

Retinal abnormalities in Universal Eye Screening of healthy, full-term newborn infant in Jakarta. The incidence and its risk factors: A Pilot study.

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Abstract

Background: To document ocular abnormalities in healthy full-term newborn infants using wide-field digital imaging and to analyze factors associated with the findings. **Methods:** A total of 1208 full-term newborn infants at a tertiary eye hospital (Cipto Mangunkusumo National Referral Hospital) and a district hospital in Jakarta (Koja Hospital) were enrolled to the study. All eligible newborns underwent fundus examination within 48 hours after birth using the RetCam shuttle (Natus Medical Incorporated, USA). Retinal hemorrhages findings were documented and analyzed according to obstetric and neonatal risk factors. **Results:** Of the 1208 newborn infants enrolled, ocular abnormalities were found in 150 infants (12.4%). Retinal hemorrhage (RH) was the most common findings (88%) in which 2.67% involved the macula, followed with chorioretinitis (4.67%). Univariate analysis showed caesarean section (C-section) (OR 0.27, 95% CI 0.18-0.41, $p < 0.001$) as the protective factor towards RH, while prolonged labor increased the risk of developing RH (OR 1.84, 95% CI 1.24-2.72, $p = 0.002$). Further multivariate analysis showed similar protective association between C-section and risk of RH (OR 0.29, 95% CI 0.19-0.44, $p < 0.001$), while other risk factors were not. **Conclusions:** Our study supports previous reports that universal eye screening is an essential procedure which may detect several important ocular abnormalities. Retinal hemorrhage is the most common ocular abnormality and is associated with the methods of delivery and duration of labor. As the ocular abnormalities may go unnoticed during standard practice, a universal eye screening program could be considered as an essential part of newborn screening especially amongst those with prolonged labors.

Background

Numerous ocular abnormalities at birth are likely led to permanent visual loss. Therefore, it is necessary to identify any eye problems as early as possible since they have significant impact on child's development.¹

Newborn eye screening is not yet a standard care in many countries and several methods have been conducted to diagnose eye diseases at birth. The American Academy of Pediatrics recommends Red Reflex Testing (RRT) for every newborn. The implication of RRT is photoscreening test using digital camera-like equipment, which has been used as a screening method for young children aged one to five years of age². Universal eye screening in healthy newborns using a wide-field digital camera has been studied in different countries to detect early ocular abnormality.^{3,4}

The reported incidence of newborn retinal hemorrhage varies widely from 2.4 – 34%.³⁻⁸ Emerson *et al*⁷ reported that retinal hemorrhage (RH) occurs more frequently in newborns delivered by vacuum extraction (75%), followed by spontaneous vaginal delivery (33%), and C-section (6.7%).⁸

Currently, the exact causes and risk factors of newborn RH remain unclear. This study aims to document ocular abnormalities in healthy full-term newborn infants using wide field digital imaging and to

investigate the risk factors contributing to RH. This is the first universal eye screening study of the healthy newborn infants reported in Indonesia.

Methods

A cross-sectional study was conducted in two different hospital, Cipto Mangunkusumo National Hospital (CM Hospital), a national referral hospital of Indonesia and Koja Hospital, a district hospital in Jakarta, from January 2015 to June 2015. We included all healthy, full-term, newborn infants: Written informed consent was given to each parent prior to the examination of their child. This study is in accordance with The Declaration of Helsinki and ~~has~~ received ethical clearance from the ethics committee of Faculty of Medicine, Universitas Indonesia. Written informed consent was given ~~to~~ by each parent prior for their infant studied Inclusion criteria were healthy, full term, newborn infants aged < 48 hours and the exclusion criteria were those with red eyes prior to the examination, or whose parents refused to participate in this study.

The eye screening was performed within the first 48 hours after birth in a room with trained technicians assisted by a neonatal nurse. We used a wide-field (130 degree, D1300 lens) digital retinal photography device (RetCam Shuttle, Natus Medical Incorporated, USA). Initially, the pupil was dilated by tropicamide 0.5% and phenylephrine 2.5%. Topical anesthetic eye drops were instilled shortly before the examination. The anterior segment was evaluated using non-contact wide- angle portrait camera lens. Thereafter, a wide-angle digital fundus camera examination was performed using the Retcam in first one eye and then the other. A minimum of five photos were taken for each eye: the posterior pole, superior, inferior, nasal and temporal retinal field. Topical antibiotic was given in each eye when the procedure is finished.

Referral to the eye clinic CM Hospital was recommended at a later date for patients in whom the eye exam demonstrated an abnormal finding.

