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Assessing Agreement of Clinical Estimation of Vertical Optic Disc Cupping against Retcam Assessment in the Premature Neonate and Prospective Observation for Changes

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ABSTRACT

Aim: To assess agreement between binocular assessment of optic disc cupping and objective evaluation with RetCam imaging in premature infants. To look for difference in changes observed in disc cupping between different birthweight groups and effect of retinopathy of prematurity, intraventricular hemorrhage and sepsis.

Methods: A cohort of premature infants were examined prospectively. At Timepoint I (31 – 36 weeks), the vertical optic disc cupping(vCDR) was assessed clinically through a 28D lens. Two RetCam fundus images centred on the optic discs were taken. A blinded assessor measured the vCDR and the average was calculated. This was repeated at Timepoint 2(37– 40 weeks). Exclusion criteria included IOP >21mmHg, abnormality in cornea, enlarged cornea size (>10.0mm) and abnormal eye. Consistency between the 2 methods was assessed with intraclass correlation coefficient (ICC). Bland-Altmann plots were used for agreement analysis.

Results: In total, 126 eyes (n= 63 infants) were examined, 504 images captured and assessed. The average vCDR by clinician was 0.30(SD:0.1) and by RetCam 0.32(SD:0.1). The ICC showed moderate correlation however, Bland-Altman plot showed a wide 95% limits of agreement (-0.24, 0.26). Paired t-test did not show significant change in vCDR between the time-points for infants in different birthweight groups but trend of change were identical for both methods. Retinopathy of prematurity, intraventricular hemorrhage and sepsis were not associated with changes in cupping in this cohort.

Conclusion: Optic disc cupping with clinical estimation is not interchangeable with RetCam values but showed identical trend of change. Mean optic disc vertical cupping in this population was 0.3 at term.

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Introduction

The good survival rates among premature infants will result in increasing number of premature infants requiring further evaluation when an enlarged cup-disc-ratio was noted during Retinopathy of Prematurity (ROP) eye screening. Baseline values for infant Cup-Disc-Ratio (CDR) are available for premature infants but many were based on measurements taken when the children were older, except Park et al who reported on infants at 36 weeks [1-6]. The most convenient method for the examination of optic disc cupping is by clinical assessment as visualized by the binocular indirect ophthalmoscope [7]. Other methods include using the RetCam or Optos imaging systems and Heidelberg OCT [8].

Many perinatal factors may impact on the appearance and cup-disc-ratio in premature infants. Jacobson reported that the presence of periventricular leukomalacia resulted in larger CDR in 17 premature children compared to normal [9]. Premature infants were found to have a vertical form of their optic discs, with 75% having a double ring sign and 89% having visible cupping by Hackl et al. [10]. McLoone et al studied RETCAM images of the optic discs of premature infants with ischaemic brain injury and found that there was a trend towards a decreased optic disc diameter, optic disc area and cup area [11]. These changes were significant in those with Grade IV intraventricular haemorrhage [12]. Glass et al studied CIRRUS OCT images of RNFL of 6 premature infants with large CDR who were otherwise healthy with non-glaucomatous eyes and found significant decrease in overall thickness. However, only superior thinning was significant compared to the other sectors. There is no consensus on whether

the documentation of optic disc cupping was important in the early neonatal period. However, in the ETROP (Early treatment of retinopathy of prematurity) cohort, 1.67% (12 of 718) eyes developed glaucoma, half of whom were diagnosed by age 9 month [13]. By 6 years of age, Bremer et al noted that all but one of these 12 eyes were blind. Erraguntla et al concluded that RetCam imaging should not be the sole criterion for monitoring glaucoma [14].

A literature search revealed only one paper compared methods of optic disc evaluation [15]. Durmus et al compared the optic disc variables between slit-lamp assessment, stereoscopic imaging and HRT imaging and found significantly large differences between their measurements of optic disc parameters to conclude that these methods should not be used interchangeably. Hence, we proceeded to evaluate agreement between the methods most commonly in use in neonatal units ie clinical estimation and RetCam imaging. Secondly there is a need for more data on optic disc in premature infants at term corrected age to establish baseline values for this group and to study the effect of selected perinatal factors on optic disc cupping changes.

