Clinical Study Report

Title: Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery

Name of IMP: Propofol

Indication: Intravenous anaesthesia

Description of study: This is a Phase IV observational study to measure the blood propofol concentrations during TCI using a point of care device.

Sponsor: Great Ormond Street Hospital for Children NHS Foundation Trust

Sponsor's Protocol Number: 12AR04

Phase: IV

Study initiation date: 18th January 2013

Date of study termination: 30th August 2013

Chief Investigator: Dr Mike Sury

Sponsor: Great Ormond Street Hospital for Children NHS Foundation trust

This is to confirm that the study was conducted in compliance with Good Clinical Practice. Archiving responsibility of essential documents located in the TMF has been undertaken by GOSH and the appropriate arrangements are in place.

Contents

Abbreviations

ABG	Arterial Blood Gas
CI	Chief Investigator
C_m	Measured Concentration
C_p	Predicted concentration
GOSH	Great Ormond Street Hospital
MHRA	Medicines and Healthcare products Regulatory Agency
PE	Performance Error
TCI	Target Controlled Infusion
TIVA	Total intra-venous anaesthesia
TMA	Trial Medical Advisor

1. Synopsis

Name of Sponsor: Great Ormond Street Hospital for Children NHS Foundation Trust	
Name of Finished Product: Propofol	
Name of Active Ingredient: Propofol	
Title of Study: Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery	
Chief Investigator: Dr Mike Sury	
Study Centre: Great Ormond Street Hospital	
Publication (reference): Measured versus predicted blood propofol concentrations in children during scoliosis surgery (accepted for publication in Anesthesia and Analgesia)	
Studied period (years): 1 **Date of first enrolment:** 5th Feb 2013 **Date of last completed:** 2nd July 2013	**Phase of development:** Phase IV **Date of report:** 11th August 2014

This is a single-Centre study in children involving one site in one Member state (UK). Twenty patients were consented and received treatment.

2. Ethics

2.1 Independent ethics committee

The study and all associated amendments were reviewed and approved by the National Research Ethics Committee – London Bloomsbury Research Ethics Committee

2.2 Ethical conduct of the study

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

2.3 Patient information and consent

The parents of the trial subjects or patients themselves provided written informed consent. The information sheet and consent forms were reviewed and approved by ethics

committee. The participants had a consultation with the investigator to discuss the study and to give written informed consent to take part if they chose to participate. Only after giving this consent were any study procedures completed. See appendices I-VIII for information sheets and consent forms used in the study.

3. Investigators and administrative structure

3.1 Chief investigator

Dr Mike Sury

Consultant Anaesthetist and Honorary Senior

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3.2 Principal Investigators

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4. Introduction

Children undergoing spinal surgery have propofol anaesthesia delivered by a computerised syringe driver (Target Controlled Infusion or TCI). Spinal surgery is associated with major blood loss. This can result in either over or under-delivery of propofol, both can result in serious problems during anaesthesia. In this observational study we measured the blood propofol concentrations during TCI using a point of care device. An appreciable variation in the blood level from the predicted level would highlight the importance of bed side measurement of blood propofol concentrations during total intravenous anaesthesia.

Major spinal surgery requires intra-operative monitoring of evoked potentials to detect spinal cord ischemia. Inhalational anaesthetic agents suppress evoked potentials and, because propofol has less effect on evoked potentials, total intra-venous anaesthesia (TIVA) with propofol is the preferred anaesthetic technique. TIVA is administered using a target controlled infusion (TCI) syringe pump. This is a microprocessor controlled pump which adjusts the infusion dose rate based on an in built algorithm. The algorithm was developed using previously measured blood propofol levels in a small sample of children. The model also predicts and displays the blood propofol levels which are used to titrate the anaesthetic to achieve a desired blood level. In children inter-patient variability is high and therefore the predicted levels may be inaccurate. Previous studies have shown that the predicted error could be greater than 20%.

During spinal surgery major blood loss occurs and often patients require large volume fluid resuscitation including blood transfusion. Blood loss and fluid resuscitation can result in significant changes to the blood levels of propofol. The TCI pump does not take this into account and therefore patients could receive inadequate or excessive propofol. A high blood concentration can cause cardiovascular depression and delayed recovery, and a low concentration permits intra-operative awareness. Both of these are serious complications.

5. Study objectives

5.1 Primary objective

To determine whether the blood propofol levels differ appreciably from the predicted levels in children undergoing major spinal surgery during total intravenous anaesthesia.