In the case of bilateral eyes being affected with different degrees of hemorrhage, the eye with the worse degree was chosen. Retinal hemorrhage was graded according to Egge's classification⁹ as seen in Table 1

Table 1: Egge's Classification of Retinal Hemorrhage

Grades	Definition
Grade I	Small, mainly less than a quarter of the disc diameter and relatively few hemorrhages in one or both eyes.
Grade II	Medium to large hemorrhages which were not exceeding the optic disc diameter in size, or a combination of few such hemorrhages and many smaller ones in one or both eyes.
Grade III	Larger hemorrhages, the diameter of which were larger than that of the optic disc, in one or both eyes and sometimes also combined with smaller and/or larger apparently pre-retinal hemorrhages

All imaging procedures were done by two trained general practitioners in using RetCam Shuttle device and was aware of the safety precautions in handling the neonates. The captured images were then analyzed by three pediatric ophthalmologist consultants. In case of discrepancies among the consultants, discussion regarding the image(s) was made to establish a final diagnosis. All findings were well documented in an excel sheet along with patient details.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) for Mac 10.5 version. The association between RH to gender, delivery method, and prolonged labor were assessed using univariate analysis. To prevent a type 2 error, only variables with a univariate p-value of 0.20 or less were selected for further multivariate analysis. Factors with a p-value less than 0.05 were considered statistically significant.

Results

A total of 1208 full-term newborns were examined in 2 public hospitals in Jakarta, and the results were as follows.

Table 2: Demographic data

		CM Hospital (N* = 436)	Koja Hospital (N* = 772)
Newborn Infant Characteristics			
Gender, n (%)	Female	241 (55.3)	388 (50.3)
	Male	195 (44.7)	384 (49.7)
Birth weight (grams)		2663 (SD ± 659)	2978 (SD ± 526)
Methods of Delivery			
Spontaneous vaginal delivery, n (%)		128 (29.4)	400 (51.8)
C-section, n (%)		282 (64.7)	348 (45.1)
C-section + forceps, n (%)		13 (3.0)	2 (0.3)
C-section + vacuum, n (%)		1 (0.2)	0 (0)
Forceps, n (%)		6 (1.4)	1 (0.1)
Vacuum, n (%)		5 (1.1)	21 (2.7)
Forceps + vacuum, n (%)		1 (0.2)	0 (0)

*: total number of patients

Table 1 shows the demographic data. Most of the newborn infants were female (55.28% and 50.26% in CM and Koja Hospital respectively), birth weight means in CM Hospital were 2663 grams and 2978 grams in Koja Hospital. The mean duration of latent and active phase during first stage labor were 518+254 minutes and 238+124 minutes, respectively in CM Hospital. Meanwhile in Koja Hospital, the mean of first labor latent phase was 574+520 minutes and first labor active phase was 280+250 minutes. More than half of the mothers in CM Hospital (64,68%) and nearly half (45%) mothers in Koja Hospital underwent C-section. There were 14 patients in CM Hospital (3.1%) and 2 patients in Koja Hospital (0.26%) who underwent combined delivery method (C-section with forceps / vacuum instrumentation).

Table 2: Results of newborn eye examination

Ocular abnormalities	CM Hospital		Koja Hospital	
	N*=436	%	N*=772	%
Retinal hemorrhage	30	6.9	102	13.1
Macular hemorrhage	0	0	4	0.5
Optic nerve head hemorrhage	0	0	1	0.1
Localized blood in the vitreous cavity / peripapillary hemorrhage	0	0	1	0.1
Chorioretinitis/Exudation Requiring Systemic Examination	1	0.2	6	0.8
Macular Dystrophy/Maculopathy	0	0	1	0.1
Intraocular tumor	0	0	1	0.1
Persistent pupillary membrane or persistent tunica vasculosa lentis	0	0	1	0.1
Optic Neuropathy dd/ Coloboma Optic	0	0	1	0.1
Iris Nodule	1	0.2	0	0

*: total number of patients

Among all infants examined, 32 (7.3%) infants in CM Hospital and 118 (34.9%) infants in Koja Hospital had ocular abnormalities. Retinal hemorrhage (Figure 1) was the most common ocular abnormalities observed, found in 6.88% and 13.11% newborns in CM Hospital and Koja Hospital respectively. Chorioretinitis (Figure 2) was the second most common ocular abnormalities found (0.57%) followed with macular hemorrhage (0.33%). Other ocular abnormalities such as retinal exudate, maculopathy, intraocular tumor (Figure 3), optic nerve head abnormality, iris nodule, persistent pupillary membrane, and localized blood in the vitreous cavity / peripapillary hemorrhage (Figure 4) were only found in 1 participant (0.08%) in other abnormalities. (Table 2).