Materials and Methods

This was a prospective observational study on premature infants recruited at the time of first Retinopathy of Prematurity (ROP) screening. The study was conducted in three parts. The first part involved data collection at the University of Malaya Medical Centre. The second part included analysis of RetCam (Clarity Medical Systems, Pleasanton, Calif.) images to obtain an objective means by which the clinical method of assessment was compared. Two images were assessed for each eye to derive average vCDR. Data analysis was carried out at the Kids Research Institute in Childrens Hospital at Westmead (CHW) in Australia by a medical statistician (EB). Institutional Ethical Board approval had been obtained prior to commencement of the study which was conducted in adherence to the Declaration of Helsinki. Consecutive infants referred to the ophthalmology department for retinopathy of prematurity (ROP) screening were included into the study. The inclusion criteria were infants with gestational age below and equal to 32 weeks gestation, infants whose birth weight were 1500 grams or less and any infant requiring oxygen therapy for more than 1 month or ventilation for more than 1 week. Exclusion criteria included enlarged cornea size (>10.0mm) and abnormal eye, intraocular pressure > 21mmHg, and infants with abnormal appearance of the cornea (corneal cloudiness, sclerocornea or scarring).

Documentation of the optic disc vertical cupping were made at 2 timepoints ie Timepoint 1 (31-34 weeks) which was the first ROP screening examination, and Timepoint 2 (37-40 weeks) which was the last ROP examination when full retinal vascularization was noted. During each examination, intraocular pressure was measured with the rebound tonometer I-Care II (Icare®-II, Finland). The readings were made according to company protocols with minimal pressure to the globe. The vertical optic disc cupping(vCDR) was assessed clinically by the pediatric ophthalmologist (MMC) through a 28D lens using the binocular indirect ophthalmoscope. Two RetCam (Clarity Medical Systems, Pleasanton, Calif.) fundus images centred on the optic discs, were taken through the 130^{o} lens. The images were retrieved later for a single masked examine r(AK) who assessed the vCDR using calipers to obtain the vertical diameter of the optic cup and vertical diameter of the optic disc. The ratio of the two measurements was calculated to produce a vCDR (RET)

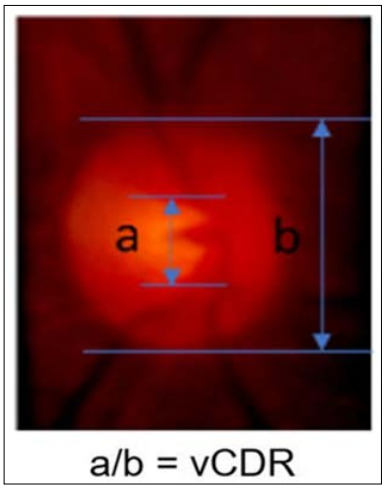

Figure 1: Retcam Image of Optic Disc to Illustrate How the Vertical Cup-Disc-Ratio(vCDR) was Derived

The sample size for this study was calculated on-line using Schoenfeld (Harvard)'s program setting significance level of 0.05 in a two-tailed t-test with the power of 0.80 that the study will detect a difference. A total sample size of 14 patients was calculated for each variable. The minimal detectable difference set at 5% from normal CDR of 0.3 was 0.015 as this was quite similar to that found by Park et al in his study who reported a CDR change of 0.016 per year in premature children [16]. Thus, a sample size of at least 56 was required for the comparison of 4 post-natal factors birthweight, sepsis, intraventricular haemorrhage and presence of Retinopathy of Prematurity (ROP). Statistical analysis was performed using SAS version 9.3(SAS Institute Inc., Cary, NC, USA), and included paired t-test for comparison of difference between vCDR over time, consistency between the 2 methods was assessed with intraclass correlation coefficient (ICC) and Bland-Altmann plots for agreement analysis between methods. Association of different post-natal factors (ROP, sepsis, intraventricular haemorrhage) with the changes in vCDR were analysed using two-sample t-tests. The values for right eye was used in analyses by birthweight as there was no statistical difference in values obtained from both methods between eyes.

Results

In total 72 infants were recruited, but only 63 infants completed the full assessments (drop-out rate of 12.5% [9/72]. A total of 126 eyes from 63 premature infants completed both clinical examination and RetCam imaging, 504 images were taken and assessed during the study period of 12 months. Table 1 shows the demographic data of the cohort. The average vCDR by clinician estimate was 0.30(SD:0.1) and by RetCam measurement was 0.32(SD:0.1). Retcam values differed from BIO values in 65% of cases although only 4 infants showed a difference greater than 0.2 between the 2 methods. The Intraclass Coefficient of Correlation (ICC) was 0.72(OD) and 0.71(OS) respectively at Timepoint I. At Timepoint 2 they were 0.59(OD) and 0.70(OS). These values showed moderate correlation, but the values were not identical. Bland-Altman plot showed a wide 95% limits of agreement (-0.24, 0.26) (Figure 2a) which showed that the RetCam and clinical values were not interchangeable.

