·Clinical Research·

Systemic changes and adverse effects induced by retinopathy of prematurity screening

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Received: 2015-04-23 Accepted: 2016-02-03

Abstract

• AIM: To estimate the potential systemic events during and after retinopathy of prematurity (ROP) screening.

• METHODS: A prospective and descriptive designed study was conducted to detect the physiologic and pathological changes 24h before, during, and 72h after ROP screening. Control blood pressure (BP), saturation, pulse rate, and body temperature were routinely taken at various time internals before and after screening. Adverse effects pertain to cardiovascular system, respiratory system, gastric system, urinary system and nervous system were retrospect 0 –72h after ROP screening at a 24–hour interval.

• RESULTS: Totally 1254 prematurity babies receiving ROP screening during Jan. 1st 2013 to Dec. 31th 2013 were enrolled in our survey. Compared to control vital sign data taken before the examination, there was a fluctuation in the diastolic BP with the increased 3.03 mm Hg (P=0.04) after 3 doses of mydriatic drops. Immediately after the examination, there was a further 12.64 mm Hg (P<0.01) increase in systolic BP and a 7.24 mm Hg (P<0.01) in diastolic BP. The mean pulse rate during examination was 22.4 bpm (P<0.01) higher than the 133.3 ±9.0 bpm control level. The oxygen saturation shared an average drop of 5% (P<0.01) during screening. In prematurity with postconceptional age less than 31wk, the incidence of apnea (23.5%), necrotizing enterocolitis (NEC) (8.7%), gastric residual (25.4%) and upper digestive tract hemorrhage (6.4%) also demonstrated a significant rise (P<0.01).

• CONCLUSION: In our study sample, ROP screening was associated with NEC, gastric residual and upper digestive tract hemorrhage. These gastrointestinal side effects, along with breath activity pattern change and vital signs indicators fluctuation, may be results of additional stress responses.

• **KEYWORDS:** retinopathy of prematurity; prematurity; screening; apnea; necrotizing enterocolitis; stress response; mydriatic drops

DOI:10.18240/ijo.2016.08.11

Jiang JB, Zhang ZW, Zhang JW, Wang YL, Nie C, Luo XQ. Systemic changes and adverse effects induced by retinopathy of prematurity screening. *Int J Ophthalmol* 2016;9(8):1148–1155

INTRODUCTION

Retinopathy of prematurity (ROP), affecting approximately 80% of premature infants with birth weight less than 1000 g [1], used to be major cause of visual impairment in the children under 5 years old in developed countries. Recently, the incidence of terminal stage ROP have declined due to a series guideline of optimal oxygen utilization, ROP screening strategy and treatments [2-3]. Over the last decade, neonatal intensive care technology has improved in a number of developing countries such as China, India and Turkey, which had contributed to an increasing population of premature survivors. This progress implies an increasing number of infants who need to receive ROP screening examination[4].

China is a middle-income country with huge population over 1.3 billion. Among 16 million newborn infants each year in China, 2.33% was extremely low birth weight infants (ELBW). For the past few years, improved neonatal intensive care technology makes increasingly number of extreme ELBW and extremely preterm infants to survive. Along with this high-risk group of ROP, the routine screening has become a major task for ophthalmologists in obstetrics and pediatrics hospital. On the other hand, some ELBW even had to receive this manipulation up to 8 times before complete retinal vascularization.

ROP screening is an essential neonatal intensive care unit (NICU) routine because ROP is a preventable and treatable disease at its early stage. Timely detection and peripheral retinal laser photocoagulation could avoid retinal detachment which eventually result in poor visual acuity prognosis after vitro-retinal surgery. On the other hand, ROP screening is

also a painful and stressful experience to the subjects since the manipulations may disturb the regular physiological wellbeing [5-6]. Initial researches have indicated changes in heart rate and oxygen saturation[7-10]. In a study by Belda *et al*[11] examined 27 infants during and 24h after ROP examination, showing more incidence of vomiting, gastric residuals, apnea, and need for higher respiratory assistance mode or setting. A pilot study used a prospective, descriptive design involving 39 infants demonstrated significantly increased apnea events (P=0.04) 24-48h after examination compared to the data before examination[12]. A case report record apnea and bradycardia during routine ROP examination in 2 prematurity[13].

