus the study design took on the form of a dose finding study using up-and-down methodology as described under chapter 3.7 Construction of the instrument.

3.3 Study Site

The study was conducted at Universitas Annex Hospital in the same ophthalmology theatre that is routinely used for general anaesthetic cases. The same Datex Ohmeda anaesthetic machine was used throughout the research data collection.

3.4 Study Population

The study population consisted of 43 children. The patients had a variety of conditions requiring an eye examination under anaesthesia. Screening of the patients in terms of inclusion and

exclusion criteria, was performed during the preoperative visit by the principal researcher Dr J de Beer. A thorough history was taken during the preoperative examination, whereby it was determined if a patient qualified for the trial and if any exclusion criteria existed, which would exclude the patient from the trial. Informed consent was obtained from the parents of the children and, where appropriate, assent from the children who fulfilled the inclusion criteria and in whom no exclusion criteria were present.

3.5 Ethical Considerations

The protocol was handed in at the Ethics committee and final approval to conduct the study was obtained on 19 May 2015.

An amendment was made to the protocol to include the data of children aged 2 months to 1 year of age. These children were excluded in the initial protocol.

3.5.1 Authorization

Consent for the conductance of the study was obtained from the CEO of Universitas Annex Hospital. Consent from the involved departments namely Anaesthesiology and Ophthalmology was also obtained from the respective departments.

Informed Consent was obtained from the parents of the children involved and the children were asked to sign an assent form if they were able to understand the procedure.

3.5.2 Participation and Informed Consent

The parents or guardians of the children were informed that participation in this study was voluntary and that if they refused to allow their child to participate in the study, it would involve no penalty or loss of benefits to which their child was otherwise entitled; The person giving consent was also informed that they may withdraw

their child at any time without penalty or loss of benefits to which their child was otherwise entitled.

Parents were told that if they gave consent for their child to be included in this study, he/she will be given a standard general anaesthetic, like any other patient that needs an eye examination and that their child will not be aware during the examination.

The informed consent document also stated that this was an experimental study during which any upward eye movements during the examination would be noted as well as the concentration of the anaesthetic vapour at which these eye movements occurred. Participants were informed that they would not be remunerated for their child's participation in the study.

3.5.3 Confidentiality

Efforts were made to keep personal information confidential but absolute confidentiality could not be guaranteed as personal information would have to be disclosed if required by law.

Participant's parents or guardians were informed that other organizations could inspect and/or copy their research records for quality assurance and data analysis. These could include the Ethics Committee for Medical Research and the Medicines Control Council. The informed consent also stated that the results of this study (that is, the statistical data, not personal information) might be used in written or oral format at meetings, congresses and in journals and that if the results were published, it could lead to individual or cohort identification.

3.6 Inclusion and exclusion criteria

3.6.1 Inclusion criteria

The study population consisted of children that had to undergo an eye examination under anaesthesia. Children aged 2 months to 10 years were included.

3.6.2 Exclusion criteria

Exclusion criteria consisted mainly of factors that would influence the MAC or the amount of anaesthetic required. Patients were excluded if they showed one of the following criteria: Neurological disorders such as cerebral palsy, peripheral neuromuscular disorders, treatment with a drug interacting with the autonomic or central nervous system, obesity, or cardiac, renal, or hepatic disorder.

Other exclusion criteria were children aged 0 to 2 months and children above 10 years, any drugs other than sevoflurane used or if premedication was required. Patients who received any other sedative or analgesic drug during the anesthesia except for the sevoflurane as described and the eye drops for ocular midriasis were also excluded.

3.7 Construction of the Instrument

After informed consent (Appendix F) was obtained from the parents of the children and assent from the children, the study was conducted as follows:

A standard general anesthetic was given to all patients by the principal researcher Dr J de Beer.

The anesthesia machine was programmed with the patients weight and age before starting each case. The age confounder for MAC was thus eliminated. The same anaesthetic machine and sevoflurane vapourizer were used during the course of the study.

Patients were fasted for solids for 6 h before surgery and clear fluids for 2 hours. They did not receive any premedication.

Standard monitoring was used throughout the study, which consisted of heart rate, electrocardiography, pulse oximetry, non-invasive blood pressure, and inspired and expired gas analysis which consisted of sevoflurane, carbon dioxide, and oxygen. Temperature was monitored by using a probe in the nasopharynx. A forced air-warming device was used to maintain normothermia.

An inhalational induction was performed with sevoflurane in an oxygen and air mixture of 50% oxygen. After the induction an intravenous line was inserted. After visualization of a central eye gaze and ascertaining the jaw was relaxed, a laryngeal mask airway (LMA) was inserted. Mechanical ventilation was started using synchronous intermittent mechanical ventilation (SIMV) with pressure support and the tidal volume, frequency and pressure support were adjusted to achieve an end tidal carbon dioxide (EtCO₂) between 35 and 40 mm Hg. Thus the patients were kept normocarbic.

The anaesthetic was maintained with sevoflurane and 40% oxygen in air mixture. Before the examination started, a steady-state period of 3 min was maintained with a stable preselected value of end tidal concentration of sevoflurane (Et_{Sevo})

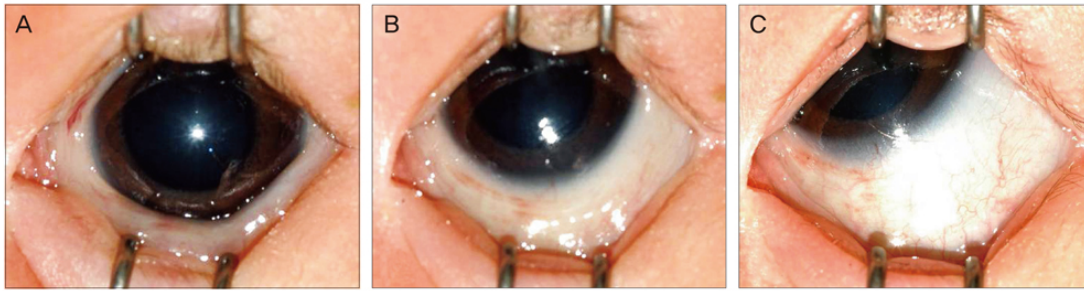
After the steady state period the scrub sister cleaned and draped the eye. Before the EUA began the following criteria had to be met:

- 1) The ET sevoflurane concentration had to be increased/ decreased to keep the predefined MAC stable for 3 minutes.
- 2) The eyeball had to be in a neutral gaze position.

