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Necrotising Enterocolitis Following the Use of Mydriatics: A Case Report of Two Triplets

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Abstract Cyclopentolate-phenylephrine eye drops are commonly used to achieve mydriasis during routine screening for retinopathy of prematurity (ROP) in preterm infants. Two cases of necrotising enterocolitis (NEC) following ROP screening in two premature Chinese triplets were reported. Literature studying and reporting the side effects of mydriatrics and the ROP examination were reviewed. Also, safety measures concerning ROP screening were discussed. In our institution two more years after adopting these safety measures, no more feeding difficulties or NEC were noted following ROP screening. We concluded that both the mydriatics and ROP examination may lead to systemic and gastrointestinal side effects in preterm babies and may be associated with NEC in high risk patients. This association warrants further study and the safety measures should be observed.

Key words Cyclopentolate; Mydriatics; Necrotising enterocolitis; Preterm infants; Retinopathy of prematurity

Introduction

Cyclopentolate-phenylephrine eye drops are commonly used to achieve mydriasis during routine screening for retinopathy of prematurity (ROP) in preterm infants. Adverse gastrointestinal effects following its use are not uncommon. We reported two babies suffering from necrotising enterocolitis (NEC) following its use.

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Case Report

In March 2008, three monochorionic triamniotic triplets were delivered by emergency Caesarean section at 28 6/7 weeks because of fetal distress and preterm labour. Their mother's first antenatal ultrasound was performed at 13 1/7 weeks. The liquor volume and the growth parameters of the foetuses were normal at that visit. Discrepant growths between the foetuses with one growing appropriately but the other two lagging behind were first detected at 21 6/7 weeks. At 27 4/7 weeks, antenatal ultrasound revealed normal liquor volume in two foetuses but just 2 cm pocket for one foetus. Thus, the mother was admitted into hospital to start on dexamethasone treatment to prepare for preterm delivery.

The triplets weighed 820 grams, 720 grams and 555 grams at birth, respectively and their first haemoglobin levels were 18.6 g/dL, 16.3 g/dL and 16.6 g/dL, respectively. All three triplets experienced similar neonatal complications, namely respiratory distress syndrome, patent ductus arteriosus, hypotension, chronic lung disease and sepsis. They were treated similarly with surfactant, prophylactic 3-day course of indomethacin, dopamine

infusion up to 10 mcg/kg/min and inhalation steroid. Only triplet III had pressor resistant hypotension, which necessitated the use of stress dose of hydrocortisone at 1 mg/kg/q8h from day 4-8. Apart from that, there was no further use of systemic steroid in all three triplets. For the patent ductus arteriosus, only triplet I required therapeutic 6-day course of indomethacin following the use of the prophylactic 3-day course. For triplets II and III, echocardiogram showed closure of the ductus arteriosus after the 3-day course of prophylactic indomethacin. Despite the early closure of the ductus arteriosus, triplets II and III were dependent on dopamine till day 28. However, triplet I could be weaned off dopamine by day 8.

At 6 weeks old when ROP screening was performed, triplet III had achieved full feeds and was on exclusively preterm formula. Triplet II had a quarter of her feeds with preterm formula and triplet I was still on parenteral nutrition because of gut motility problem. All of them had received one drop of 2.5% phenylephrine and 1% cyclopentolate eye drops twice one hour before ROP examination. Oxybuprocaine eyedrops was applied immediately before examination to reduce discomfort.

Triplet III developed milk intolerance and abdominal distension 5 hours after examination with pneumatosis intestinalis seen on abdominal X-rays. She responded to conservative treatment and did not require surgical intervention. Triplet II had increased gastric aspirate 5 hours after the examination. Triplet I had no clinical deterioration following the examination.

Only triplet II required a second ROP screening at the 7th week to look for rush disease as stage 1 ROP was noted when vessels development reached posterior zone II at 6th week. At that time, she was on 164 ml/kg/day of preterm formula. Immediately after the application of the eye drops, she developed desaturation with bradycardia, requiring resuscitation. Eye drops re-application and ROP examination were abandoned. Thirty minutes later, the abdomen was found to be distended with 16 ml milk curd aspirated. Despite fasting, antibiotic treatment and full supportive treatment, abdominal distension progressed. Eighteen hours after instillation of eye drops, her abdomen became stony hard and bowel sounds could not be heard. She was then transferred to surgical centre and laparotomy was performed 2 days later. The operative findings were extensive NEC with full thickness necrosis between 38 cm to duodeno-jenunal junction and 1 cm proximal to ileocecal valve.

Post gut resection, triplet II remained dependent on parenteral nutrition. At 7 months old, she died from massive pulmonary haemorrhage with parenteral nutrition related cholestasis. For triplets I and III, they were discharged on day 112 and day 164, respectively. They were doing well when last seen at 26 months.

Discussion

The first case report on the association between mydriatic eye drops and NEC was reported in 1973.[1] Bauer et al reported a pair of preterm twins who developed vomiting, abdominal distension, and ileus shortly after the administration of 10% phenylephrine and 1% cyclopentolate. While twin I developed NEC and succumbed, twin II recovered and survived. The systemic concentrations of cyclopentolate examined 24 hours after the instillation of the eye drops measured 22 and 2 μg per ml of plasma in twin I and II, respectively. Cyclopentolate intoxication was thus blamed as the cause of the twins' deterioration.