This study is aimed at monitoring and analyzing alterations in infant's medical status and physiologic events associated with ROP screening based on a large sample scale so as to provide a clinical clue for subsequent evaluation and assessment of the feasibility of recent ROP screening criteria. Here, we provide evidence that modification to the exam technique regarding analgesia and sedation strategy, extra medical attention during and after ROP screening is required.

SUBJECTS AND METHODS

Subjects and Protocol From Jan. 1st 2013 to Dec. 31th 2013, we collected 1254 premature infants who were hospitalized in Guangdong Province Women and Children's Hospital NICU. The Ethics Board of Guangdong Province Women and Children's Hospital approved the study by 6 decisions. As the study was based on medical record review of infants undergoing a routine procedure, exemption was authorized from obtaining parental consent. The study investigated all the infants need to be screened according to Chinese National screening criteria and Guangdong Provincial ROP screening criteria [14] [*i.e.* birth weight (BW) <2000 g or gestational age (GA) <34wk. The initial examination should be undertaken 4-6wk after birth, or at 32-34wk postmenstrual age (PMA)]. Infants who received laser photocoagulation, intravitreal monoclonal antibody of vascular endothelial growth factor bevacizumab injection or vitreoretinal surgery were considered as ineligible during the period of data collection, since additional ocular management may become confound blow.

Infants in the supine position who met the criteria for fundus examination were inspected by the same attending ophthalmologist on the battery-powered radiant warmers or incubators. Indirect ophthalmoscopy on both eyes of all patients under local anesthesia (1 drop of 0.5% proparacaine eye drops 5min before the screening, repeat every 5min until finishing the procedure) was performed by a vitreoretinal specialist. Pupils were dilated with topical compound tropicamide eye drops (0.5% tropicamide and 0.5% phenylephrine) three times before the examination at an interval of 5-10min prior to the screening, 1 drop each time. Each infant was inspected starting with the speculum placed in the left eye. Squint hook was placed in the conjunctival fornix to gently rotate the globe to make the central and peripheral retina visible. The right eye is inspected with the same procedure. All the therapies like ventilation or parenteral nutrition were continued during the screening. ROP grading and treatment was based on the international committee on classification of acute ROP and early treatment of ROP criteria[15-16].

Data included gender, birth weight, gestational age, postconceptional age (PCA), adverse events, feeding history, medications, and any other therapeutic procedures were collected from medical records. The registered nurse and research assistant collected data jointly on all infants. Inter-rater reliability checks were then reviewed on 5% of medical records drawn at random by the principle investigator.

An intensive medical record audit was performed by nurses and doctors from 24h before until 72h after the eye examination, in order to track the parameters of respiratory, gastrointestinal condition, cardiovascular stability and neurological status. Detailed daily progress notes and treatments are also essential routes of positive events.

Variables and the Measurements The variables were consisted of 2 parts; one part was vital sign readings including temperature, pulse, oxygen saturation and blood pressure (BP), another part of variables was positive events. Specifically, main pathophysiological conditions variables classified by different systems are described as following: respiratory system: oxygen saturation <88% , upgrade ventilation mode or setting, abnormal tracheal aspirates (pulmonary hemorrhage); cardiovascular system: bradycardia (heart rate <90 beats per minute), tachycardia (heart rate >180 beats per minute), arrhythmia, capillary refill time >2 sec; digestive system: gastric residual, vomiting or reflux, necrotizing enterocolitis, upper digestive tract hemorrhage; nephrology and urology: input and output balance; neurology: seizures.

Vital sign and saturation readings were taken according to the NICU nursing guide every 2h. Control BP, saturation, pulse and temperature recordings were taken 3 times over a 6h period before screening and repeated immediately before the examination. Saturation and pulse rate were recorded 3 times during the examination. In order not to disturb the procedure, BP and temperature were only obtained immediately after the screening rather than during the screening. Subsequent BP, pulse, saturation were taken 15 and 60min after the end of the screening, temperature was read 1, 2 and 6h after the end of the screening. BP, pulse, and saturation readings were taken from the neonatal cardiorespiratory monitor (Graseby Medical, model 901). Readings were accepted only when a satisfactory trace was

Table 1 No. of ROP screening (n) and initial screening age according to PCA in gestational age groups