At the end of the steady-state period, the ophthalmology registrar was allowed to start with the examination under anaesthesia by inserting an eye speculum. In addition to the normal anaesthetic chart data, the principal researcher recorded the following data in conjunction with the examining ophthalmology doctor on a separate data sheet: Patient number, age, weight, gender, temperature, qualification level of the ophthalmology doctor, minimum alveolar concentration, End tidal concentration of sevoflurane, eye response during the examination, grading of the eye response and the stimulus responsible for a positive eye response.

The dosage of sevoflurane that each patient received was predetermined. We used Dixon's 'up and down method' to determine the MACBell. The response of the preceding patient determined the end-tidal concentration of sevoflurane given to the next patient. We chose a starting MAC of 1.0 and thus the first patient was started on a MAC of 1.0. This MAC was decreased by 0.1% if there was no Bell's response elicited (Bells -) or increased by 0.1% in case of a witnessed Bell's response (Bells+). Successive patients were assigned a dose similarly by the response of the previous patient using MAC increments or decrements of 0.1.

In the case of a positive eye response, it was further graded as follows: A minimal response was defined as upward eye movement but where the center of the cornea was still visible while a full response was defined as upward eye movement but where the center of the cornea was not visible anymore.



A) Negative response

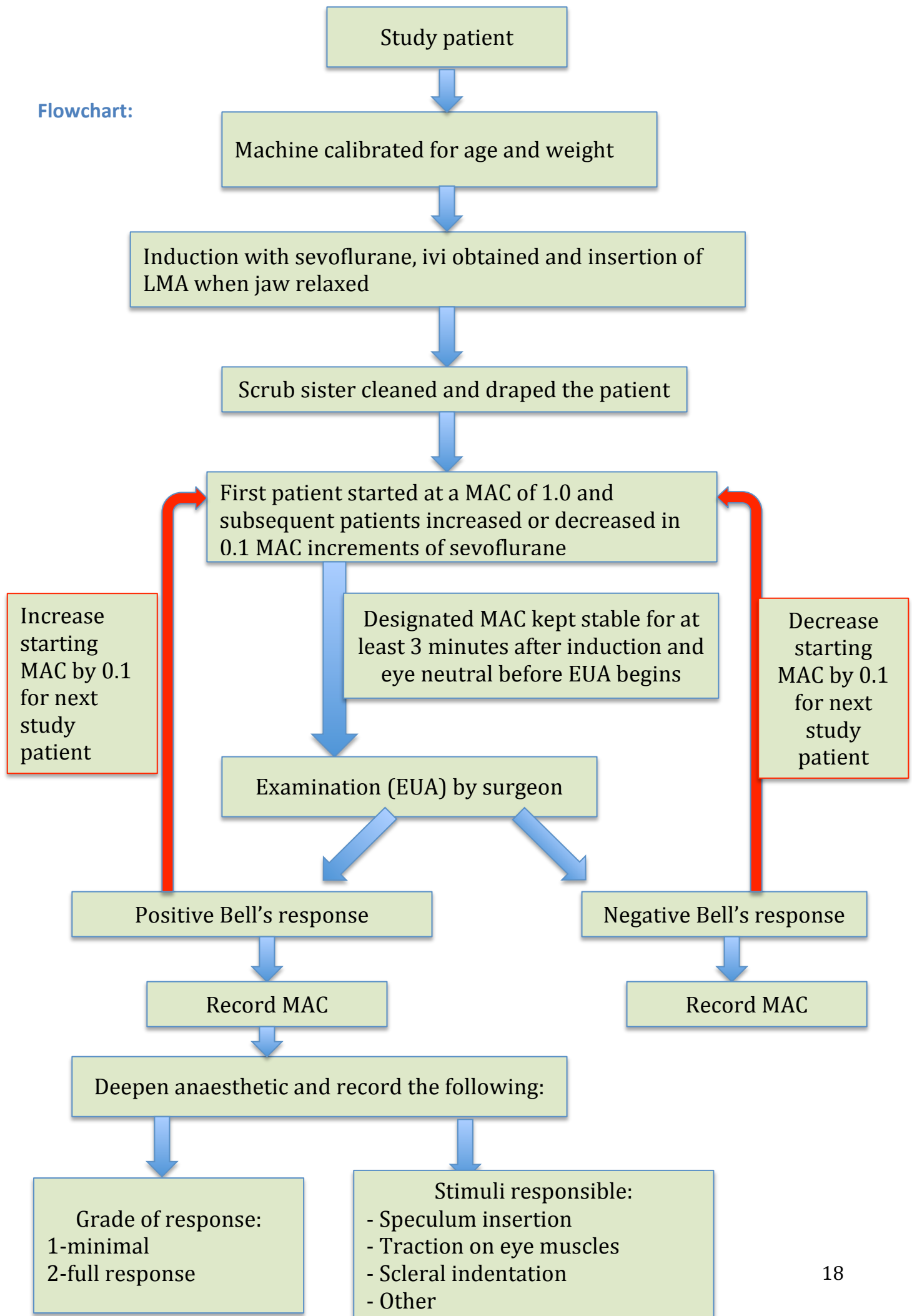
B) Positive minimal response (eyeball rotated upwards but center of cornea still visible)

C) Positive full response (eyeball rotated upwards and center of cornea not visible)

The stimulus responsible for a positive response was also recorded as one of the following:

- 1-Insertion of the eye speculum
- 2-Traction on the eye muscles
- 3-Scleral indentation
- 4-Other

Flowchart:



3.8 Technical challenges

Children are often scared and apprehensive about going to the operating theatre, whether it be for a surgical operation or an examination under anaesthesia. For very anxious children it is standard practice to prescribe a sedative premedication pre-operatively. However, parental separation is a frequent cause of pre-operative anxiety and by allowing the child's parent or guardian to accompany the child in theatre until anaesthesia is administered, it is standard practice in this institution not to routinely administer sedative premedication to children scheduled for EUA. Furthermore, most of these cases are booked as day-cases and sedative premedication may extend into the postoperative period and delay discharge home. Sedative premedication are known to influence anaesthetic requirements and thus the MAC required; therefore children who were deemed in need of a sedative premedication were excluded from the study.