5.2 Secondary objective

To determine the factors contributing to the difference between the measured and predicted blood levels and the potential value of bed side measurement of propofol for accurate delivery of total intravenous anaesthesia.

6. Methodology

6.1 Subject recruitment

Patients who undergo spinal surgery were identified through the anaesthetic team and information leaflet were sent in advance. Further information was provided during the pre-operative assessment either in the pre-assessment clinic or in the ward. Written consent was obtained by one of the researcher.

6.2 Study treatment

There was no change in the anaesthetic technique from the standard routine technique for spinal surgery. General anaesthesia was induced by either intravenous propofol or inhaled sevoflurane (intra-venous or gaseous induction), according to the clinical need or patient's

choice. For intravenous induction, 2% propofol was administered using a Target Controlled infusion device (TCI) using the “Paedfusor” model. If a sevoflurane induction was performed TCI is initiated after loss of consciousness and sevoflurane was gradually reduced when desired propofol blood level is achieved. Also remifentanil (an opioid analgesic) was infused as part of balanced anaesthesia.

The Paedfusor pharmacokinetic model was used for the delivery of TCI. This model was chosen because it has the least bias and imprecision of all available models in children. This is part of routine care for spinal surgery patients at GOSH. An intra-arterial cannula is routinely placed for direct arterial blood pressure monitoring and blood sampling. Electroencephalography (EEG) is routinely used and interpreted during anaesthesia.

6.3 Blood Propofol Measurement

Measurement of blood levels of propofol was performed during the maintenance phase of anaesthesia. For the study, blood samples (< 1 ml) were taken from the existing arterial line for measurement of propofol levels. Samples were taken every 20 to 40 min during the maintenance phase of anaesthesia and thereafter until consciousness has returned. Also additional measurements were performed when there is a sudden increase in blood loss and following fluid resuscitation.

During spinal surgery blood samples were routinely taken for Arterial Blood Gas (ABG) analysis, blood sugar measurement and measurement of haemoglobin at the discretion of the anaesthetist. Where possible, the propofol measurements were performed using the same blood taken for routine care. Additional blood sampling for study purposes were performed as mentioned above. However the total number of samples taken per patient was limited to 10.

The samples were taken by a trained investigator or the anaesthetist. The measurements were performed using the Pelorus 1500 analyser (Sphere Medical, UK) - A validated and CE marked bedside propofol measurement device by a trained investigator. The results of the measurement were concealed from the clinical team. The maximum numbers of samples were limited to 10 per patient.

6.4 Data Collection

The following data were collected:

- Propofol blood level, predicted by the TCI pump
- The target and predicted blood levels, along with the dose rates and their timings were recorded and stored in the infusion pump(This data was downloaded into a PC for analysis later)
- Intra-operative physiological variables was downloaded into a PC using the iX-Trend software (blood pressure, heart rate, temperature, saturation and end-tidal and

patient's haemoglobin (iSTAT and Hemacue) was recorded according to the anaesthetists clinical judgement.

- Timing and volume of intravenous fluids (including blood)

6.5 Use of device within the trial

The Pelorus 1500 blood analyser - a bed side propofol analyser was used to measure propofol concentration. This device is CE marked and has been shown to be precise and accurate for measurement of blood propofol concentrations up to 12mcg/ml (8). A trained investigator, not involved in the direct clinical care of the patient, was performed the measurements. The Alaris Asena PK TCI syringe driver is a standard tool for spinal patients having TIVA at GOSH. It is maintained by the Biomedical Engineering department.

7. Number of patients (planned and analysed)

20 children between the age of 5 and 18 years were included in the study

8. Diagnosis and main criteria for inclusion

- 20 children undergoing major spinal surgery under propofol TCI
- Age range between 5 and 18 years
- Children having surgery expecting to last more than 3 hours.

9. Exclusion criteria

- Surgery expecting to last less than 3 hours
- Patients with major hepatic or renal disease

Withdrawal of Subjects:

Participants or the parents are free to withdraw from the study at any time for any reason

10. Treatment dose

2% propofol was administered using a Target Controlled infusion device (TCI) using the "Paedfusor" or "Marsh" models.

11. Duration of treatment

20 subjects were recruited within a year.