Among all retinal hemorrhages found, 64 infants (48.5%) had a grade III RH, 59 infants (44.7%) were considered as a grade II RH and lastly, 9 infants (6.8%) had a grade I RH. (see Figure 1)

Table 3: Risk factor analysis of retinal hemorrhage

Variables	Univariate analysis (OR (CI 95%))	P value	Multivariate analysis (OR (CI 95%))	P value
Gender (Female)	0.74 (0.52 - 1.07)	0.11	1.33 (0.92 - 1.92)	0.13
Methods of delivery				
C-section ^a	0.27 (0.18 - 0.41)	<0.001	0.29 (0.19 - 0.44)	<0.001
Delivery method with instrument (vacuum, forceps, or both) ^a	0.78 (0.34 - 1.79)	0.561	0.73 (0.32 - 1.69)	0.47
Prolonged labor ^b	1.84 (1.24 - 2.72)	0.002	0.81 (0.54 - 1.23)	0.33

^a: compared to spontaneous vaginal delivery

^b: prolonged labor is defined as prolonged duration of delivery at any stage (stage 1, stage 2, or combined)

Table 3 demonstrates the risk factor analysis of retinal hemorrhage in neonates. Using univariate analysis C-section delivery method reduced the risk of RH (OR 0.27, 95% CI 0.18-0.41, $p < 0.001$) while prolonged labor increased the risk of RH (OR 1.84, 95% CI 1.24-2.72, $p = 0.002$). Both gender and instrument-assisted delivery showed no significant association towards RH ($p > 0.05$). Furthermore, C-section was shown as a protective factor towards RH in multivariate analysis (OR 0.29, 95% CI 0.19-0.44, $p < 0.001$) while other risk factors were not.

Discussion

In most developing countries including Indonesia, universal eye screening of the newborn is not a common practice. Techniques and technologies in retinal examination have improved during the last few decades. This may result in finding ocular abnormalities among newborns easier.

During our study, we found that there was a difference in delivery pattern between our two hospitals. In CM Hospital, the rate for caesarean section was 64.7% compared to the rate in Koja hospital (45.1%). This difference is due to the fact that CM Hospital is the top referral hospital in Jakarta, that predominantly managed high-risk pregnancy which caesarean section was indicated. On the other hand, Koja Hospital is a district hospital, hence simpler, uncomplicated cases where spontaneous delivery can still be achieved.

In our study, we screened a total of 1208 healthy newborns and found that RH (Figure 1) was the most common ocular abnormalities (10.93%), followed by chorioretinitis (0.58%) and macular hemorrhage (0.33%). Other ocular abnormalities such as macular dystrophy, intraocular tumor, optic nerve head abnormality, iris nodule, and persistent pupillary membrane were the least common abnormalities (0.08% each).

We found 7 out of 150 patients with ocular abnormalities, suspected with chorioretinitis. Most likely the exudative retinal lesion found in this study was due to intrauterine infection because the lesion is located in the perivascular area (as seen in Figure 2). Serological test would be required to confirm the diagnosis, which was not the standard diagnostic procedures during the antenatal care.

Table 4: Retinal hemorrhage prevalence in other countries

Country	Study	Population	Prevalence
China	Li LH, et al ³	3573 healthy newborns	21.5% (769/3573)
India	Vinekar A, et al ⁴	1021 healthy newborns	2.4% (25/1021)
United Kingdom	Callaway NF, et al ⁵	202 healthy newborns	20.3% (41/202)
New Zealand	Simkin S, et al ⁶	285 healthy newborns	11.8% (33/285)
Indonesia	Present study	1208 healthy newborns	10.9% (132/1208)

Our finding is in accordance with previous studies done in several countries as shown in Table 4. The prevalence ranged from 2.4% to 21.53% with RH as the most common ocular findings.

Using univariate analysis of risk factors associated with retinal hemorrhage, C-section delivery was shown as a protective factor (OR 0.27, $p < 0.001$) compared to spontaneous vaginal delivery, while prolonged labor was associated with increased risk of retinal hemorrhage (OR 1.84, $p = 0.002$). C-section delivery was significantly associated towards retinal hemorrhage on multivariate analysis (OR 0.29, $p < 0.001$) while other risk factors were not. Compared to other studies, C-section delivery has been shown to have a protective factor towards the development of retinal hemorrhage, while spontaneous vaginal delivery increases the risk. Zhao Q¹⁰ et al showed that a history of caesarean delivery is associated with lower rates of retinal hemorrhage (OR 0.296, p value 0.002), meanwhile a spontaneous vaginal delivery is associated with higher risk of developing retinal hemorrhage (OR 4.909, p value < 0.001). A systematic review by Watts P et al¹¹ demonstrate similar result.