Keeping the MAC stable at a certain value for the duration of the EUA proved challenging whilst conducting the study. To avoid errors due to different equipment used, a single Datex Ohmeda anaesthetic machine was used with a paediatric circle system. A single sevoflurane vapouriser was used for the whole study period. The anaesthetic machine was programmed with the child's age and weight to compensate for age and weight differences in MAC. Bloemfontein is 1400 meters above sea level and the anaesthetic machine used was calibrated to the same altitude above sea level.

3.9 Data Management/Analysis

Descriptive statistics, namely means and standard deviations or medians and percentiles, were calculated for continuous data. Frequencies and percentages were calculated for categorical data. The analysis was done by the Department of Biostatistics.

CHAPTER 4

4. RESULTS

4.1 Introduction

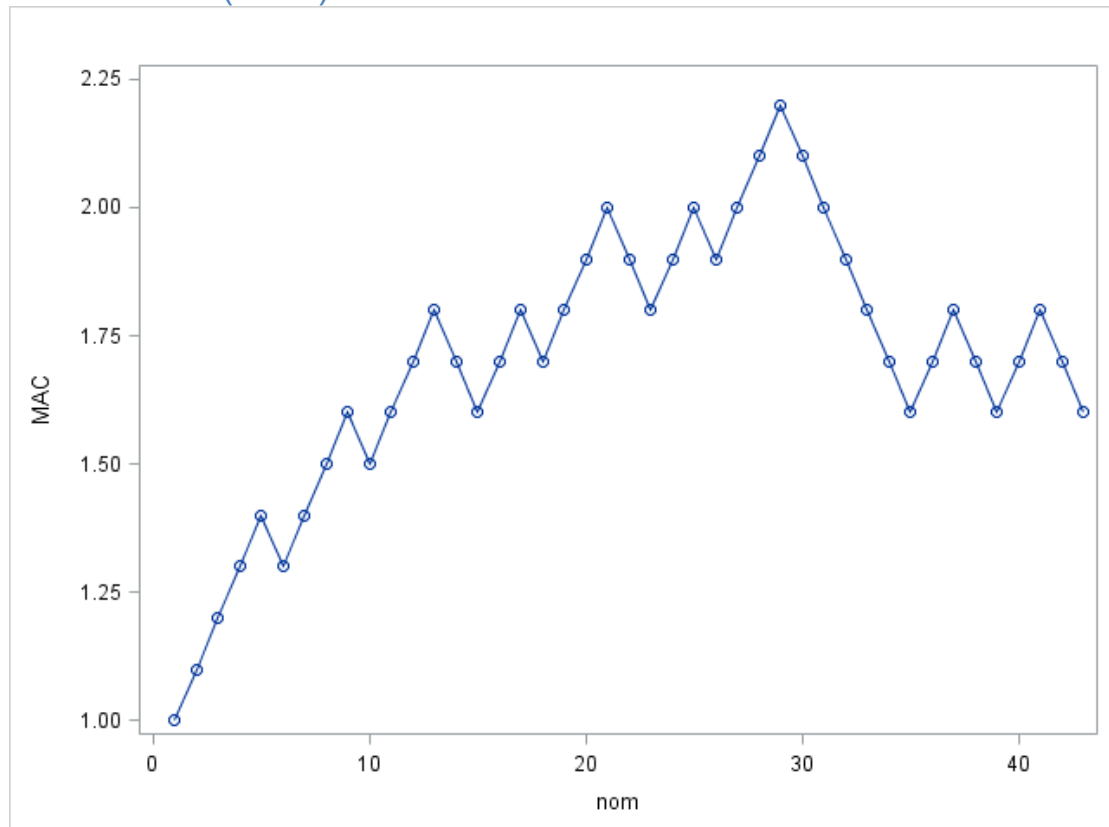
Forty-three (n=43) patients were included in the investigation. Data analysis was performed on recordings from these 43 subjects. In a sub-analysis the first 11 patients were excluded so that a pairing could be made of equal amounts of positive and negative eye responses to be able to calculate the ED50. The sub-analysis consisted of 32 patients.

4.2 Sample and Exclusions

During the study, 6 patients were excluded because they did not meet the inclusion and exclusion criteria.

4.3 Results

Figure 1: Sequential eye responses of patients with corresponding MAC values (n=43)



The up – down progression is shown in Figure 1. It can be noted that initially all the children had a positive Bell's response from the starting MAC of 1 to a MAC of 1.4. The highest MAC value at which a positive response was still noted was 2.1

With the initial results 58.1 % (n=25) had a positive Bell's reflex while 41.9% (n=18) had no Bell's reflex. The starting MAC of the study was set to start at a MAC of 1.0 and this estimation was too low because all the initial children had a positive Bell's response.

Figure 2: Sub-analysis of equally paired sequential eye responses with corresponding MAC values (n=32)