12. Criteria for evaluation

Primary Outcome:

The measured (Cm) and predicted (Cp) blood propofol concentrations in each patient were plotted against time. The distribution of all Cm-Cp was described for the patient group. The performance of a TCI model was evaluated using published descriptors (Varvel JR, Donoho DL, Shafer SL. Measuring

the predictive performance of computer-controlled infusion pumps. *J Pharmacokinet Biopharm* 1992; 20(1):63-94).

Secondary Outcome:

The effect of blood loss was examined by correlation of the cumulative intravenous fluid volume with Performance Error (PE), and also the relationship between the change in PE and the increment of IV volume infused between each blood propofol measurement.

Modelling:

A proportional correction factor, made on a single measurement of Cm after 30 minutes of TCI (Correction factor = Cm at 30 min/Cp at 30 min; $Cp_{(corrected)}$ = Cp*correction factor) was applied to all subsequent Cps and corrected PEs were calculated.

13. Statistical methods

Descriptive statistics was used in the final analysis of the study

13.1 Primary Endpoint

The difference between the predicted and measured blood levels of propofol during the maintenance stage of anaesthesia. The difference is calculated as a proportion to the predicted blood level – and is termed Prediction or Performance Error (PE) (11)

PE = (Cm – Cp / Cp) * 100%;

Cm = Measured Concentration, Cp = Predicted concentration.

13.2 Secondary Endpoints

- Median prediction error (MDPE)
- a descriptor of the centre of the distribution of PE
- known as “bias”
- Median absolute prediction error
- Median | PE |
- A descriptor of the variation in PE
- Wobble
- PE-MDPE
- A descriptor of variation of PE around bias
- Drift

- Regression coefficient of PE v time

14. Efficacy evaluation

There was no efficacy end point in the study.

15. Safety evaluation

The study does not involve any active intervention other than blood sampling through an existing arterial cannula. No adverse events were reported relating this study.

16. Discussion and overall conclusions

In the 20 children, the ages ranged from 9 to 17 y (mean 15 y), body weight 24.5 to 95 kg (mean 48.4 kg), the sex ratio was 10/10. 14 had scoliosis related to Neuromuscular disease of a Muscular Dystrophy. The Paedfusor model was used in 16 children of whom 13 weighed <61 kg and were ≤18 y old: 3 others weighed 95, 74 and 66 kg and were 12, 14, and 17y old respectively. The Marsh model was used in 4 children aged 14, 14, 16 and 16 y who weighed 69, 73, 60 and 56 kg respectively.

Surgery lasted > 2 h in all but one patient and > 4 h in 9 patients. Blood losses, and IV fluid volumes were higher, and the lowest hemoglobin concentrations were lower in the Paedfusor group; the smallest patients tended to lose more blood and have more IV fluids in proportion to their body weight. In any patient, the lowest pH, base excess and blood glucose level was 7.21, -3.2 and 3.9 $mmol.L^{-1}$ respectively, and the highest blood lactate concentration was 4.31 $mmol.\ L^{-1}$.

Anesthesia was induced with sevoflurane in 8 children. Target propofol concentration was set between 3 and 7 $\mu g.ml^{-1}$ during surgery. There were a total of 154 blood propofol measurements. The numbers of blood samples collected in children were as follows: 6 samples in 5 children, 7 in 3, 8 in 7, 9 in 3 and 10 in 2. Technical problems delayed measurements in one patient for 185 minutes.

Cm-Cp and PE were normally distributed (Shapiro-Wilk 0.865 and 0.9194 respectively). Cm was usually higher than Cp and that there was a trend for Cm-Cp to decrease over time.

Using all data points in all children, mean Cm-Cp was 1.5 $\mu g\ ml^{-1}$ (LOA -1.4 to 4.5)[1] and mean PE was 44.7% (LOA -40.1 to 130.2).[24] For the whole patient sample, there was a trend for PE to decrease over time (Pearson correlation coefficient = -0.47, $p < 0.0001$, $r^2 = 0.22$).

Cm was almost always greater than Cp and therefore MDPE and MDAPE were equal except for 2 patients. The median of MDPEs for the patient group was 39.8%: the MDPE was > 50% in 8 children. The MDPE was not associated with body weight (Spearman correlation rho = 0.36, p = 0.23). Two children had consistently lower Cm than Cp. Their lowest Cm(s) were 1.74 and 1.96 when the Cp was 3mcg ml^{-1}. Both had the Paedfusor model and their body weights were 28 and 33 kg.