Gestational age at birth (wk)	Infants (*n*)	Average PCA[1] when taken the initial screening (wk)	Total screening No. of times (*n*)	Average No. of screening for each infant (*n*)
25+	3	29	7	2.3 ([1]1)
26+	6	29	26	4.3
27+	12	29	67	5.6
28+	27	29	142	5.3
29+	35	30	206	5.9
30+	56	31	332	5.9
31+	72	32	368	5.1
32+	88	32	532	5.2
33+	142	33	518	3.6
34+	226	34	453	2.2
35+	247	36	440	1.7
36+	269	36	400	1.2

[1]Among 3 cases of 25+ infants, 1 case wean, 2 cases have ROP in 33wk and 35wk postmenstrual age, all of them are excluded from further survey.

observed. Temperature was obtained using electronic thermometer (Berrcom, JXB-178).

Physiologic changes and pathological events were counted in 24-hour blocks starting 24h prior to the procedure and ending 72h after the screening. In our survey, PCA at the time of examination were sorted and explored by 4 groups: 1) group A: 31wk or younger; 2) group B: 31 to (33+6)wk; 3) group C: 34 to (36+6)wk; 4) group D: 37wk or older.

Apnea events were defined as cessation of breathing for longer than 20s or for any duration if accompanied by cyanosis and bradycardia [17]. Apnea events were notified either by nurse bedside or cardiorespiratory monitors. Neonatal necrotizing enterocolitis (NEC) is characterized by various degrees of mucosal or trans-mural necrosis of the intestine, a variety of signs and symptoms and plain abdominal radiographs are essential to make a diagnosis of NEC. In our survey, we limited NEC diagnosis to Bell's stage 2 or greater.

Statistical Analysis Measurable and categorical variables are expressed as mean (SD, standard deviation) or median (II, interquartile interval) and range, or frequency distribution (95% confidence intervals), respectively. Changes in normally distributed data were analyzed using the paried Student's *t*-test. McNemar's test was used to analyze changes in the occurrence of side effect events (*i.e.* apnea) for the 24h period before, 0-24h, 25-48h periods, and 49-72h periods after ROP screening. Data were calculated using SPSS 19.0 software (IBM, USA).

RESULTS

A total of 1254 premature infants were investigated, among them 740 were male (59.0%), 514 were female (41.0%). The mean gestation was 32.2±2.8wk (range, 25 to 37wk) and the mean birth weight was 1627±369 g (range, 650 to 2890 g).

Supplemental oxygen was given to 402 (32.0%) infants by nasal cannulae, high flow nasal cannulae, high frequency pressure ventilation or synchronized intermittent mandatory ventilation. Totally 357 (28.5%) infants were diagnosed as respiratory distress syndrome. Cardiovascular abnormalities (exclude patent ductus arteriosus and patent foramen ovale) were found in 34 infants. Other risk factors for ROP included sepsis in 58 (4.6%) cases and blood transfusion in 87 (6.9%) cases. Forty-two (3.3%) infant had intraventricular hemorrhage, periventricular leukomalacia or other cerebral problems. During the follow-up, significant ROP developed in 204 eyes of 111 infants. The prevalence of ROP was 8.8%.

Totally 3491 examinations were performed during the study period. Mean ROP examinations time was 4.3 (range, 3.1-10.0min) There was a median of 3 examinations per infants (range, 1 to 8) during their hospitalization. The detailed information about screening point and times related to gestational age was showed in Table 1. Specifically, the most premature patience (25wk of gestational age) received their initial screening 4wk after delivery. Theoretically infants from small gestational age group should be received more screen number of times than near term infants. The actual cases were few of them could survive due to medical technology or guardian's supports. The 29+ weeks' and 30+ weeks' group received most screening numbers up to 5.9 times during their hospitalization. The screening number dropped according to gestational age.