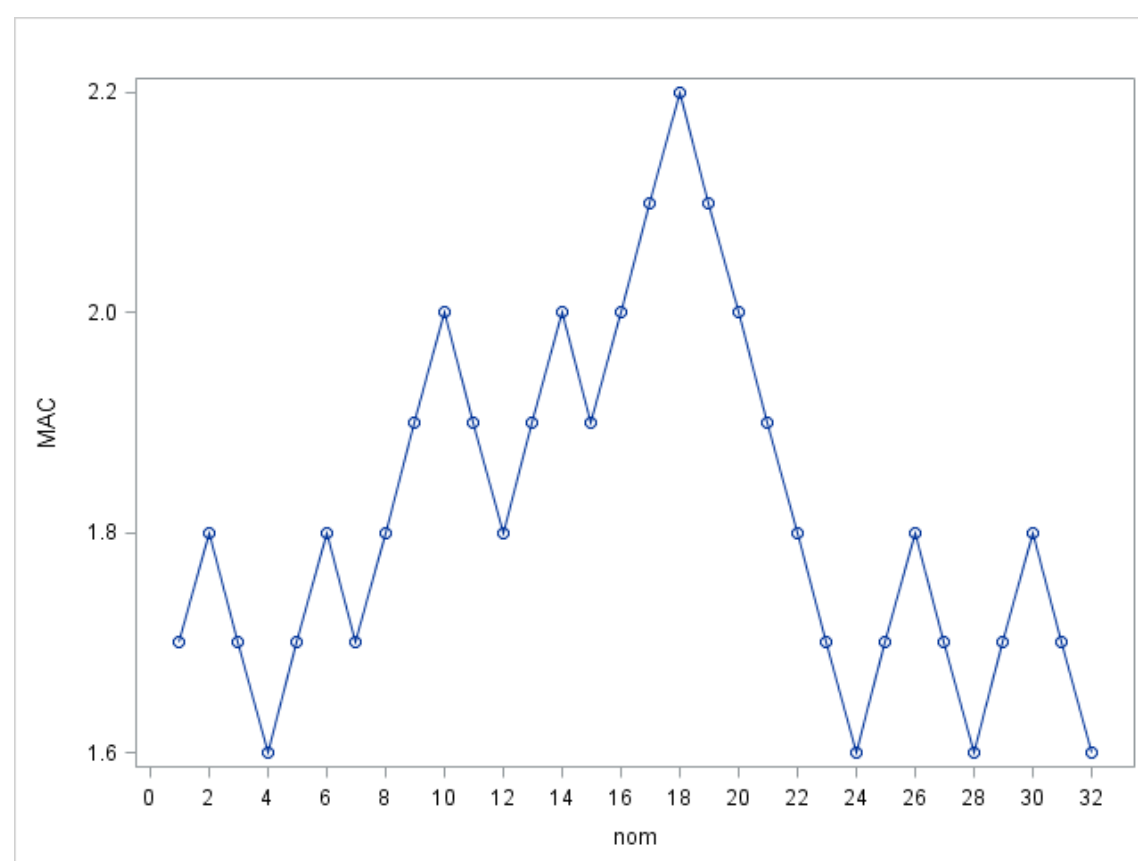


Figure 2 shows the sequential eye responses of patient's number 11 to 43 (n=32). The first 11 patients data was omitted to be able to pair the patients with positive eye responses to equal amounts of patients

without a Bell's response. The ED50 could then be obtained by the median value, ie a MAC of 1.8.

Table 1: Frequency of eye responses (n = 32)

Eye response	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Positive	16	50	16	50.00
Negative	16	50	32	100.00

Table 2: Frequency of MAC values of participants (n=32)

MAC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1.6	4	12.50	4	12.50
1.7	9	28.13	13	40.63
1.8	7	21.88	20	62.50
1.9	5	15.63	25	78.13
2	4	12.50	29	90.63
2.1	2	6.25	31	96.88
2.2	1	3.13	32	100.00

Table 3: Age distribution of participants

Age(months)	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2	1	3.13	1	3.13
8	1	3.13	2	6.25
11	1	3.13	3	9.38
12	2	6.25	5	15.63
13	1	3.13	6	18.75
14	1	3.13	7	21.88
15	3	9.38	10	31.25
17	1	3.13	11	34.38
21	1	3.13	12	37.50
24	1	3.13	13	40.63
29	2	6.25	15	46.88
33	1	3.13	16	50.00
34	1	3.13	17	53.13
37	1	3.13	18	56.25
40	1	3.13	19	59.38
41	1	3.13	20	62.50
42	1	3.13	21	65.63
43	1	3.13	22	68.75
44	1	3.13	23	71.88
45	1	3.13	24	75.00
46	1	3.13	25	78.13
58	1	3.13	26	81.25
60	1	3.13	27	84.38
61	1	3.13	28	87.50
71	2	6.25	30	93.75
73	1	3.13	31	96.88
120	1	3.13	32	100.00

Table 4: Gender distribution of participants

Gender	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Male	15	46.88	15	46.88
Female	17	53.13	32	100.00

The children were more or less equally distributed according their gender. Of the included subjects 46.88% (n=15) were male and 53.13% (n=17) were female.

Table 5: Age, temperature, weight and MAC of patients (n=32)

Variable	N	Mean	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
Age(months)	32	36.1	33.5	15	45.5	2	120
Temperature	32	36.1	36.2	36	36.4	34.9	37.1
Weight(kg)	32	13.5	14.5	9.5	16.5	4.8	22
MAC	32	1.8	1.8	1.7	1.9	1.6	2.2

The mean temperature of the children was 36.1 degrees Celsius. (range 34.9 degrees Celsius to 37.1 degrees Celsius). The mean weight of the children was 13.5kg (range 4.8 kg - 22 kg).

Table 6: Qualification level of ophthalmology doctor performing the eye examination

<u>Ophthalmology Doctor</u>	<u>Frequency (%)</u>
Consultant	3 (9.4%)
Registrar	29 (90.65%)

Regarding the experience of the ophthalmology doctor performing the EUA, the majority 90.6% (n=29) were on registrar level while only 9,4 % (n=3) of the EUA's were performed by a consultant.

Table 7: Grading of positive eye responses

Grade	Frequency n=25 (%)
Minimal response	18 (72.0)
Full response	7 (28.0)

Of these 25 positive responses, 18 (72%) were graded as a minimal responses and in 7 (28%) the responses were graded as full responses, with the center of the cornea not visible anymore.

Table 8: Stimulus responsible for eliciting a positive eye response

Stimulus	Frequency (%)
Eye speculum insertion	7 (28%)
Traction on eye muscles	17 (68%)
Scleral indentation	1 (4%)

The stimuli that were responsible for the positive Bell's response were traction on the eye muscles at 68%(n=17) and eye speculum insertion 28%(n=7); only 1 patient showed a response during scleral indentation.

4.4 Summary of Results

In summary, we have shown that inhibition of the Bell's reflex in response to stimulus required a minimum alveolar concentration (MAC) of 1.8. This response may not be abolished in the usual

clinical range of sevoflurane concentrations if a MAC of only 1.0 is administered.

The stimulus that was responsible for most of the positive Bell's responses was traction on the eye muscles.

CHAPTER 5

5. DISCUSSION

5.1 Interpretation of findings

In this study, we have demonstrated that the MAC_{bell} of sevoflurane (1.8) was markedly higher than the surgical MAC (1)

The Dixon method¹⁵ is a useful statistical approach of MAC calculation, requiring moderate sample size of subjects. Each of them has the same weight in MAC calculation, and the finality of this method is to determine the value predicting a 50% probability of response. This is provided by the average of successive opposite responses (pairs). The reliability of the Dixon method increases with an increasing number of pairs; indeed, six pairs are considered as optimal for a clinical study. In our study, at least six pairs of opposite responses were found.