The median (and range) of the Wobble was 13.6% (4.0 to 42.3). All but one patient had a negative Divergence. Two children had Wobble > 30%; they also had the Paedfusor model and their body

[1] LOA = 95% limit of agreement. LOAs, being wide, were estimated as = mean +/-SD*2, and calculated for repeated measures, taking into account covariance within subjects[24]

weights were 24.5 and 55.9 kg. The measures of performance tended to be highest (i.e. worse) in children who had the Paedfusor model.

The estimated blood loss was not accurate enough to justify analysis. The effect of IV fluid infusion on performance was examined. Total IV fluid volume infused was not associated with MDPE (Spearman correlation rho = -0.25, p = 0.29). Combining all data, PE decreased with time and also with the cumulative IV fluid volume replacement (Pearson correlation coefficients 0.476 and 0.51 respectively); combining both time and IV volume into a regression model did not improve the correlation over the effect of IV volume alone. There was no association between increment of IV volume infused and the change in PE (Pearson correlation R= -0.051, p = 0.56).

Discussion

There was often a major difference between Cm and Cp during scoliosis surgery and, usually, the Cm was higher than Cp. There was no evidence of accumulation. Divergences were negative except in one patient in whom the highest Cm at the end of surgery was 5.64 μg ml^{-1} (Cp = 3.5). Two children however, had Cm appreciably lower than Cp: during Cp 3μg ml^{-1} their lowest Cm(s) were 1.74 and 1.96 and at these levels there may have been a risk of intraoperative awareness. The limits of acceptable TCI performance, proposed by Schüttler and colleagues, are that the mean PE should be < 20% and the mean |PE| should be < 30% . The median PE exceeded 20% in all but one of our patients.

Wide differences between Cm and Cp may be foreseen given the potential variation in the physical and physiological characteristics of children. Many of the children in this study had scoliosis associated with syndromes for which the pharmacokinetics of propofol is unknown. For children with uncommon diseases, it may be impractical to study enough cases to calculate a pharmacokinetic model specific to that patient group. The influence of other anaesthesia drugs, especially remifentanil, on the kinetics of propofol may also be important. There was a dilemma in deciding which model to use for children ≥ 61 kg and < 16 y. Our data are not sufficient to support the preferment of either Marsh of Paedfusor models, but the performance variables of the Paedfusor TCI model tended to be worse in younger and smaller children.

Blood loss tended to be higher in the smaller patients and the influence of blood loss and intravenous fluids may have been important. Nevertheless, there was no relationship between the volume of IV fluids administered and change in PE i.e. the PE increased or decreased, equally as often, irrespective of IV fluid volume infused. Blood loss may reduce Cm because propofol is lost with the blood, but this may be offset by a reduction in the central compartment volume, which might increase Cm if Cp is maintained.

Continuous monitoring of the concentration of propofol in blood would be a major step forward but is not yet available. Now that reliable, albeit intermittent, point of care blood propofol assay is feasible the performance of TCI can be checked and an adjustment made to the TCI model for the individual patient. This has been proposed by Cowley and Clutton-Brock (Cowley N, Clutton-Brock T. Use of a device to measure blood propofol levels to improve inter-patient bias of propofol target controlled infusion. Annual Scientific Meeting: Society for Intravenous Anaesthesia UK (SIVA UK); Nottingham, 2012) who showed that the performance of the Marsh TCI model can be appreciably improved in individual patients by recalibrating the model using a proportional correction factor,

made on a single measurement of Cm after 30 minutes of TCI (Correction factor = Cm at 30 min/Cp at 30 min; $Cp_{(corrected)}$ = Cp*correction factor). We have applied this process to our data. First, a correction factor for each patient was calculated based on the first Cm taken > 30 minutes after starting TCI (the first Cm could be much higher than Cp and was therefore ignored). The correction factor was applied to all subsequent Cps and corrected PEs were calculated. Performance was appreciably improved by this adjustment. The mean of uncorrected and corrected MDPEs were 41.5% and -9%: mean difference 50.5%, 95% CI 36.4 to 64.6. The means of uncorrected and corrected MDAPEs were 45.6% and 16.8%: mean difference 28.9%, 95% CI 10.9 to 46.8.

Our study is of a small sample of heterogeneous children and our results may not reflect the performance of TCI in children generally or in other specific situations. Nevertheless, wide and variable differences between Cm and Cp during major prolonged surgery may be found elsewhere and this report may serve as a warning to clinicians if they encounter unexpected clinical signs of either excessive or inadequate propofol anaesthesia at what they perceive as a safe and effective dose.