Table 1: Demographic Data of Premature Infant Cohort in our Study

Parameter	At Birth, Mean (SD, Range)	At Pre-Term, or First ROP Examination, Timepoint 1, Mean (SD, Range)	At Term, or Last ROP Examination, Timepoint 2, Mean (SD, Range)
Gestational/Corrected Age (Weeks)	29.5 (2.4, 23.9-35.6)	35 (1, 31-36)	40 (1,37-43)
Birth Weight (grams)	1190 (346, 510-2020)		
Birth Length (cm)	36.9 (4.3, 29-47)		
Head Circumference at Birth (cm)	26.3 (2.6, 20.5-31.5)		
Right Eye vCDR from Binocular Indirect Ophthalmoscopic (BIO) Examination		0.29[0.12, 0.1-0.65]	0.34[0.13, 0.1-0.75]
Right Eye vCDR from RetCam Images Calculation		0.30[0.11, 0.2-0.75]	0.32[0.11, 0.2-0.75]
Intraocular Pressure (mmHg)		12.7(3.2)	13.7(3.2)

Abbreviations: SD=standard deviation; ROP=retinopathy of prematurity; vCDR=vertical cup-disc-ratio; BIO=binocular indirect ophthalmoscope.

More importantly, Figure 2a illustrates that the difference between each method was within 0.2 in majority of cases except several outliers. The value 0.2 was taken to draw the lines in Figure 2, as values >0.2 is the cut-off used to denote clinically significant change of cupping in conditions like glaucoma. When reviewing the change of vCDR cupping over the 2 timepoints for the different birthweight groups, the trend of change between Retcam and clinical method were similar (Fig 3). Another observation to note in this figure was that while average vCDR in those with BW <1000grams showed little change at term (timepoint 2) from the average at first examination, the trend seen in those who were between 1001-1500 grams were increased in average vCDR while the infants with BW >1500grams showed a decrease in vCDR at term (timepoint 2). However, there was no significant association between vCDR with birthweight in the whole cohort. What was more relevant to the first aim of this study was the trend showed similarity between both methods, even as the infants were divided into different birthweight groups. The effect of post-natal factors like presence of intraventricular haemorrhage (Grade 1-4), ROP and sepsis on progression of vertical CDR was analysed using two-sample t-tests. None of these factors tested showed any association with the increase in vCDR recorded in our cohort.

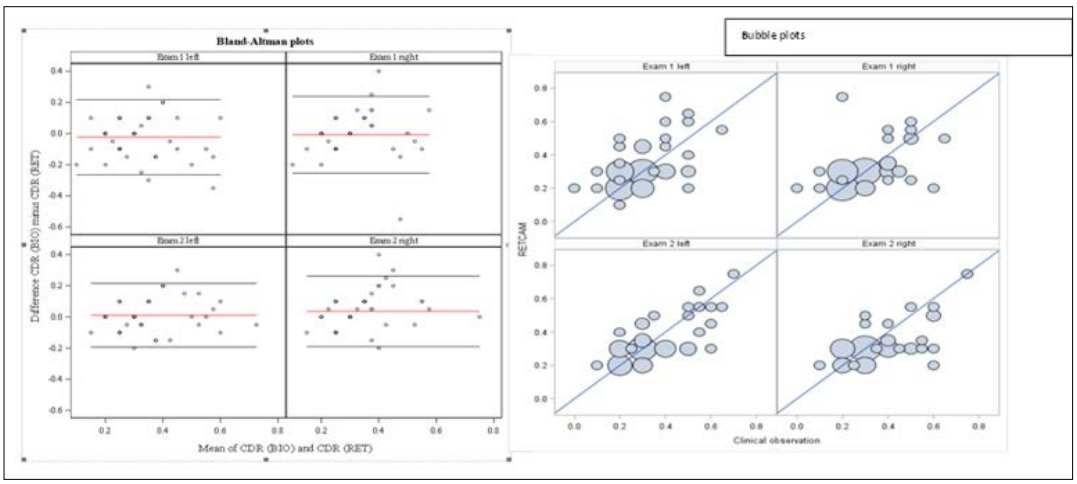

Figure 2: 2a: Bland-Altman plots of all values. 2b: Bubble-plots of all values.
To show firstly that all the values were not interchangeable between the RetCam and clinical examination due to wide limits of agreement and secondly to show that although there were differences, majority of changes observed over time were within 0.2, where any change >0.2 were considered to be clinically significant.