The variability in responses probably reflects the large interindividual variability that is frequently observed in young children and classically related to different rates of physiological maturation. The variability in responses can also be due to different ophthalmology doctors with differences in their skills and techniques.

5.2 Comparison with published work

The surgical MAC of sevoflurane, resulting from inhibition of motor response to skin incision, has been estimated to be 2.5% in children and 2.2% in young adults, while the MAC_{BAR} resulting from inhibition of autonomic cardiovascular response to skin incision has been estimated at 1.9 MAC.¹⁹ These data demonstrate that inhibition of autonomic cardiovascular centers located in the medulla requires higher concentrations of sevoflurane than inhibition of the spinal cord. In this study, the values of MAC_{bell} corresponded to a MAC of

1.8, suggesting that the concentrations of sevoflurane required to block the Bell's reflex are markedly higher than those required to inhibit the spinal cord and more similar to those required to prevent autonomic responses. Thus, the dissociation between moving and Bell's responses observed under sevoflurane may be explained by different sensitivities of the brain structures involved in these processes.

Velly et al ²⁰ showed that in subjects anaesthetized with propofol or sevoflurane, the parameters collected by standard EEG (cortical) predicted loss of consciousness but not the motor response to laryngoscopy, whereas the parameters from the EEG recorded in the deep areas of the brain (subcortical) predicted the motor response to laryngoscopy but not unconsciousness. Thus, it appears that different anaesthetics agents have different brain targets, cortical and subcortical, where different processes are integrated: loss of consciousness in the cortex and pain response in subcortical areas. Anaesthetics have dissociated effects on these two targets in accordance with the agents and doses.

Higher concentrations of sevoflurane can predispose subjects to the risk of EEG and clinical seizures. Indeed, in a previous study by Bourgeois et al. two children demonstrated a brief episode of tonic-clonic movements at a End tidal sevoflurane concentrations of 5.3% and 5.7% respectively²¹ No clinical seizures were observed in our study.

5.3 Discussion of potential limitations and shortcomings of the study

Clinical trials are always subject to limited patient availability and the economic constraints of minimizing the number of subjects, therefore a sequential study design is often preferred. The up-and-down method experiment is a simply performed type of sequential

design for dose finding at the 50th quantile and that was the method used in this study. Because in an up and down methodology experiment the assigned doses are concentrated around the target dose for the 50th quantile, the relatively modest sample size prevents any precision in target dose estimators for the lower and upper tails of the tolerance curve.

Certain physiological and pathological states may alter MAC. In infants MAC is higher and in the elderly is lower.²² Also; MAC increases with hyperthermia, alcoholism and thyrotoxicosis. Likewise, hypothermia, hypotension (mean arterial pressure < 40 mmHg), and pregnancy decrease MAC. Duration of anesthesia, gender, height and weight seem to have little effect on MAC. Opioid analgesics and sedative-hypnotics, often used as adjuvants to anesthesia, decrease MAC.

MAC can be altered by several physiological and pharmacological variables. One of the most striking is the 6% decrease in MAC per decade of age. Three of the study subjects were less than one year. This deviated from the original protocol that excluded children less than one year, and approval was obtained from the ethics committee to include the data of these subjects in the study. In this study the anesthesia machine was programmed with the patient's age and weight to compensate for any age related difference in MAC. Although three of the subjects were between 2 months and one year, their age and weight were programmed into the anaesthetic machine and would thus not bias the MAC values of these subjects. The anaesthetic machine was also calibrated to 1400 meters above sea level and a single sevoflurane vaporizer was used with a pediatric circle system to standardize the equipment used to deliver the anaesthetic.

MAC is relatively unaffected by sex or duration of anesthesia.

MAC decreases 4% to 5% per degree centigrade decrease in core temperature. Therefore a forced air warming device was applied to all patients to maintain normothermia. Despite this one of the patients in our study cooled down to a temperature of 34.9 °C and this would have decreased this patients MAC requirements. This specific patient received a designated sevoflurane dose of a MAC of 2.2. and did not have a positive Bells response.

Drugs eg. local anesthetics, topical anesthesia, opioids, ketamine, barbiturates, benzodiazepines and other sedatives are known to decrease the MAC and were avoided in this study. Muscle relaxants were also avoided, as they abolish eye movements.

In our study the MAC and end tidal concentration of sevoflurane were kept constant for 3 minutes before the EUA started.

The time taken to reach a steady state or equilibrium between end tidal alveolar concentration and brain partial pressure differs between the different inhalation agents. This is due to differences in blood solubility of the different agents. The systemic uptake of volatile anaesthetics and their subsequent distribution and elimination have usually been described by multicompartnment models. The kinetic profile of a volatile agent is mainly determined by its physicochemical properties. The rate of induction of anaesthesia as well as the rate of recovery from anaesthesia is inversely related to anaesthetic solubility in the blood and fatty tissues. In addition, agent distribution is dependent on circulatory factors (e.g. organ perfusion) which themselves are modified by the agent. Common pharmacokinetic properties, such as protein binding, metabolism and renal excretion, have only a minor impact

on the time required by inhalational anaesthetics to reach MAC. The uptake of a volatile anaesthetic is described by the rate of increase of the FA/Fi ratio; where FA is the alveolar concentration of anaesthetic (measured at the end of expiration) and Fi is the inspired anaesthetic concentration.

Inter observer and intra observer variation in the recording of data was eliminated because all the data was collected by the Principal Researcher. Unfortunately the ophthalmology doctor performing the examination could not be standardized to a single examiner and there may have been inter-examiner variation regarding the strength of the stimulus during the EUA's. Conversely, this may also make the results of this study more applicable to the real life situation.

CHAPTER 6

6. CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In summary, this study has shown that inhibition of Bell's reflex in response to noxious stimulus required a minimum alveolar concentration (MAC) of 1.8 in 50% of cases. This response may not be abolished in the usual clinical range of sevoflurane concentrations.

The nociceptive stimulus that was responsible for most of the positive Bells responses was traction on the eye muscles.

6.2 Suggestions for practice and further research

Due to the high MAC_{Bell} value that is required to prevent the Bell's reflex during examination of the eye under anaesthesia, the following suggestions are made: The use of local anaesthetic eye drops can be used to abolish any nociceptive input contributing to this reflex and thus possibly lower the MAC needed to prevent eye movement. The sequence of tests performed during the examination could be rearranged so that the most noxious stimuli are performed at the end of the examination so that a positive Bell's reflex does not interfere with the rest of the eye examination. During such times of intense stimulation the MAC could be increased to 1.8 to prevent this reflex eye movement.