17. Appendices

17.1 Patient Information Sheet 6-10 years old

Comparison of measured versus predicted blood propofol concent
children undergoing spinal surgery: the Propofol study

Patient Information Sheet 6-10 years old

1. Why is this study being done?

You need a special sleep medicine to keep you asleep during your operation which is given by a special pump. This special pump also says how much medicine is in your body. In this study, the doctor wants to double-check that the special pump is correct.

2. Why have I been asked to take part?

The doctors are asking all children having spinal operation to take part. For this operation you will be given a special medicine called propofol to make you sleep.

3. Did anyone else check the study is OK to do?

The study has been checked by a group of people called a Research Ethics Committee and they think it is OK to do the study.

4. Do I have to take part?

No, you don't have to. Your treatment will be the same if you take part or don't take part.

5. What will happen to me if I take part in the study?

You will go to sleep as usual. When you are asleep we will take a small amount of blood and use it to see how much special medicine is in your blood.

6. Is there another sort of medicine I can have instead?

The doctors will decide which special sleep medicine is better for you before the operation and this will not be changed by this study.

7. Might anything about the study upset me?

Nothing should upset you about this study. You will not feel anything as you will be sleeping. If something does upset you, please tell your mum and dad and the doctors who will be happy to talk with you.

8. Will joining in help me?

We cannot promise the study will help you but it might help other children in the future.

9. What happens when the research stops?

Nothing different will happen - you will go back to the ward as you would anyway.

10. Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

All your medical details will be kept safe and nobody else other than the doctors and nurses, and the people involved in this study will see any of the information.

11. What if I don't want to do the research anymore?

If you don't want to do the research, just tell your mum and dad, or the doctor. Nobody will mind.

12. What if something goes wrong?

This study is safe and there is little chance of anything going wrong. If you are worried about anything please talk to your mum and dad. You can also speak with the doctors who will be happy to talk with you about any worries you have.

13. Who to contact?

If you would like to ask questions or find out more about the study, you can speak to the study doctor. His name is Doctor Mike.

Dr Michael Sury (Chief Investigator)

Department of Anaesthesia

Great Ormond Street Hospital

London WC1A 7AS

Tel no: 0207 829 8865

Email: Mike.Sury@gosh.nhs.uk

Thank you very much for reading this.

17.2 Patient Information Sheet 11-15 years old

Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery: the Propofol study

Patient Information Sheet 11-15 years old

1. Why is this study being done?

You need a medicine called propofol to keep you asleep during your operation which is given by a special pump. This pump is controlled by the anaesthetist, the doctor whose job it is to make sure you are asleep and safe during your operation. This special pump also tells us how much medicine is in your body. We want to check what the pump tells us and if it is accurate or not.

2. Why have I been asked to take part?

We are asking all children having spinal operation to take part.

For this operation, you will need a medicine called propofol. Propofol is an anaesthetic medicine, which makes people sleep during operations. Propofol will be given to you through a small tube in your arm to keep you asleep during your operation.

3. Did anyone else check the study is OK to do?

The study has been checked by a group of people called a Research Ethics Committee and they think it is right and safe.

4. Do I have to take part?

No, you don’t have to. Your treatment will be the same if you take part or not.

5. What will happen to me if I take part in the research?

You will go to sleep as usual. When you are asleep, we will take a small amount of blood and use it to measure the amount of propofol in your blood. You will not notice it because you will be asleep throughout the operation.

6. Is there another sort of medicine I can have instead?

The doctors will decide which sleep medicine is better for you before the operation and this will not be changed by this study.

7. Might anything else about the research upset me?

Nothing should upset you about this research. If something does upset you please tell your parents. You can also speak to the study doctor who would be happy to answer your questions.

8. Will joining in help me?

We cannot promise the study will help you but it might help other children in the future.

9. What happens when the research stops?

Nothing different will happen - you will go back to the ward as you would anyway.

10. Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

All your medical details will be kept safe and nobody else other than the doctors and nurses, and the people involved in this study will see any of the information.

11. What if I don’t want to do the research anymore?

If you don‘t want to do the research, just tell your parents, or the doctor. Nobody will mind.