BP reading is plot in Figure 1. At the three control point 2, 4, 6h before the screening is constant. After 3 doses of mydriatic drops, the mean systolic BP and diastolic BP went to 75.4±19.3 mm Hg (P=0.078) and 43.5±11.8 mm Hg (P=0.04), respectively, right before the examination start. Immediately after the examination, there was a further rise in systolic BP to 84.2±20.3 mm Hg (P=0.00) and diastolic BP to 47.7±13.4 mm Hg (P=0.00). There was statistically

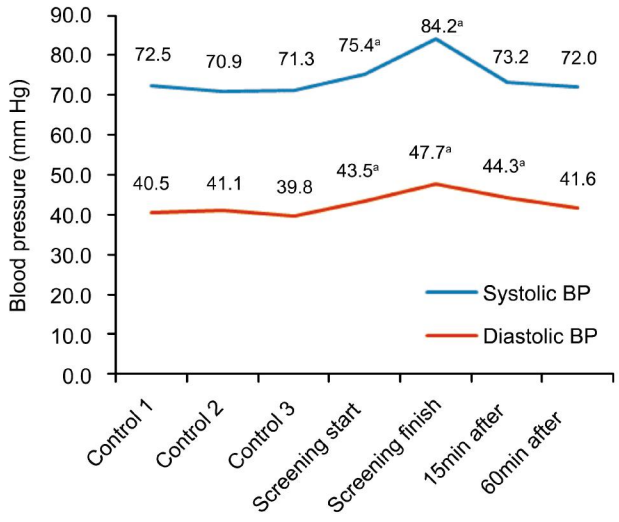

Figure 1 Mean systolic and diastolic BP change during the course of the study Mean length of examinations (from screening start point to screening finish point) was 4.3 (range, 3.1 to 10.0)min. Control 1: 6h before screening start, Control 2: 4h before screening start, Control 3: 2h before screening start. [a]Statistical difference compared with mean control data.

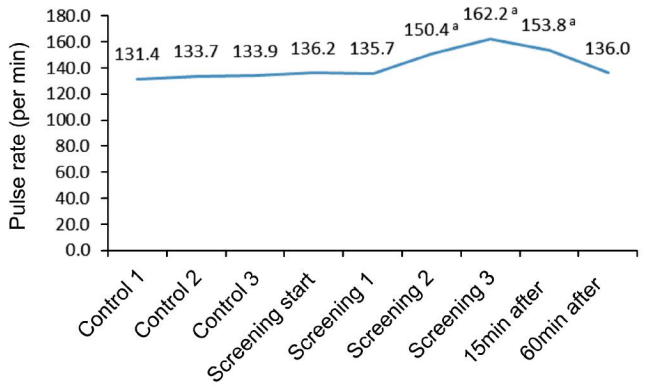

Figure 2 Mean pulse rate changes during the course of the study Mean length of examinations (from screening start point to screening finish point) was 4.3 (range, 3.1 to 10.0)min. Control 1: 6h before screening start, Control 2: 4h before screening start, Control 3: 2h before screening start. [a]Statistical difference compared with control data.

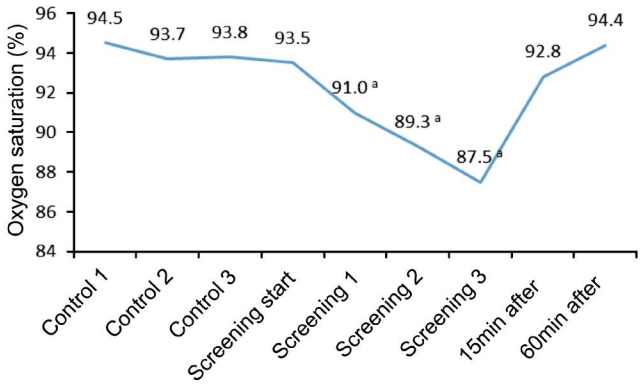

Figure 3 Oxygen saturation changes during the course of the study Mean length of examinations (from screening start point to screening finish point) was 4.3 (range, 3.1 to 10.0)min. Control 1: 6h before screening start, Control 2: 4h before screening start, Control 3: 2h before screening start. [a]Statistical difference compared with control data.

significant compared with data before the examination. 15min after the examination, diastolic BP declined to 44.3± 12.9 mm Hg (P=0.01), still demonstrated a significance with the control data, however, systolic BP dropped to 73.2 mm Hg (P=0.13). No significance change of BP was observed 60min after the screening.