The ED₅₀ is commonly used as a measure of the reasonable expectancy of a drug effect, but does not necessarily represent the dose that a clinician might use as it will only be effective in 50% of the population. Logistical regression may be derived from the Dixon

data, allowing wider calculation of probability of occurrence of positive response such as ED95.

In a study by S.Sator - Katzenschlager it was shown that sevoflurane and propofol decreases intraocular pressure equally during non-ophthalmic surgery and recovery.¹² The high ED50 of sevoflurane required to prevent Bell's phenomenon may decrease intraocular pressure. This may make the intraocular pressure measurements made by the ophthalmologist inaccurate. A solution to this may be to use local anaesthetic eye drops prior to the examination under anaesthesia to abolish painful nociceptive stimuli that is responsible for eliciting the Bell's reflex.

Further studies are required to evaluate the MAC needed to prevent Bell's reflex if local anaesthetic eye drops are used in conjunction with general anaesthesia.

CHAPTER 7

7. References

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APPENDICES

Appendix A: Ethics approval certificate

Research Division
Internal Post Box G40
☎ (051) 4017795/4
Fax (051) 4444359

E-mail address: EthicsFHS@ufs.ac.za

Ms M Marais/jdpls

2015-04-09

REC Reference nr 230408-011
IRB nr 00006240

DR J DE BEER
DEPARTMENT OF ANAESTHESIOLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr De Beer

ECUFS NR 59/2014

PROJECT TITLE: THE MINIMUM ALVEOLAR CONCENTRATION (MAC) OF SEVOFLURANE REQUIRED TO PREVENT BELL'S PHENOMENON DURING EXAMINATION OF THE EYE UNDER ANAESTHESIA.

1. You are hereby kindly informed that the Ethics Committee approved the above study after the Signed permission letter from Dr S Gaelejew, Clinical Services, Universitas Academic Hospital was submitted. It will be ratified at the meeting scheduled for 19 May 2015:

1.1 The Ethics Committee also approved the following:

- **Request for the extension of the study period until December 2016**
2. Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
 3. Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
 4. The Committee must be informed of any serious adverse event and/or termination of the study.
 5. All relevant documents e.g. signed permission letters from the authorities, institutions, changes to the protocol, questionnaires etc. have to be submitted to the Ethics Committee before the study may be conducted (if applicable).
 6. A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

Ethics Committee
Office of the Dean: Health Sciences

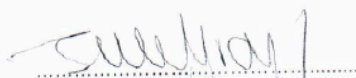
T: +27 (0)51 401 7795/7794 | F: +27 (0)51 444 4359 | E: ethicsfhs@ufs.ac.za
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
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7. Kindly refer to the ECUFS reference number in correspondence to the Ethics Committee secretariat.

8. Thus, this letter only serves as conditional approval.

Yours faithfully


.....
DR SM LE GRANGE
CHAIR: ETHICS COMMITTEE

Cc Prof G Lamacraft

Appendix B: Ethics approval of amendment to protocol



IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

27 January 2016

DR J DE BEER
DEPT OF ANAESTHESIOLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr De Beer

ECUFS NR 59/2014

DR J DE BEER

DEPARTMENT OF ANAESTHESIOLOGY

PROJECT TITLE: THE MINIMUM ALVEOLAR CONCENTRATION (MAC) OF SEVOFLURANE REQUIRED TO PREVENT BELL'S PHENOMENON DURING EXAMINATION OF THE EYE UNDER ANAESTHESIA.

1. You are hereby kindly informed that, at the meeting held on 26 January 2016, the Health Sciences Research Ethics Committee (HSREC) approved the following:
 - *Amendments to the protocol*
2. Kindly use the ECUFS NR as reference in correspondence to the HSREC Secretariat.
3. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act, No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes 2015; SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

PROF WJ STEINBERG
FOR CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences

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59/2014.

To Prof Diedericks, Head of Anaesthesiology department

I (Dr. J de Beer) would like to request permission to conduct the following study as part of my post graduate M.Med degree in Anesthesia.

Title:

To determine the minimum alveolar concentration (MAC) of Sevoflurane that is needed to prevent Bell's phenomenon during an examination of the eye under anesthesia.

Researcher:

Dr J de Beer
Tel: 0826623393

Discription of the study:

The aim of this study is to investigate how deep a child must be under anesthesia to prevent the eye from moving upwards during an eye exam under anesthesia.

The question we aim to answer with this study will therefore be:

What is the minimum alveolar concentration (MAC) that is necessary to prevent upward movement of the eyeball during an examination under anesthesia (EUA)?

Involved parties:

The research will be conducted on children that are booked for an eye examination under anesthesia

The research will be conducted at National hospital theatre complex

The departments involved is anesthesia and ophthalmology

This study will not involve extra time from the children because it is conducted at the same time as the eye examination.

The results of this study may be presented at a congress or published

I hereby give consent for the above study



Signature(Anaesthesiology HOD)

To Dr. W Marais, Head of Ophthalmology department

I (Dr. J de Beer) would like to request permission to conduct the following study as part of my post graduate M.Med degree in Anesthesia.

Title:

To determine the minimum alveolar concentration (MAC) of Sevoflurane that is needed to prevent Bell's phenomenon during an examination of the eye under anesthesia.

Researcher:

Dr J de Beer
Tel: 0826623393

Discription of the study:

The aim of this study is to investigate how deep a child must be under anesthesia to prevent the eye from moving upwards during an eye exam under anesthesia.

The question we aim to answer with this study will therefore be:

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The research will be conducted on children that are booked for an eye examination under anesthesia

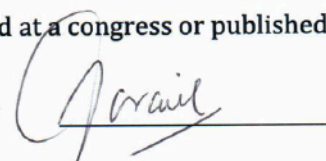
The research will be conducted at National hospital theatre complex

The departments involved is anesthesia and ophthalmology

This study will not involve extra time from the children because it is conducted at the same time as the eye examination.