12. What if something goes wrong?

This study is safe and there is little chance of anything going wrong. If you are worried about anything please talk to your parents. You can also speak with the doctors who will be happy to talk with you about any worries you have.

13. Who to contact?

If you would like to ask questions or find out more about the study, you can speak to the Dr Michael Sury (Chief Investigator)

Department of Anaesthesia

Great Ormond Street Hospital

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Tel no: 0207 829 8865

Email: Mike.Sury@gosh.nhs.uk

Thank you very much for reading this.

17.3 Patient Information Sheet 16 and over

Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery: the Propofol study
Patient Information Sheet 16 and over

1. Why is this project being done?

During spinal surgery an intravenous anaesthetic medicine called Propofol is administered continuously to keep you asleep. This method is the standard and the preferred anaesthetic technique for spinal surgery because it does not interfere with the methods used to detect damage to the spinal cord during the operation.

The medicine is administered using a special pump controlled by the anaesthetist, the doctor who makes you sleep safely. The anaesthetist sets a "target" level of propofol in the blood and the pump delivers the medicine according to this target. The pump also informs the anaesthetist a "predicted" blood level of the drug, continuously during the operation. The pump is able to deliver the medicine and predict the target level based on a program derived from previous studies. This technique is called Target Controlled Infusion (TCI) and is considered to be the most reliable method of administering the anaesthetic.

During spinal surgery there can be a considerable amount of blood loss. This can affect the accuracy of the prediction. Also the predicted values are more likely to be inaccurate in children, when compared to adults.

For these reasons, the doctors are interested to know if there is an important difference between the "predicted" and the "measured (true)" levels of propofol.

2. Why have I been asked to take part?

You have been asked to participate as you will be undergoing spinal surgery and will be receiving propofol as your main anaesthetic during the operation.

3. Do I have to take part?

No. You do not need to take part if you do not wish to. We will ask your permission and if you want to, you can sign a form. If you decide to stop, or say no for any reason, that will be OK. You will get the same treatment whether you take part or not.

4. Did anyone else check the study is OK to do?

This study has undergone review internally at Great Ormond Street Hospital NHS Trust and has also been checked and approved by an independent Research Ethics Committee.

5. What will happen to me if I take part?

Your anaesthetic is not changed for this study. Your anaesthetist will explain you how you will go to sleep. When you are asleep, we will take a small amount of blood from a cannula placed into one of your blood vessels inserted routinely for spinal surgery. We will use this blood to measure your blood levels of the anaesthetic. These values will not be revealed to your anaesthetist. You will not have any additional skin punctures for this study.

6. What will I have to do?

You will be fully asleep when the samples are taken and so you will not notice.

7. What are the possible disadvantages and risks of taking part?

There are no anticipated risks involved in this study. Your anaesthetic is not being changed by the study. The total amount of blood taken is less than 10 ml which is unlikely to cause any harm.

8. What are the possible advantages and benefits of taking part?

It is unlikely that you will benefit from taking part in this project. The information generated from this study could be useful in the future to help Anaesthetists improve anaesthesia in children during spinal surgery.

9. What if there is a problem?

It is unlikely that there will be any problems as a result of your participation in this study.

If you are worried about anything please talk to your parents. You can also speak with the doctors who will be happy to talk with you about any worries you have.

10. Will my taking part in the study be kept confidential?

Yes. Your personal details will not be stored in the research records and will be kept confidential. Only members of the clinical care team will have access to your data.

11. What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any point. This will not affect the care that you receive. Your treatment and your anaesthesia will be the same whether you take part or not.

12. Will my GP be notified of my participation?

With your assent (and your parents' consent) we will contact your GP to notify him/her that you will be taking part in this study.

13. Who is organising and funding the research?

The study is being sponsored and organised by Great Ormond Street Hospital NHS Foundation Trust. Some funds are provided by Brighton and Sussex Medical School and the Ernest Leach Fund. The researchers are not paid for completing this project.

14. Contact details of the research team members

If you would like to ask questions or find out more about the study, you can speak to the study doctor. His name is Doctor Mike Sury.

Dr Michael Sury (Chief Investigator)

Department of Anaesthesia

Great Ormond Street Hospital

London WC1A 7AS

Tel no: 0207 829 8865

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Thank you for your time and reading this Information Sheet.

17.4 Parent Information Sheet

Parent information sheet
Title: Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery

Why is this project being done?