Figure 2 demonstrates the pulse rate change we observed. The mean pulse rate remained in 133.3±9.0 per minute 2, 4, 6h before the screening and 136.2 ±11.3 per minute right before the examination start. The first pulse rate reading after the examinations begin was 135.7 ±9.2, which wasn't a significant change. The next two mean pulse rate during examination rose to 150.4±13.7 (P=0.00) and 162.2±15.3 (P=0.00) per minute, which became significant. Fifteen minutes after the examination finish, the pulse rate remained at 153.8±14.9 (P=0.00), still significantly higher compared to the control data. Sixty minutes after the examination the pulse rate dropped back to 136.0±10.4 (P>0.05) per minute.

During the control period, the mean oxygen saturation remained in 94% and remained the same until the examination started. Figure 3 shows the saturation changes during the whole course of our study. Saturation level reduced to 91.0% (P=0.04), 89.3% (P=0.001), and 87.5% (P=0.00) for the duration of the examination, sharing an average drop of 5%. The oxygen saturation returned to 92.8% 15min after the examination finished or several minutes after the handing discontinued. There were 17 infants who experienced desaturation below 75% while recovered immediately on discontinuing of the examination. Four out of these 17 infants need oxygen supply temporarily during the next examination.

There is no significant difference in the temperature change. Respiratory rate monitor showed a great variation during the screening procedure due to vigorously crying, sedation administration, and kinds of ventilation supports, so we terminated subsequent analysis.

The number of times of ROP examinations analyzed in each PCA group was 192 (5.5%) in <31wk (group A), 570 (16.3%) in 31 to (33+6)wk of age (group B), 1212 (34.7%) in 34 to (36+6)wk (group C), and 1517 (43.5%) in 37wk or older (group D). No significant difference in the incidence of the following adverse events before, during and after the ROP examinations were reported: pulmonary hemorrhage, mechanical ventilation upgrade, arrhythmia, signs of seizure activity, capillary refill >2s, positive blood cultures indicating sepsis, vomiting or reflux and daily urine production.

Table 2 shows the frequency of apnea 0-72h after ROP examinations. Totally 2989 screening events carried out to infants whom were not ventilated during the study were analyzed for apnea events. There were significant increases

Table 2 Changes in frequency of apnea events after ROP screening *n* (%)

Variables	New onset apnea 0-24h after screening	New onset apnea 25-48h after screening	New onset apnea 48-72h after screening
PCA<31wk (*n*=119)	28 (23.5) (*P*=0.009)[a]	18 (15.1) (*P*=0.362)	19 (16.0) (*P*=0.281)
PCA 31-33+6wk (*n*=415)	67 (16.1) (*P*<0.01)[a]	38 (9.2) (*P*=0.002)[a]	29 (7.0) (*P*=0.193)
PCA 34-36+6wk (*n*=1060)	42 (4.0) (*P*<0.01)[a]	37 (3.5) (*P*<0.01)[a]	21 (2.0) (*P*=0.511)
PCA>37wk (*n*=1395)	15 (1.1) (*P*=0.019)[a]	3 (0.2) (*P*=1.000)	1 (0.07) (*P*=0.125)

[a]*P*<0.05, statistical difference.

in the number of infants experiencing apnea (P<0.05) 0-24h period after the eye examination in every group. In infants with PCA<31wk, 28 cases presented new onset of apnea 0-24h after the screening. In group B, C and D, there were 67, 42 and 15 cases of new onset apnea 0-24h after screening. Twenty-five to forty-eight hours after the screening, 38 and 37 infants experienced significant new onset apnea in group B (P=0.002) and C (P<0.01), respectively. In all the 4 groups, there were no statistically significant relationships between ROP screening and the frequency of apnea events 48h after the screening.

As demonstrated in Figure 4, the occurrences of new onset NEC after ROP screening increased significantly in all the 4 PCA groups (P<0.01). Compared to an overall incidence of 12.4%, 8.5%, 5.7% and 2.1% in each group. Within 72h after the screening, 12 (8.7%) new cases of NEC were recorded in group A, 38 (6.1%) new NEC events in group B, 37 (3.4%) cases in group C and 42 (2.9%) cases in group D. Less number of infants were enrolled to the survey concerning gastric residual, because only infants with nasogastric tube could be evaluated. Infants with PCA <31wk presented a significant high incidence of new onset gastric residual up to 25.4% (n=192, P<0.01) compared to the original figure 18.1%. Infants with PCA between 31 to 34wk also shared an increased incidence of new onset gastric residual to 3.5% (n=570, P<0.01). There is no statistic relation between gastric residual and ROP screening when the PCA is older than 34wk. With regard to upper digestive tract hemorrhage, incidences were significantly high in group A (n=9, 6.4%, P=0.00), B (n=30, 4.8%, $P\leqslant$0.01), C (n=100, 0.7%, P<0.01) compared to the cases presented before ROP screening.