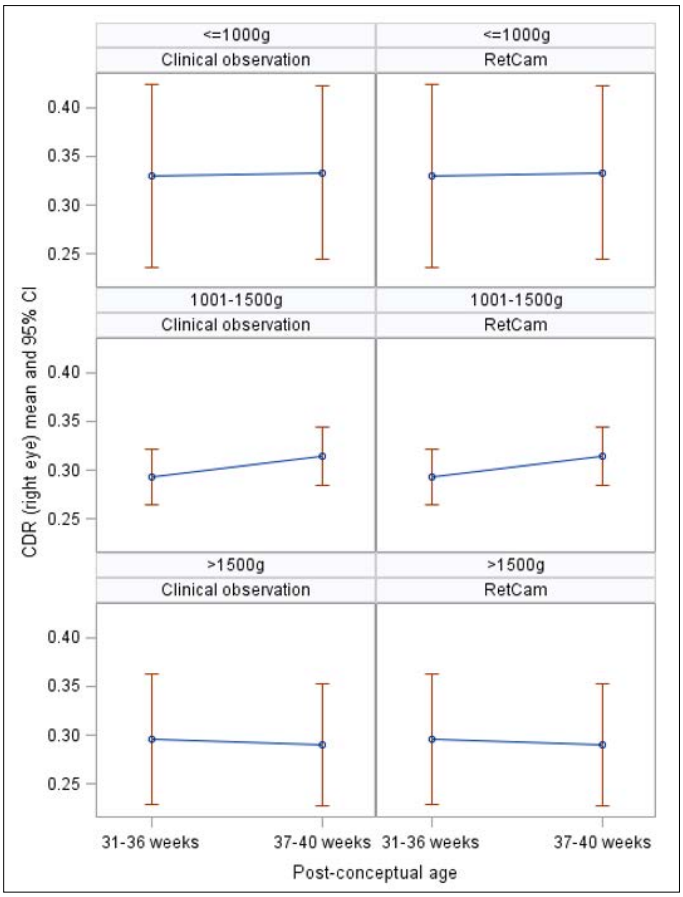

Figure 3: Chart Showing Changes in Mean vCDR from First to Second Timepoints, Observed between Different Birth Weight Groups. While those in ELBW category were observed to have almost stable cupping, those in the birthweight groups between 1000 - 1500grams were found to have increased cupping on reaching term.

Discussion

The optic nerve in a premature infant is not fully developed at the time of birth [17]. These changes range from continuing development and attrition of axons with their myelin sheaths and subsequent regression of the myelin sheath from the retina, occurring up to age 2 years [18]. Assault to the optic nerve during this development may result in irreversible changes [19]. This was observed in many studies [2-5,9,10,18, 20]. The most observable aspect of this change is in the optic nerve head size and shape, cup-disc-ratio and neuro-retinal rim thinning. Our study looked at the vertical optic disc cup-disc-ratio to compare the findings obtained with clinical examination to that of RetCam image calculation.

The RetCam values showed difference with clinical examination in 65% eyes in our cohort. The clinician's method in evaluating optic disc cupping was done under binocular viewing and seen by the examiner as actual cupping. RetCam values were calculated from 2-dimensional captured images and what was thought to be the optic disc cup may have been a difference in color within the optic discs (Figure 1). The Bland-Altmann plots showed that BIO findings and RetCam findings were not in agreement and gave a wide 95% C.I. from all the readings of both eyes at the 2 time points. As both methods were not interchangeable it is best not to compare values measured by different methods. Both methods will provide a baseline value for future observations. RetCam images can be taken by a different operator at different timepoints while clinical examination is more reliable if the same person does the examination over different periods.

Additionally, the observations from our cohort showed similar trend of changes in average vCDR in premature infants from the first ROP examination and at the final examination in both methods used when patients were grouped by birthweight groups. The infants who had birthweight <1001grams showed little change in average cupping when comparing between Timepoint 1 and 2. Those infants with birthweight between 1001-1500 grams had increase in cupping at Timepoint 2 compared to Timepoint 1, while infants who were >1500grams at birth had smaller average cupping by Timepoint 2. Our findings suggest that the time to document a baseline value should be at discharge from ROP screening when retinal vascularization is complete, in view of these early variations.