The results of this study may be presented at a congress or published

I hereby give consent for the above study



Signature(Ophthalmology HOD)

Appendix E: Permission from hospital



health

Department of
Health
FREE STATE PROVINCE

20 May 2014

Dr J de Beer
Department Anaesthesiology
082 662 3393

Dear Dr de Beer

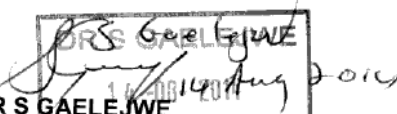
RESEARCH PROJECT: TO DETERMINE THE MINIMUM ALVEOLAR CONCENTRATION (MAC) OF SEVOFLURANE THAT IS NEEDED TO PREVENT BELL'S PHENOMENON DURING AN EXAMINATIONS OF THE EYE UNDER ANAESTHESIA."

Herewith permission for the mentioned project to be done at Universitas Annex Hospital on the following conditions:

1. The research should not expose the users and the Department to any avoidable harm.
2. Annual progress reports should be submitted and also a research report at the end of the research process.
3. Reporting of Adverse Events related to the research process must be done within 48 hours of discovery.
4. There shall be provision for obtaining informed consent from all patients/staff where appropriate.
5. Briefing sessions should be conducted with all stakeholders prior to commencement and at the end of the study to provide feedback where appropriate.
6. That approval is obtained from the Ethics Committee.
7. All records belong to UAH and must be returned intact.

The Chief Executive Officer must be notified if the findings of the project will be published and a research report needs to be sent to the Head Clinical Services as soon as the study is completed.

Yours sincerely


DR S GAELEJWE
ACTING HEAD: CLINICAL SERVICES
UNIVERSITAS ACADEMIC HOSPITAL
ACTING HEAD: CLINICAL SERVICES: DR S GAELEJWE
Private Bag X20660, Bloemfontein, 9300. Tel. No.: 051-4053868,
Fax: 051-4053634, First Floor, Universitas Academic Hospital
Email: gaelejwes@universitas.fs.gov.za

INFORMATION DOCUMENT

Study title: The minimum alveolar concentration (MAC) of sevoflurane required to prevent Bell's phenomenon during examination of the eye under anaesthesia.

Dear Patient

Thank you for your time in reading this information leaflet.

I, Dr Johann de Beer, under the guidance of Prof G Lamacraft of the department of Anaesthesiology of the University of the Free State, am currently doing research on the dosage of anaesthetic that is needed to prevent the eye from moving during the examination under anaesthesia.

Research is just the process to learn the answer to a question.

During the eye examination under anaesthesia it is sometimes noted that the eyeball moves upwards. Although the patient is not aware of this under anaesthesia it interferes with the eye examination and therefore we want to prevent it. In this study we want to learn what concentration of the anaesthetic (Sevoflurane) is needed to prevent the eye from moving upwards during the eye examination under anaesthesia

Twenty (20) to Fifty(50) patients, all South African citizens, between the ages of 1 and 10 years, will be participating in this study that will be conducted over a period of three months

We hereby invite you to give consent for your child to be included in this study.

If you give consent for your child to be included in this study, he/she shall receive a standard general anaesthetic, like any other patient that needs an eye examination. Your child will not be aware during the examination.

This is an experimental study during which we shall note if there is any upward eye movements during the examination and at what concentration of the anaesthetic vapour this occurs.

Your child's participation in this study does not hold any further risk, as in someone who did not participate in the study, because in both instances a general anaesthetic is needed.

This study will help us to determine the optimal dose of the anaesthetic drug that is necessary to prevent the eyeball from moving upwards during the eye examination under anaesthesia

You will be given pertinent information on the study while involved in the project and after the results are available.

Participation in this study is voluntary and refusal to allow your child to participate will involve no penalty or loss of benefits to which your child is otherwise entitled;

You may withdraw your child at any time without penalty or loss of benefits to which your child is otherwise entitled.

You will not be remunerated for your child's participation in the study.

Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council

The results of this study (that is, the statistical data, not personal information), may be used in written or oral format at meetings, congresses and in journals. If the results are published, this may lead to individual or cohort identification.

Please feel free to contact me, should you have any queries.

Dr J de Beer 0826623393

For reporting complaints or problems:

Secretariat and Chair of the Faculty of Health Sciences, University of the Free state
051-4052812

INLIGTINGSDOKUMENT

Die minimum alveolere konsentrasie Sevofluraan benodig om die Bell's verskynsel te voorkom tydens oogondersoek onder algemene narkose

Beste Pasiënt

Baie dankie dat u tyd neem om hierdie inligtingstuk te lees.

Ek is Dr Johann de Beer en onder leiding van Prof G Lamacraft van die Departement Anesthesiologie van die Universiteit van die Vrystaat, is ek tans besig om navorsing te doen oor die hoeveelheid narkose damp wat benodig word om te verhoed dat daar oogbewegings plaasving tydens die oogondersoek onder narkose.

Navorsing is slegs die proses waardeur die antwoord op 'n vraagstuk verkry word. Tydens die oogondersoek onder narkose beweeg die oogbal somtyds opwaarts. Alhoewel die pasiënt nie hiervan bewus is onder narkose nie, bemoeilik dit wel die oog ondersoek en daarom will ons dit probeer voorkom. In hierdie studie wil ons vasstel watter konsentrasie van die narkose middel (Sevofluraan) benodig word om te voorkom dat die oog opwaarts beweeg tydens die oogondersoek onder narkose.

Twintig (20) pasiënte, almal Suid-Afrikaanse burgers, tussen die ouderdomme 1 en 10 jaar, gaan deelneem aan die studie, wat oor 'n tydperk van drie maande gaan strek.

Ons nooi u hiermee uit om toestemming te gee om u kind by hierdie navorsingstudie in te sluit.

Indien u sou toestemming verleen dat u kind in hierdie studie ingesluit word sal hy/sy op die dag van die oog ondersoek 'n standaard algemene narkose ontvang, net soos enige ander pasiënt wat 'n oogondersoek benodig. U kind sal dus nie bewus wees tydens die ondersoek nie.

Hierdie is 'n eksperimentele studie waar ons tydens die oog ondersoek sal kyk of die oogbal enigsins opwaarts beweeg aldan nie. En by watter konsentrasie van narkose middel dit plaasvind aldan nie.

