PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS study protocol
AUTHORS	Pirlich, Nina; Grehn, Franz; Mohnke, Katja; Maucher, Konrad; Schuster, Alexander; Wittenmeier, Eva; Schmidtmann, Irene; Hoffmann, Esther

VERSION 1 – REVIEW

REVIEWER	Liu, Xing Sun Yat-Sen University Zhongshan Ophthalmic Center, Glaucoma
REVIEW RETURNED	28-Dec-2020

GENERAL COMMENTS	1. The effect of propofol on IOP is not clear. There are published papers demonstrated that propofol had no effect on IOP. And the mechanisms of IOP decrease by propofol is not clear. It is generally believed that propofol induction causes a decrease in systemic arterial pressure, which may cause a sharp drop in IOP. But the clinical significance of blood pressure changes concerning IOP in the pediatric population is largely unknown. So we consider it important to set up a proper control. And measurement of IOP before anesthesia is suggested. How to evaluate the IOP lowering effects on children of propofol? And the IOP lowering effects may be quite varied in different person. How to eliminate the individual variance for propofol? 2. The IOP lowering effects of Sevoflurane and propofol in pediatric population are different, so the data are suggested to separate in the analysis of the link between the magnitude of IOP and depth of anesthesia (Line29-31). 3. It is reported that iCare tonometer tends to overestimate intraocular pressure (IOP), even in anesthetized children. And in high IOP values, measurements with the iCare tonometer do not correlate well with the applanation tonometer. How to analysis these variations caused by the instrument used in IOP measurement? 4. As the Perkins tonometer is a contact applanation tonometer, the exclusion criteria are suggested to include the contradictions of measurement.

REVIEWER	Ruiz-Villa, Joaquín O. Universidad Nacional de Colombia
REVIEW RETURNED	14-Jan-2021

GENERAL COMMENTS	A very interesting protocol, addressing a problem commonly underestimated. Glaucoma in children is a cause of blindness that requires awareness. This protocol creates an opportunity to standardize terms in research around this topic. I suggest you to pay special attention in the effect size of midazolam premedication in

	those children, recording BIS readings since T0 is an strength that you have in this protocol. Since it can be used in a regression model. Y

REVIEWER	Turcu-Stiolica, Adina University of Medicine and Pharmacy of Craiova, Department of Biostatistics
REVIEW RETURNED	01-May-2021

GENERAL COMMENTS	The paper aimed to report the design and baseline characteristics of a study registered in ClinicalTrials.gov with the number NCT03972852. Please provide the CONSORT checklist.

REVIEWER	Zhang, Q Wills Eye Hospital
REVIEW RETURNED	26-May-2021

GENERAL COMMENTS	Suggested changes: Page 3 Line 8: data on normal distribution…: please remove normal. page 6 line 49: please clarify if the same person will collect using both iCare and Perkins page 8 line 3: change future studies to future report? Page 9 line 12: please clarify if this is a two sided or one sided test? Same place as above: please clarify if both eyes of a subject will be included or just one eye, if one eye – how it is chosen? What time point is selected to measure the primary outcome of correlation? there are three measures in total at three times. Page 9 line 19: please explain what you mean by: the smaller correlation between IOP and BIS are still detectable with sufficient power? How much smaller? Page 9 lines 31-36: how is time included in the model, please list exact variables in the model. Why random effects on subject is selected? Not clear how the data from 20 healthy children will be handled in the analysis and in the model. How is the agreement among the four experts in this setting?

REVIEWER	Stratton, Irene Gloucester Hospitals NHSFT, Gloucestershire Retinopathy research Group
REVIEW RETURNED	14-Jun-2021

GENERAL COMMENTS	I found this paper and wondered whether you had considered differences by age in the performance of the BIS and if a larger sample with age stratification might be worthwhile? Paediatr Anaesth . 2017 Apr;27(4):399-408. doi: 10.1111/pan.13086. Epub 2017 Feb 17. Effect of age on the performance of bispectral and entropy indices during sevoflurane pediatric anesthesia: a pharmacometric study Alberto Sciusco 1, Joseph F Standing 2, Yucheng Sheng 3, Pasquale Raimondo 1, Gilda Cinnella 1, Michele Dambrosio 1 There is no justification of the sample size of 20 for the control group. f there are only 20 then one patient is going to be determining the confidence intervals if a non-parametric method is used. With the concerns from the Sciusco paper about differences by age then a larger sample stratified by age would seem to be sensible.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Xing Liu, Sun Yat-Sen University Zhongshan Ophthalmic Center

Comments to the Author:

1. The effect of propofol on IOP is not clear. There are published papers demonstrated that propofol had no effect on IOP. And the mechanisms of IOP decrease by propofol is not clear. It is generally believed that propofol induction causes a decrease in systemic arterial pressure, which may cause a sharp drop in IOP. But the clinical significance of blood pressure changes concerning IOP in the pediatric population is largely unknown. So, we consider it important to set up a proper control. And measurement of IOP before anesthesia is suggested. How to evaluate the IOP lowering effects on children of propofol?