During spinal surgery an intravenous anaesthetic drug called Propofol is administered continuously to keep your child asleep. This method is called Total Intravenous Anaesthesia (TIVA). This is the standard and the preferred anaesthetic technique for spinal surgery because it does not interfere with the monitoring techniques (Evoked potentials) that are used to detect any damage to the spinal cord during the operation.

TIVA is administered using a special microprocessor controlled pump which is in turn controlled by the anaesthetist. The anaesthetist sets a "target" level of propofol in the blood and the pump delivers the drug according to this target . The pump also feeds back the anaesthetist a "predicted" blood level of the drug, continuously during the operation. The pump is able to deliver the drug and predict the target level based on an algorithm derived from previous studies. This technique is called Target Controlled Infusion (TCI) and is considered to be the most reliable method of administering the anaesthetic.

During spinal surgery there can be a considerable amount of blood loss. This can affect the accuracy of the predicted blood levels by the pumps. Also the predicted values are more likely to be inaccurate in children, because of the inherent high variability between children when compared to adults. This could result in a high or low levels of the drug in the blood which can cause serious complications. A high level can cause an undue drop in blood pressure and a low level can cause awareness during the operation.

For these reasons, we are interested to know if there is an important difference between the "predicted" and the "measured (true)" levels of propofol.

Why has my child been asked to take part?

Your child has been asked to participate as he/she will be undergoing spinal surgery and will be receiving propofol based anaesthetic for the operation.

Do I have to take part?

No. You and your child do not need to take part if you do not wish to.

Did anyone else check the study is OK to do?

This study has undergone review internally at Great Ormond Street Hospital NHS Trust and has also been checked and approved by an independent Research Ethics Committee.

What will happen to my child if I take part?

The Anaesthetic technique is NOT changed. As routine, your child will be sent to sleep either by breathing the anaesthetic gas or by administering propofol through an intravenous cannula. Your child will then be kept asleep using a continuous propofol infusion as described above.

For this study, we will take a small sample of blood (<1ml) for measuring the blood propofol levels. This will be taken from an existing cannula into one of the small arteries, inserted as routine after your child is fully anaesthetised. We will only take a maximum of 10 samples.

We will not reveal the results of the measurement to the anaesthetist. The anaesthetist uses his clinical judgement based on the available monitoring to ensure that your child is asleep.

What will I or my child have to do?

None. Your child will be asleep when the blood samples are taken.

What are the possible disadvantages and risks of taking part?

There are no foreseen risks involved in this study. The anaesthetic is not being changed by the study. The total amount of blood taken from your child will not exceed 10 ml, and this is unlikely to cause any harm. The blood will only be taken from the existing cannula placed routinely for surgery. NO further skin punctures will be performed for study purposes.

What are the possible advantages and benefits of taking part?

It is unlikely that you or your child will benefit from taking part in this project. The information generated from this piece of work could be useful in the future to help Anaesthetists improve anaesthesia in children during spinal surgery.

What if there is a problem?

It is unlikely that there will be any problems as a result of your (and your child's) participation in this study. However, if you wish to make a complaint, please do so in writing to the Chief Investigator (Dr Michael Sury, contact details in section 12) of this study. You will need to follow the NHS Complaints Procedure. In the event that you believe that your child has been harmed due to negligence then you may have grounds to seek compensation.

Will my taking part in the study be kept confidential?

Yes. Your child's personal details will not be stored in the research records and will be kept confidential. Only members of the clinical care team will have access to your child's data.

What will happen if I don't want to carry on with the study?

You and your child are free to withdraw from the study at any point. This will not affect the care that your child receives. The treatment and anaesthesia will be the same whether you take part or not.

Will my child's GP be notified of my participation?

With your assent we will contact your child's GP to notify him/her that you will be taking part in this study.

Who is organising and funding the research?

The study is being sponsored and organised by Great Ormond Street Hospital NHS Trust. Some funds may be sought from the "Ernest Leech Fund", a small grant offered by the National Institute of Academic Anaesthesia (NIAA). Also some funds are provided by Brighton and Sussex Medical School and the Welcome Foundation. The machine for measuring the blood propofol levels (Pelorus 1000) will be provided 'on loan' by Sphere Medical Ltd (Cambridge, UK). The researchers are not paid for completing this project.

There are no conflicts of interest.