Some postulations on why changes in the optic disc cupping occur in early neonatal period resulting in the differences of cupping change depending on birthweight can be explained from previous published works [21]. Tornqvist et al reported that prematurity was one of several factors associated with optic nerve hypoplasia. This infers that the nerve fiber numbers are smaller [22]. Dutton summarized that assault to white matter in the immature brain between 29 to 34 weeks resulted in periventricular leukomalacia, and a large proportion of the infants presented with increased cupping. This may explain why those who were below 1500grams but above 1000grams had increased cupping, as any assault would reduce axons and hence produced increase in cupping as observed in our patients [17]. An interesting study by Provis et al explains why in our cohort, infants below 1001grams showed little change in average cupping by the time they reached term compared to initial ROP examination [17]. Provis et al studied post-mortem specimens of 9 premature human fetuses, and noted that from 16 weeks the number of axons began attrition and reached just over 1 million fibers by 33 weeks. Hence those who were born earlier, and by inference extreme low birth weight (<1001g) infants, still had excess axons that had not gone through physiological attrition, and thus even after experiencing further assaults, the effect of losing axons was not so marked.

The main points to conclude from all the earlier studies mentioned were that there was smaller-sized optic discs, larger cupping and thinner neuro-retinal rim observed in children with a history of prematurity compared to children born at full term [2,3,5,7,20]. There were not many studies that reported actual CDR for premature infants in early infancy [7]. Park et al found in their cross-sectional study of RetCam images taken at 36 weeks corrected age in 97 infants, 71.6% had CDR of 0.15 and only 3.1% had CDR of 0.5 or more. Apart from Park's study, all other reported CDR were taken in children aged 3 years or older. In the Sydney Childhood Eye Disease Study of children at age 12 years, the 71 eyes from those children with history of low birthweight, CDR was reported as a mean of 0.2(range: 0.17-0.22) [5]. Progrebniak et al found mean vertical CDR of 0.627 in the eyes of 28 children with history of prematurity compared to 0.285 for 55 full term children [23]. The age range at which their fundus images were taken was wide, between the age of 1 to 16 years. A more recent study using Heidelberg Retinal Tomograph III by Alshaarawi et al reported mean CDR of 0.24 from 32 premature children aged between 8-16 years. The observations from our study show that although in the early neonatal period cup disc ratio changes occurred, the final cdr in all birth weight groups eventually averaged to 0.3 to 0.35 at Term (Timepoint 2) for all birthweight groups. This differed with Park et al who reported majority of their cohort had cdr <0.15.

Premature infants are a unique subset of the pediatric population. They present additional challenge to clinicians as factors like birthweight, oxygen use, mechanical ventilation, presence of intracranial haemorrhage, sepsis and development of retinopathy of prematurity may further affect optic nerve development. There are few studies on the association with the various perinatal factors with optic disc cupping [18,20]. Fledelius analysed children who were premature (n=268) and found that cup size was not related to birth weight, sex or visual acuity [4]. Hellstrom et al found the optic disc area negatively correlated with gestational age in his study of premature children at age 4-6 years of age, but the study did not look at CDR [10]. Hackl et al found significant negative correlation between the form of the optic disc with birth weight and gestation [7]. Park et al showed that birthweight did not show any correlation with optic disc changes, similar to our findings. We showed in our cohort that the different birth weight groups showed different trend in cupping which have not been reported previously. There are no reported studies of post-natal factors like oxygen therapy, mechanical ventilation, intracranial haemorrhage, sepsis and retinopathy of prematurity which may have association with optic disc cupping changes. Our cohort did not show any significant associations with sepsis, intracranial hemorrhage and retinopathy of prematurity.

The limitation of this study was the small sample size, however this number is one of the larger series in comparison to previous studies. The observer for RetCam images was a masked single observer, who was a different consultant from the clinical observer, to reduce bias and inter-observer variability. These were compared to clinical observations made by a senior pediatric ophthalmologist who examined premature infants regularly. The functional significance for the changes of CDR in these infants is not known. Follow-up study of this cohort may focus on further CDR changes in relation to visual acuity and visual field findings.

Conclusion

Optic disc cupping with clinical estimation was not interchangeable with RetCam values. RetCam imaging is important for additional documentation if deviation from normal mean vCDR is noted on clinical examination. Mean optic disc vertical cupping in this population was 0.3. In view of earlier variation, CDR documentation can be done at the last ROP screening examination to serve as a baseline for comparison for future detection of diseases like glaucoma or other optic disc abnormalities. We conducted electronic searches of the Ovid MEDLINE (1946 to March 2024), Embase (1974 to March 2024) and CINAHL (1982 to March 2024) with the keywords optic disc cupping, premature infants.

Conflicts of Interest: The authors declare no conflict of interest.

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