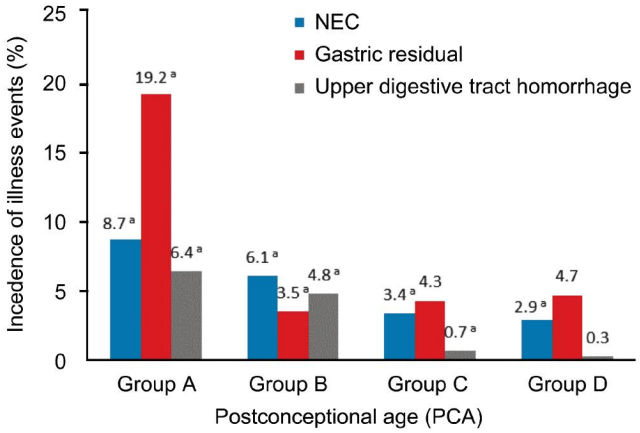

Figure 4 Incidence of new onset NEC, gastric residual and upper digestive tract hemorrhage 0–72h after ROP screening according to PCA [a]Statistical difference.

DISCUSSION

This study demonstrates several systemic changes and adverse events that occur before, during and after ROP screening. Since ROP screening has become a regular protocol in NICU management guide line and major task for ophthalmologists working in the obstetrics and gynecology hospitals or children's hospitals, it's important, therefore, for clinicians caring for preterm infants to understand how this manipulation will potentially affect the prematurity. Several researchers have printed out that prematurity are susceptible to mydriatic drops and sclera indentation, however, the published articles refer to this issue are limited. In the previous report [18], main outcome measure was variation in cardiorespiratory parameters. In our study, we take the vital signs and oxygen saturation data as the systemic indicators. We also observed the several most common pathological symptoms among prematurity from 24h before throughout to 72h after the ROP screening. This design provided a more comprehensive assessment of the physical and pathological changes in prematurity.

Our study showed a significant increase of BP right before the examination, which is most likely an effect of the mydriatic drops. The BP was even 11% higher at the final point compared with the data 0-6h before screening. Undulate BP is related to intraventricular hemorrhage, ROP and NEC, however, the correlation between ROP screening induced BP fluctuation and above clinical changes requires confirmation.

Clarke *et al* [19] described the oculocardiac reflex developed in 13% of the prematurity at the start of the screening, which is associated with the speculum, 31% of the infants developed bradycardia during the examination. In our survey, the pulse begun to rise from the second record point during examination. The highest pulse was recorded at the end of screening, showing an average of 21.3 per minute higher than the baseline. Infants presented large diverse change regarding pulse: some suffered profound tachycardia up to 206 per minute while others developed transient bradycardia as 72 per minute during scleral indentation. Overall, the pulse was 18.9 per minute higher 15min after

screening. The recorded changes in pulse rate and BP after the examination may reflect the screening induced adrenergic response to stress.

Specialists claimed a proportion of premature infants suffered from cyanosis during following-up ROP screening after discharge. In some cases, oxygen supplement was applied since there was no pediatrician at hand in the ophthalmology clinics. Our study demonstrated that the oxygen saturation fell after the screening begun and remains decline until the end of the procedure. The lowest saturation was 87.5% , which is below the suggested optimal oxygenation of ELBW [20-22]. Fortunately, in our study, no matter the infants were crying or sleeping during the examination, the saturation level returned to previous level quickly after the examination finished.