In our case, although the concentration of cyclopentolate was not measured, the temporal sequence of events and the fact that triplet II was haemodynamically stable and tolerated milk well for at least two weeks prior to eye examination gave credence to our belief that the mydriatics did play a significant role in the aetiology of NEC. The pathophysiology of NEC remains elusive and is likely multifactorial.[2] Since premature infants are at higher risk for NEC, immaturity of the intestinal tract has been implicated in the development of NEC.[2] Immaturity of these functions results in impaired mucosal defense, and intestinal motility and function.[2] These factors result in microbial overgrowth and an increased susceptibility of mucosal injury by hyperosmolar feeds and ischaemic insult, as observed in our cases. Both triplet II and III were on exclusive preterm formula feeding when they developed NEC. The close temporal relationship between the NEC and the application of mydriatics suggested that ischaemia was the final event in causing the decompensation in an already compromised gut.

Phenylephrine is a synthetic sympathomimetic compound, similar to epinephrine, which produces rapid mydriasis. Cyclopentolate is an anticholinergic, antimuscarinic tertiary amine with atropine-like actions, which produces additional mydriasis as well as rapid and intense cycloplegia. In a cohort of 50 preterm infants, an increased incidence of feeding difficulties, including abdominal distension and increased gastric aspirate, had been observed on the day that mydriatics (2.5%

phenylephrine and 0.5% cyclopentolate) were instilled.[3] Moreover, one infant among this cohort developed NEC during the 24-hour post ophthalmic examination.[3]

In another case series, Nair et al realised the possible association of ROP screening with NEC when they reviewed their cases.[4] During the two years' study period, four among 41 cases of stage II/III NEC occurred 4 to 24 hours following ROP screening.[4] The authors believed that the process of eye examination did play a significant role in the aetiology of NEC because of the close temporal sequence and the fact that all of them were haemodynamically stable, feeding and apparently thriving well for at least two weeks prior to the eye examination.[4]

Concerning the gastrointestinal effects of the mydriatics, Isenberg et al have shown that cyclopentolate 0.5% can significantly inhibit gastric acid output in preterm infants.[5] Bonthala et al recorded antral and duodenal fasting motor activity with a low compliance continuous perfusion manometric system in 11 preterm infants at three time intervals, before and after the instillation of mydriatics (0.2% cyclopentolate and 1% phenylephrine) and after ROP screening.[6] They found that duodenal motor contractions decreased nearly fourfold after the instillation of mydriatics versus that seen before ($p<0.01$) and this change persisted after the completion of the eye examination. Moreover, gastric emptying was significantly delayed after the completion of the eye examination. According to the sequence of findings, these effects appear to be due specifically to the systemic effects of mydriatics and not to the stress of the eye examination.

The stress of ophthalmological examination itself on the immature gut may also cause the feeding intolerance. However, in triplet II, the ROP examination was abandoned. Thus, the extensive NEC in triplet II was not due to the ophthalmological examination itself. While in triplet III, her NEC developed after the ROP screening. In her case, NEC might be attributed to the mydriatics as well as the ophthalmological examination itself.

Laws et al prospectively studied the systemic effects of screening for ROP, paying particular attention to the 110 physical examinations on 56 extremely / very low birth weight babies.[7] Using a definition of the oculocardiac reflex as a 10% drop in pulse rate, 24% of the infants developed the reflex at the start of the examination. This decrease was followed by a gradual rise as the examination was continued until the end of the examination. Only till ten minutes after the examination did the mean pulse rate drop back to pretest level. The authors believed that the rise in pulse rate and blood pressure at the end of the examination was an adrenergic response to the stress of the procedure, indicating that the procedure is uncomfortable for the infant.

Another side effect of physical manipulation of the globe noted in the study was the drop in oxygen saturation.[7] Oxygen saturation was reasonably stable before any topical therapy and during administration of the drops but fell after placement of the speculum and remained reduced until the end of the procedure. This observation was made both in infants who cried and those who slept through the examination. No infant, including the three with greater than 20% saturation drop, suffered a clinically significant apnoeic episode after the examination stopped and saturation levels rapidly returned to earlier levels in most cases.

Laws et al remarked that there was no clinically significant systemic complication directly attributed to ROP screening in their study although statistically significant changes were observed.[7] No particular infant group appeared to be at particular risk.[7] As the physical examination was related to the greatest observed response, the eye examination should be kept as brief as possible.[7]

Realising the gastrointestinal adverse effects of cyclopentolate, the mydriatic regimen in screening of ROP in our institution was changed to Mydrin®-P, tropicamide 0.5% and phenylephrine 0.5%. In Chew et al's randomised, double masked clinical trial comparing three mydriatic regimens in screening of ROP, the group on cyclopentolate 1% + phenylephrine 2.5% regimen had the maximum effect on blood pressure when compared with tropicamide 1% + phenylephrine 2.5% and cyclopentolate 0.2% + phenylephrine 1%.[8]

Moreover, efforts were made to decrease the systemic absorption of mydriatics. These included wiping excess fluid off the cheek immediately after instillation, to prevent absorption through the skin.[9] Applying gentle and sustained pressure at the inner corner of the eye for 3 minutes to occlude the nasolacrimal system after instillation can also reduce the systemic absorption.[9] In babies with prior history of feeding intolerance or abdominal distension, feeds were withheld before and after the ophthalmological examination.

Since 7 May 2008, the use of the combination of 1% cyclopentolate and phenylephrine 2.5% was stopped in our institution and the aforementioned measures were adopted. From that time onwards till 31 July 2010, 28 extremely low birth weight babies and 86 very low birth weight babies had undergone the ROP screening in our institution. Pupils were dilated adequately with Mydrin®-P eyedrops for fundal examination in ROP screening. No more feeding

intolerance, abdominal distension or NEC was noted on the day of ophthalmological examination in our preterm babies.

We concluded that both the mydriatics and ROP examination may lead to systemic and gastrointestinal side effects in preterm babies and may be associated with NEC in high risk patients. This association warrants further study and the safety measures should be observed.

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