Contact details of the research team members

Dr Michael Sury (Chief Investigator)

Department of Anaesthesia

Great Ormond Street Hospital for Children

London WC1N 3JH

Tel no: 0207 829 8865

Email: surym@gosh.nhs.uk

Other Researchers:

(Dr. Selva Panchatsharam, Dr. Mike Callaghan, Dr. Jonathan Smith,

Miss. Rachel Day;

Department of Anaesthesia, Great Ormond Street Hospital for Children)

Thank you for your time and reading this Information Sheet.

17.5 Parent Invitation Letter

Family address

Date:

Dear Parent

Re name and date of birth of child

Your child is due to have an anaesthetic for his/her spinal surgery and we would be most grateful if you would consider taking part in a research project called: “Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery”

Briefly, for this surgery, an anaesthetic drug called “Propofol” is administered through a special pump. This pump is controlled by the anaesthetist who sets a target level of propofol in the blood. The pump then feeds back the anaesthetist a “predicted” blood level of the drug, continuously during the operation.

We would like to find out, what is the difference between this predicted level and the true level in the blood, by using a device which can measure the blood levels of propofol.

Your child’s anaesthetic will NOT be altered by this study. All we are asking is to

take small samples of blood when your child is asleep, during the operation, to measure the blood levels of the anaesthetic drug - propofol.

We will not carry this out unless you give your written consent and we aim to meet you during your anaesthetic pre-assessment and ask your permission.

We can answer any questions when we meet you but you are welcome to contact us beforehand to say that you are not interested, or to ask any questions.

We are most grateful.

Yours sincerely

Dr Michael R. J. Sury (Consultant Anaesthetist at Great Ormond Street Hospital and Honorary Senior Lecturer at Portex Department of Anaesthesia ICH/UCL)

Mobile: 07967 507 884

Tel no: 0207 829 8865

Email: Mike.Sury@gosh.nhs.uk

On behalf of researchers:

Dr. Selva Panchatsharam (Honorary research registrar, Great Ormond Street Hospital)

Dr. Michael Callaghan (Clinical Fellow, Great Ormond Street Hospital)

Dr. Jonathan Smith (Consultant Anaesthetist, Great Ormond Street Hospital)

Miss. Rachel Day (Medical student, Brighton and Sussex University

17.7 Participant Consent Form

Study Number: 12AR04

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery

Name of Researchers:

Dr. Selva Panchatsharam, Dr. Michael Callaghan, Dr. Jonathan Smith, Miss. Rachel Day, Dr. Mike Sury

Please initial box

I confirm that I have read and understand the information sheet dated.. 18/02/2013. (version. 2 / 12AR04) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the researchers named above, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to my GP being informed of my participation in the study. ☐

I agree to take part in the above study.

Name of Patient _____ Date _____ Signature _____

Name of Person _____ Date _____ Signature _____

taking Consent

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

17.8 Parent Consent Form

Study Number: 12AR04

Patient Identification Number for this trial:

CONSENT FORM for Parents or Guardian of the child

Name of child _____ _____

Title of Project:

Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery

Name of Researchers:

Dr. Selva Panchatsharam, Dr. Michael Callaghan, Dr. Jonathan Smith, Miss. Rachel Day,

Dr. Mike Sury

Please initial box

I confirm that I have read and understand the information sheet dated. 18/02/2013 (version. 2 /12AR04) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that the participation of my child is voluntary and that we are free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I understand that relevant sections of my child's medical notes and data collected during the study, may be looked at by the researchers named above, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records. ☐

I agree to my child's GP being informed of my participation in the study. ☐

I agree to allow my child to take part in the above study.

Name of Parent/Guardian_____ Date _____ Signature

Name of Person _____ Date _____ Signature

taking Consent

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

17.8 ASSENT FORM FOR CHILDREN

To be completed by the child

Project title: Comparison of measured versus predicted blood propofol concentration in children undergoing spinal surgery

Child /young person to circle and initial all they agree with:

Has somebody else explained this project to you?	Yes/No	☐
Do you understand what this project is about?	Yes/No	☐
Have you asked all the questions you want to?	Yes/No	☐
Have you had your questions answered in a way you understand?	Yes/No	☐
Do you understand it is OK to stop taking part at any time?	Yes/No	☐
Are you happy to take part?	Yes/No	☐

If any answers are “no‟ or you don’t want to take part, don’t sign your name!

If you do want to take part, you can write your name below

Your name _____

Date _____

The doctor who explained this project to you needs to sign too:

Print Name _____

Sign Date _____

Thank you for your help.