As you suggest, we perform a measurement of IOP before induction of anesthesia. At time point 1 (t1) we perform a first IOP measurement after titrated propofol application (2-4 mg/kg body weight). This dose is noticeably less than a "bolus sleep dose". The lower dosage and the slow administration by titrating propofol minimize the risk of a drop in blood pressure. It is in the nature of things and the central topic of this study protocol that neonates and young children require an examination under sedation/anesthesia to avoid crying or squinting of the eyes which may lead to falsely high values. To evaluate the IOP lowering effects of propofol in children we perform a second measurement of IOP at time point 2 (t2) when deep anesthesia is obtained by a "sleep bolus" of propofol (4-5 mg/kg body weight).

And the IOP lowering effects may be quite varied in different person. How to eliminate the individual variance for propofol?

We share your view that IOP lowering effects may be different from person to person. Therefore, our study has a sample size of 100 children each with suspected glaucoma and 20 controls without glaucoma.

2. The IOP lowering effects of Sevoflurane and propofol in pediatric population are different, so the data are suggested to separate in the analysis of the link between the magnitude of IOP and depth of anesthesia (Line29-31).

Thank you for that information. Of course, we will exclude data from children who had to undergo mask induction with sevoflurane from the main analysis and analyze them separately (Page 10, subgroup analysis).

3. It is reported that iCare tonometer tends to overestimate intraocular pressure (IOP), even in anesthetized children. And in high IOP values, measurements with the iCare tonometer do not correlate well with the applanation tonometer. How to analysis these variations caused by the instrument used in IOP measurement?

Thank you very much for this comment. Indeed, the iCare overestimates IOP in high IOP values. The overestimation has not been proven in children with glaucoma, buphthalmos and in supine position under general, standardized anesthesia. Data is still lacking on this relationship. However, the comparison of the two measurement methods is one of the planned substudies (secondary outcome). Up to now, Goldmann applanation tonometry is still the reference standard. We do not expect high correlation between the two methods. Moreover, the comparison might underline the importance of applanation tonometry even under standardized conditions. As said above, the use of two tonometers is not intended to find high correlations since two different methods never agree completely. By using regression-based Bland Altman statistics we will be able to analyze the difference between the instruments.

4. As the Perkins tonometer is a contact applanation tonometer, the exclusion criteria are suggested to include the contradictions of measurement.
Thank you very much for this great suggestion. We have added a sentence to the methods section.

"The agreement between the instruments (Perkins applanation tonometry and ICare rebound tonometry) has been evaluated only in a few studies under different conditions than our study. Rebound tonometry has been shown to overestimate IOP in high IOP values."

Reviewer: 2
Dr. Joaquín O. Ruiz-Villa, Universidad Nacional de Colombia

Comments to the Author:
A very interesting protocol, addressing a problem commonly underestimated. Glaucoma in children is a cause of blindness that requires awareness. This protocol creates an opportunity to standardize terms in research around this topic. I suggest you to pay special attention in the effect size of midazolam premedication in those children, recording BIS readings since T0 is an strength that you have in this protocol. Since it can be used in a regression model.
Thank you for this excellent point. We will perform a regression model for effect size of midazolam as a secondary endpoint.
At this point, we first want to point out that the differences of the BIS values between timepoint t0 und t1 are of much more interest than the absolute values.

Reviewer: 3
Dr. Adina Turcu-Stiolica, University of Medicine and Pharmacy of Craiova

Comments to the Author:
The paper aimed to report the design and baseline characteristics of a study registered in ClinicalTrials.gov with the number NCT03972852. Please provide the CONSORT checklist.
Dear reviewer, thank you very much. Our study is not a randomized clinical trial. Our study is a prospective clinical cohort study, not involving any randomization to a specific treatment. Therefore, we have not prepared the CONSORT statement. However, we have registered our prospective trial at clinicaltrials.gov. We have furthermore, updated our records on the clinicaltrials.gov homepage.

Reviewer: 4
Dr. Q Zhang, Wills Eye Hospital

Comments to the Author:
Suggested changes:

page 3 Line 8: data on normal distribution…: please remove normal.
We removed ´normal´.

page 6 line 49: please clarify if the same person will collect using both iCare and Perkins
Yes, the same person will collect IOP data. We have changed the wording accordingly.

page 8 line 3: change future studies to future report?
We removed this term.

page 9 line 12: please clarify if this is a two sided or one sided test?
It is a two-sided test. We have clarified this in the text.