According to our survey, there is a significant increased incidence of new onset of apnea 24h after screening in every PCA groups. Twenty-five to forty-eight hours after screening, PCA between 31-36wk still show a high incidence of apnea. Apnea, manifested by unstable respiratory rhythm, reflects the immaturity of the respiratory control system of prematurity. It appears to be harmful to the brain when associated with significant hypoxemia. The idiopathic apnea during 1-2wk after birth is considered to be benign, however, the onset of apnea is often delayed if there is RDS or other causes of respiratory distress. In our survey, even some near term infants suffer from new onset apnea after ROP screening. The potential reasons for screening related apnea could be stress response, deoxygenated situation during screening and secondary digestive tract reflux. This finding indicates that closer attention and necessary intervening measures towards the high risk infants 0-48h after screening is necessary. In some cases, infants receive their last screening immediately before being discharged. Parents of these infants should be cautioned of the possibility of apnea, taught to monitor for apnea. Most important, they should know how to apply appropriate stimulation when apnea arise. For certain high risk infants, it might also be necessary for the doctor to consider a 48h of inpatient observation before discharge. However, more prospective study is needed to evaluate the impact.

Among the side effect events according to different system, we find that a proportion of premature infants developed NEC, gastric residual or upper digestive tract hemorrhage. Interestingly, all these events are related to feeding intolerance, which is the most common issue when confronting stress, hypoxia and hypovolemia. Although NEC is an infectious disease mostly combined with premature and sepsis, abundant reports have revealed the relationship between NEC and hypoxia induced body response [23]. Another publication of our group also indicated that significant infants suffered from NEC after retinal laser photocoagulation and general anesthesia could reduce these risks compared with topical eye drop anesthesia [24]. Infants with smaller gestational age are more likely to develop the gastrointestinal side effect events. Following that, clinical instruction regarding after-screening feeding strategy may be proceeded to reduce these side events. Some NICU specialists prefer to keep the infants fasting in case the patient develop apnea and relaxation of the esophageal sphincter, which could in turn cause aspiration. Furthermore, mitigating ophthalmic aparatus such as blunt pediatric surgical localizer or cotton-tipped wooden stick could be applyed instead of the muscle hook to perform scleral depression in order to minimize the pain. However, it's worthwhile to point out that there was no standard protocol on feeding restriction prior to and after the procedures in our survey, hence it's not appropriate to attributing NEC to ROP screening without sufficient evidence. The GIS side effects could due to prematurity, screening or drops. Our study did not enable us to determine if screening is causal for NEC, however, a number of biological plausible etiologies for NEC caused by stress reaction, intestinal ischemia and inflammatory response. However, prospective study to determine causality may prove to be difficult to perform.

One of the most common concerns about the ROP screening comes from the mydriatic drops. Mydriatic eye drops are routinely administered before ROP eye examinations to dilate the pupils. Here we apply the compound tropicamide eye drop compromise 0.5% of tropicamidea and 0.5% of phenylephrine. Tropicamidea, an anticholinergic drug blocks pupil constriction as well as inhibits the sphincter pupillae muscle. Phenylephrine, an alpha-adrenergic drug that directly acts on the ciliary muscle. Although a regular prescription for optometry, ophthalmic drops those have anticholinergic and alpha adrenergic propertied could be absorbed systemically, causing side effect, especially when the volume within each drop administrated to neonates is the same as to adults and a ductus nasolacrimalis compression is not applied to neonates. Several adverse effects directly related to systemic absorption of mydriatic eye drops have been documented following ROP screening, as the α-adrenergic effect of phenylephrine rinses peripheral resistance and BP[25-28]. Baseline assessment values were taken in our survey 6h prior to administering the drops so as to detect the possible reported side effects. After 3 doses of mydriatic drops, the BP increased to 75.4/43.5 mm Hg, significantly high compared to the control BP. This is a direct effect induced by the eye drop since not any other extra process was applied at this point. Abdelhalim *et al* [29] reported a case of intraoperative severe hypertension and acute pulmonary edema occurring in an 18 kg-weight child during retinal surgery after possible systemic absorption of topical phenylephrine eye drops. Here we demonstrate a similar situation that mydratic drop could result in increased BP. The possible reason could be systemic absorb and pain