U kind se deelname aan die studie hou geen verdere risiko in as iemand wat nie sou deelneem aan die studie nie omdat 'n algemene narkose in beide gevalle benodig word

Hierdie studie sal ons dan instaat stel om die optimale dosis van die narkose middel te bepaal om te verhoed dat die oogbal opwaarts beweeg tydens die oogondersoek onder narkose

U sal pertinente inligting ontvang aangaande die uitkomst van die studie nadat dit voltooi is en die resultate beskikbaar is.

Deelname aan hierdie studie is vrywillig en weiering om deel te neem sal geen boete of verlies van voordele waarop u of u kind andersins geregtig is behels nie; U

kan te eniger tyd u kind onttrek sonder boete of verlies van voordele waarop u of u kind andersins geregtig is.

U gaan nie geldelik vergoed word vir u kind se deelname aan die studie nie. Daar is ook geen koste verbonde aan u kind se deelname in die studie nie.

Daar sal gepoog word om persoonlike inligting vertroulik te hou. Volkome vertroulikheid kan nie gewaarborg word nie. Persoonlike inligting kan bekend gemaak word as die wet dit vereis.

Organisasies wat u navorsingsrekords mag ondersoek en/of kopieer vir kwaliteitsversekering en data-analise sluit groepe soos die Etiekkomitee vir Mediese Navorsing en die Medisynebeheerraad in

Die resultate van die studie (d.w.s die statistiese data, nie persoonlike inligting nie) mag gebruik word in mondelingse of geskrewe formaat by vergaderings, kongresse en in joernale. Indien die resultate gepubliseer word, kan dit lei tot individuele- of groepsidentifikasie

U kan my gerus skakel indien u enige navrae het,

Groete

Dr Johann de Beer

0826623393

Vir rapportering van klagtes of probleme:

Sekretariaat en Voorsitter: Etiekkomitee van die Fakulteit
Gesondheidswetenskappe, Universiteit van die Vrystaat (051) 4052812

CONSENT DOCUMENT

CONSENT TO PARTICIPATE IN RESEARCH

PROJECT TITLE: The minimum alveolar concentration (MAC) of sevoflurane required to prevent Bell's phenomenon during examination of the eye under anaesthesia.

You have been asked to allow your child to participate in a research study.

You have been informed about the study by Dr J de Beer

You or your child will not be receiving any form of compensation as a result of study-related procedures.

You may contact Dr J de Beer at 0826623393 any time if you have questions about the research or if you are injured as a result of the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and neither you nor your child will be penalized or lose benefits if you refuse to allow your child to participate or decide to terminate participation.

If you agree to allow your child to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my child's involvement in the study means and I voluntarily agree to allow my child to participate.

Signature of Participant

Date

Signature of Witness
(Where applicable)

Date

Signature of Translator
(Where applicable)

Date

TOESTEMMINGSDOKUMENT

TOESTEMMING TOT DEELNAME AAN NAVORSING

PROJEKTITEL: Die minimum alveolere konsentrasie van Sevofluraan benodig om Bell's verskynsel te voorkom tydens 'n oog ondersoek onder narkose

U is versoek om u kind toe te laat om aan 'n navorsingstudie deel te neem.

U is oor die studie ingelig deur Dr J de Beer

U of u kind sal geen finansiële vergoeding ontvang vir u deelname in die studie nie.

U kan Dr J de Beer enige tyd kontak by 0826623393 indien u vrae oor die navorsing het of as gevolg van die navorsing beseer is.

U kan die Sekretariaat van die Etiekkomitee van die Fakulteit Gesondheidsweteskappe, UV by telefoonnommer (051) 4052812 kontak indien u enige vrae het oor u regte as 'n proefpersoon.

U kind se deelname aan hierdie navorsing is vrywillig, en u of u kind sal nie gepenaliseer word of voordele verbeur as u weier om u kind te laat deelneem of besluit om deelname te staak nie.

As u instem om u kind te laat deelneem, sal 'n ondertekende kopie van hierdie dokument sowel as die deelnemerinligtingsblad, wat 'n geskrewe opsomming van die navorsing is, aan u gegee word .

Die navorsingstudie, insluitend die bogenoemde inligting is verbaal aan my beskryf. Ek begryp wat my betrokkenheid by die studie beteken en ek stem vrywillig in om my kind te laat deelneem.

Handtekening van deelnemer

Datum

Handtekening van getuie
(Waar van toepassing)

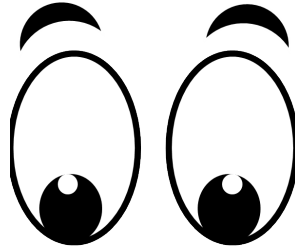
Datum

Handtekening van Vertaler
(Waar van toepassing)

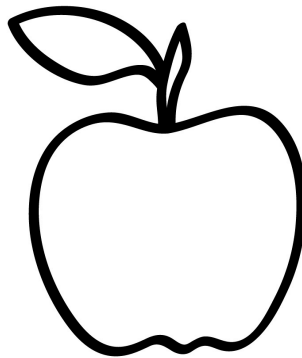
Datum

Appendix H: Child assent form

You are being asked to take part in a research study being done by Dr. de Beer of the University of the Free State. In this study, we are interested to know how deep you need to be asleep under anaesthesia for the eye doctors to examine your eyes. We have asked your parent or caregiver whether it is OK for you to participate, but now we want to see if it is OK with you.



If you decide to take part in this study, you will be given a mask to inhale some gas that will make you asleep so that the doctors can examine your eyes. The gas smells like a sweet apple. This is not painful and all the children whose eyes are examined get this medicine to help them sleep. After the examination we will wake you up again.



By signing this you are showing that you understand what is going to be happening and have asked any questions you may have about the research. You can also ask questions later if you cannot think of them now. Signing this form does not mean that you have to finish the study- you can pull out from the study at any time without explaining why.

Child's signature

Date

Time

Appendix I: Data collection sheet

: Patient number

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: Age years;months

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: Weight (kg)

		.	
--	--	---	--

: Gender

- male

-female

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: Temperature (degree celcius)

		.	
--	--	---	--

: Ophthalmology qualification

- Consultant

- Registrar

- Medical officer

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: MAC

	.	
--	---	--

: Et sevoflurane(%)

	.	
--	---	--

: Eye response

-positive

-negative

--

f positive response then answer J and K

: Grade of Bell's response

-minimal response

-full response

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: Stimulus responsible for response

-Speculum insertion

-Traction on eye muscles

-Scleral indentation

-Other, specify_____

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