Same place as above: please clarify if both eyes of a subject will be included or just one eye, if one eye – how it is chosen? What time point is selected to measure the primary outcome of correlation? there are three measures in total at three times.

Yes, both eyes of a subject will be included. For the correlation time point t1 and t2 are selected. Time point t3 is selected for the secondary endpoint: influence of the cuff pressure of the laryngeal mask on IOP by obstructing the venous return.

page 9 line 19: please explain what you mean by: the smaller correlation between IOP and BIS are still detectable with sufficient power? How much smaller?
The sample size consideration is based on observations on one eye at one point in time. Including measurements on both eyes and at three time points will provide more information and thus increase power or – for fixed power – allow to detect smaller effects. However, there is neither previous information about the correlation between IOP-measurements between eyes within a patient during the planned procedure nor previous information about the correlation between time points. Therefore, a more precise statement is not possible. We have altered the wording and hope, this has become clearer.

page 9 line 31-36: how is time included in the model, please list exact variables in the model. Why random effects on subject is selected? Not clear how the data from the 20 healthy children will be handled in the analysis and in the model. How is the agreement among the four experts in this setting? The data from the 20 healthy children will be analysed separately. Agreement between the three (not four) experts is assumed to be high as they follow a standard protocol and as they are experienced in the methods. Multiple measurements by different examiners have shown good inter and intraobserver agreement in case of applanation tonometry and iCare tonometry:

- *Tonnu PA, Ho T, Sharma K, White E, Bunce C, Garway-Heath D. A comparison of four methods of tonometry: method agreement and interobserver variability. Br JOphthalmol. 2005 Jul;89(7):847-50*

- *Avitabile T, Longo A, Rocca D, Amato R, Gagliano C, Castaing M. The influence of refractive errors on IOP measurement by rebound tonometry (ICare) and Goldmann applanation tonometry. Graefes Arch Clin Exp Ophthalmol. 2010, Apr;248(4):585-91.*

Reviewer: 5
Prof. Irene Stratton, Gloucester Hospitals NHSFT, home

Comments to the Author:
I found this paper and wondered whether you had considered differences by age in the performance of the BIS and if a larger sample with age stratification might be worthwhile?
Paediatr Anaesth.2017 Apr;27(4):399-408. doi: 10.1111/pan.13086. Epub 2017 Feb 17. Effect of age on the performance of bispectral and entropy indices during sevoflurane pediatric anesthesia: a pharmacometric study
Alberto Sciusco 1, Joseph F Standing 2, Yucheng Sheng 3, Pasquale Raimondo 1, Gilda Cinnella 1, Michele Dambrosio 1
We thank you very much for this information. Some studies have shown that BIS values for children also under propofol anesthesia are significantly associated with age (Wang et al. Variation of bispectral index in children aged 1-12 years under propofol anesthesia: an observational study. BMC Anesthesiol. 2019: 19: 145 and Jeleazcov C et al. EEG variables as measures of arousal during propofol anesthesia for general surgery in children: rational selection and age dependence. Br J Anaesth. 2007: 99:845-54).
The study of Sciusco had a possible limitation using adult sensors. In our study we used a specific pediatric sensor. For our correlation between IOP and BIS, the differences of the BIS values between timepoint t0 und t1 are of much more interest than the absolute values. By the way, Sciosco et al. studied age-associated BIS values in 8 infants (1-12 months), 22 toddlers (13-36 months) and 18 children (37-144 months). Our sample size of 100 children with known or suspected glaucoma has been chosen with feasibility and it is likely that we achieve the same number of age-grouped patinets like Sciusco et al.

There is no justification of the sample size of 20 for the control group. If there are only 20 then one patient is going to be determining the confidence intervals if a non-parametric method is used. With the concerns from the Sciusco paper about differences by age then a larger sample stratified by age would seem to be sensible.

The sample size has been chosen with feasibility in mind. This part is more of a feasibility study and the sample size was not formally calculated.
In the meantime, we are conducting a further study in healthy children with a sample size of 100.

VERSION 2 – REVIEW

REVIEWER	Stratton, Irene Gloucester Hospitals NHSFT, Gloucestershire Retinopathy research Group
REVIEW RETURNED	18-Aug-2021

GENERAL COMMENTS	Thank you for your replies to my queries. Perhaps you should include in the paper, as you did in your reply, that the 20 control patients are "more of a feasibility study"?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 5
Prof. Irene Stratton, Gloucester Hospitals NHSFT, home
Prof. Irene Stratton, Gloucester Hospitals NHSFT, home
Comments to the Author:
Thank you for your replies to my queries.
Perhaps you should include in the paper, as you did in your reply, that the 20 control patients are "more of a feasibility study"?

Thank you again. We have added a sentence to the manuscript (under “Sample size considerations”)