response caused by the administration. Cohen *et al* [30] utilized the Premature infant pain profile (PIPP) scores to evaluate the physiological and behavioral pain responses of premature infants following instillation of mydriatic eyedrops for ROP examinations. One-third of infants were found to present clinically significant pain response. BP is the only physical change we observed before examination start. Post-mydriatic events potentially reflect effects of both the mydriatic drops and the pattern the screening was performed. Another important reason for pathophysiologic changes such as desaturation and apnea following ROP screening is the widely accept opinion that it is a painful procedure and it is likely to result in stress response. Pain is a multifactorial phenomenon with physiological and behavioral aspects, modified in infants by factors such as gestational age, state of health (sepsis and hypovolemia may lead to tachycardia and changes in BP), and maturity. A transient short-term pain and stress response occurs with both binocular indirect ophthalmoscope and wide-field digital retinal imaging [31]. A subset of babies presented persistent changes on a standardized neonatal pain assessment scale 24h after screening. The use of lid speculums and scleral depression appear to be the strongest painful stimuli. On the other hand, infants may experience pain not only from the ROP screening, but also from the mydriatic drops. Mydriatics such as tropicamide and cyclopentolate may cause pain reaction upon application to the ocular surface. Previous studies in adults and adolescents demonstrate transient but significant amount of discomfort associated with mydriatic drops described as burning or stinging[32]. Here we suggest applying topical anesthetic before the mydriatic drops to attenuate the discomfort. A prospective randomized study was performed by Kabaras *et al* [33] to investigate the efficacy of 15 mg/kg oral paracetamol 60 min before ROP screening. As a result, paracetamol modestly reduced PIPP scores during eye examinations. Cochrane study have drawed a conclusion that Sucrose is safe and effective for reducing procedural pain from single events, yet sucrose use in extremely preterm, unstable, ventilated (or a combination of these) neonates needs to be addressed[34]. Kangaroo care will be another way to reduce the pain especially in outpatient department.

A prospective randomized cross-over pilot study showed that screening using a RetCam or a speculum and indirect ophthalmoscope caused more stress to the infant, as indicated by physiological and behavioral changes, than screening using an indirect ophthalmoscope without a speculum [35]. These effects should be considered when deciding on the appropriate screening method for examining particularly sick infants. The fact that scleral indentation was not necessary to visualize the retina is of paramount importance because this factor is significantly related to pain and stress. The lower light intensity used during screening might cause less photophobia and less discomfort for the infant. RatCam is nowadays more and more popular utilized in hospital, although it possesses number of advantages compared with traditional screening method, an improvement is urgent to be made to reduce the dissamenity.

Our study had a number of limitations. Firstly, a portion of infants who were enrolled in the study have any significant systemic diseases (*e.g.* respiratory or cardiac diseases). Those disorders may have compounded the registered finding. Secondly, we directly estimate the pain and stress through vital sign changes and several side events to evaluate the stress and pain response related to ROP screening. However, some other assessment method such as Neonatal Therapeutic Intervention Scoring System (NTISS) and PIPP score, two indicators proofed to be effective to evaluate the therapeutic intensity and illness severity in neonates, could be applied in the future study in order to provide quantitative or semi quantitative results. Thirdly, as we performed retrospective, observation survey, some side effect events collection such as NEC and upper digestive tract hemorrhage is in view of the diagnosis, clinical doctor may not be able to establish a diagnosis as soon as they observe the symptom. The pathophysiologic process of gastrointestinal disorder may have been subtly initiated before the screening, but the diganosis was established after the screening. This could lead to overestimation of the new onset of GI disorders with ROP screening. Thus, our findings should be interpreted with caution. Ideally, a large, carefully designed, prospective population-based randomized cohort study of ROP should be conducted. Attributing NEC to ROP screening without sufficient evidence is dangerous.

In conclusion, this study revealed that part of infants undergoing ROP screening suffered from deteriorative clinical condition, including fluctuant BP, increased pulse rate and desaturation. Zero to seventy-two hours after fundoscopy expose, a portion of infants present apnea, NEC, gastric residual and upper digestive tract hemorrhage, which are considered to be stress and pain response. Modifications to the examination technique, anesthetic and sedation strategy aim to reduce the impact of stress and pain induced by ROP screening are needed to optimize the clinical outcomes of vulnerable preterm infants.

ACKNOWLEDGEMENTS

Foundation: Supported by the National Natural Science Foundation of China (No.71173055).

Conflicts of Interest: Jiang JB, None; **Zhang ZW,** None; **Zhang JW,** None; **Wang YL,** None; **Nie C,** None; **Luo XQ,** None.

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