The underlying mechanism of retinal hemorrhage in neonates following spontaneous vaginal delivery was proposed by Yanli Z, et al¹². During vaginal delivery, the intracranial pressure suddenly rises due to the compression of the fetal head when the fetus descends. This is accompanied by increased pressure

in the central retinal vein, dilatation of the scalp- and intracranial veins simultaneously due to venous return obstruction. If this mechanism occurs in newborns where the vascular walls are thinner, they may rupture easily.

In prolonged labor, especially during the second stage of labor, the uterine contractions are longer, the cervix is fully dilated, and the fetal head has descended. It is possible that the umbilical cord is compressed, thus making the fetus prone to fetal uterine ischemia and hypoxia. Hypoxic condition may create an acidic environment, which excites the vagus nerve, accelerates bowel movement, and in the end contaminates the amniotic fluid with meconium, which can cause further fetal hypoxia.¹² Hypoxia may cause an autoregulatory cerebral vasodilatation that may lead to increased intracranial pressure, which eventually leads to an increased risk of retinal hemorrhage in fragile vascular walls of newborns.¹³

In light of instrument-assisted delivery, our study showed different results compared with previous studies. In our population, neither vacuum extraction nor forceps deliveries were statistically associated with RH (OR 0.561, p value 0.56). This result was not in accordance to a previous study from Watts P et al¹¹, which demonstrated that using instruments during delivery increases the incidence of RH (OR 1.75, p = 0.0002). Our result may be due to the low rate of instrument-assisted delivery used in our study population (4.1%). Thus, our findings may not show the exact relationship between instrument-assisted deliveries and the incidence of retinal hemorrhage.

We could not follow up 51 of 132 neonates with RH completely until the end of study. Of these infants, 51% (26 of 51 neonates) had severe RH (grade 3) and the remaining 49% had grade 2 RH. It is generally understood that retinal hemorrhages will resolve quickly during the first few weeks⁸, however prolonged macular hemorrhage can create a long-term impact on visual function¹⁴. Among children with retinal hemorrhages and especially those with macular hemorrhage, further longitudinal studies are needed in order to investigate the potential impact of retinal or macular hemorrhage to the visual function during the critical period of the eye development.

Several important ocular abnormalities may be overlooked as universal eye screening is not yet an established practice. We found a small number of ocular abnormalities, such as intraocular tumor (one case) and chorioretinitis (seven cases) which required further immediate workup and appropriate therapy.

Our study did not cover some issues regarding the cost-effectiveness of universal eye screening, such as financial, health personnel, and logistics. It is important to address these issues prior to establishing a universal eye screening as a program at an institutional, or a national level. Other limitations include the lack of data on the antenatal care of the mothers and the unavailability of the follow-up laboratory assessments.

Conclusions

Our study showed that a number of important ocular abnormalities can be detected through a universal eye screening in healthy neonates. Retinal hemorrhage is the most common ocular abnormality and is associated with the methods of delivery and the duration of labor. As the ocular abnormalities may go unnoticed during the standard practice, a universal eye screening program should be established especially among those with prolonged labors.

Abbreviations

- C-section : Caesarian section surgery
- CM Hospital : Cipto Mangunkusumo National Referral Hospital
- OR : Odds ratio
- RH : Retinal hemorrhage
- RRT : Red reflex testing
- SPSS : Statistical Package for the Social Sciences (computer program)

Declarations

- **Ethics approval and consent to participate**

This study is in accordance with The Declaration of Helsinki and has received ethical clearance from the Human Research Ethics Committee of Faculty of Medicine, Universitas Indonesia-Ciptomangunkusumo Hospital. Written informed consent was obtained from each parent prior to the participation of their child(s) in this study.

- **Consent for publication**

Not applicable, since individual details of the image submitted are not identifiable.

- **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests

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RetCam Shuttle (Natus Medical Incorporated, USA) device was provided by PT. Meta Mata Medika.

- **Authors' contributions**

All authors listed made substantial contributions to the conception and design of the research project. RSS, IMP, RR, JDB, DEY, ISW: acquired the data and perform the analysis of the work. All authors have read and approved the manuscript.

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Not applicable

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Figures



Figure 1

Retinal hemorrhage grade III with flame shape pattern involving macular area



Figure 2

White exudative lesion involving temporal peripheral quadrant of the retina, as indicated by the yellow circle



Figure 3

White mass at supero-nasal quadrant of the retina, suspected of intraocular tumor, as indicated by the yellow circle



Figure 4

Localized blood in the vitreous cavity, peripapillary hemorrhage