Abstract

Advances in neonatal intensive care have improved survival rates in extremely premature an infant, which has led to an increase of Retinopathy of Prematurity (ROP) in the developed world. Left untreated, infants are at risk of developing strabismus, myopia, vitreous haemorrhage, vitreo-retinal fibrosis, retinal detachment, secondary angle closure glaucoma and ultimately complete loss of vision. The improvements in the understanding and treatment of ROP have been supported by seminal research, and its complexity is still being explored. However the importance of early screening and treatment is essential in the prevention and treatment of this disease. The following paper will examine the causes and treatments of ROP, as well as implications for future neonatal practice.

Retinopathy of Prematurity (ROP) is a proliferative disorder of the immature retinal vasculature. The retina has no blood vessels until around 16 weeks' gestation, the vessels grow out from the optic disc and only reach the periphery of the eye one month after birth (Kanski, 2011). ROP was recognised in 1942 in Boston, U.S.A. by Theodore L. Terry and initially named Retrolental Fibroplasia (RLF). It was described as a "fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens" (Fleck and McIntosh, 2008). Whilst Terry (1942) identified 'fibroblastic overgrowth' he did not identify the specific aetiological connection to oxygen. Further research undertaken by Dr. Patz in the 1950's in Washington DC, showed that premature infants now cared for in closed cot/incubators who received high concentrations of oxygen in a confined space were more likely to develop ROP than those who received low levels. This discovery resulted in oxygen levels administered to preterm infants being restricted to a maximum of 40% which resulted in increased levels of morbidity and mortality. Thus, the importance of adequate oxygenation with careful monitoring of

blood gas measurement and saturation monitoring was seen as the way forward in preventing ROP.

Advances in neonatal care in the 1980's led to improved survival rates for very premature infants, but the increased immaturity of these babies made them much more likely to develop ROP, causing its re-emergence as a significant cause of sight loss in the developed world (Fleck and McIntosh,2008). According to Brennan et al (2003), around 30% of all premature infants with a birth weight <1500g develop ROP in the first weeks of life. This increase has led to the need for those health professionals caring for neonates to have an increased knowledge and understanding of ROP to ensure optimum care is delivered.

POSSIBLE CAUSES

It is difficult to identify the cause of ROP due to the complexity of the physiological instability of very premature infants. However, the delivery of appropriate oxygen levels is thought to be an important factor in the prevention of ROP. Oxygen therapy for premature infants often fluctuates due to their susceptibility to apnoeic episodes and bradycardias. In utero, oxygen saturations are 65-70% at best, resulting in high levels of vascular endothelial growth factor (VEGF) which is thought to contribute to normal retinal development (Kaniski 2013). After premature birth, immature lungs and cardiac circulation i.e. patent ductus arteriosis result in the infant requiring oxygenation which causes V.E.G.F. levels to drop which in turn slows down retinal growth.

York et al (2004) hypothesised that it is fluctuations in arterial oxygenation that place the infant at higher risk rather than the amount and duration of oxygen delivery. Chen et al (2010) advocated the initial use of low rates of oxygenation for infants born at less than 32 weeks gestation, and the later use of high rates of oxygen delivery to reduce the risk of developing ROP. Castillo et al (2010) focused their research on the need for careful pulse

oximetry and the choice of oximetry monitoring equipment, which were recognised as important factors in reducing the frequency of wide changes in oxygenation and hyperoxaemic episodes.

Another factor thought to cause ROP is the general growth of the premature infant, as hyperglycaemia and metabolic disturbances would appear to contribute to the formation of an abnormal retina. Low levels of Insulin such as Growth Factor-1 (IGF-1) may affect retinal progress (Hellstrom et al, 2003). Appropriate nutrition can help to prevent ROP, Hylander et al (2001) reported that breast milk did help to prevent the disease. However, Kao et al (2010) explored the association between serum bilirubin levels and breast milk feeding with ROP and found that high serum bilirubin levels appeared to protect against ROP, but that breast milk alone appeared to have no effect on the development of ROP.

Most studies that look at the causes of ROP concentrate on the infant post delivery (Kao et al 2010, Chen et al 2010, Castillo et al 2010), but Fortes Filho et al (2011) considered maternal health as a determinant of an infant developing ROP. They reported in a study of 324 infants, that some antiangioangenic factor produced by the pre-eclamptic mother might cross the placental barrier to the foetus providing protection from ROP for several months following delivery (Fortes Filho et al 2011). They also discovered that very low birth weight infants delivered to mothers with pre eclampsia, had a 60% reduction in risk of developing ROP. Other factors that would appear to put the infant at an increased risk of developing ROP include; low weight for gestational age, low APGAR scores at 5 minutes, use of CPAP (continuous positive airway pressure), use of erythropoietin or surfactant, the presence of sepsis, meningitis, patent ductus arteriosis, intraventricular haemorrhage, abdominal distension, diet intolerance or needing blood transfusions (Fortes Filho et al 2011, Eckert et al 2012, Neutze and Ferracotta 2013). In general studies report that the smallest, sickest babies are those most at risk of developing ROP.

Screening

Guidelines for the screening and treatment of ROP were developed collaboratively in 2008 with the Royal College of Paediatrics and Child Health, the Royal College of Ophthalmologists, the British Association of Perinatal Medicine and the premature baby charity BLISS (UK ROP Guidelines, 2008). Current guidelines on screening are as follows; Babies born below 32 completed weeks gestation or whose birth weight is below 1501g should be screened and all babies born below 31 completed weeks gestation or whose birth weight is below 1251g MUST be screened. Ideally screening should take place at either 30-31weeks PMA (Post Menstrual Age) for babies born before 27 weeks completed weeks of gestation and 4-5 weeks post delivery for babies born between 27-32 weeks of gestation. If for any reason a baby is unable to be screened, for example, too unwell, this must be clearly stated in the medical notes and the screening rescheduled within one week of the intended examination.

Screening can be stressful for both infants and their parents, and the need for careful preparation is vital. Written information should be given to parents prior to screening which explains the reasons for screening and the implications of its findings (Smith 2012). Time should be allowed for parents to ask questions and voice any concerns they may have. Preparation of infants begins one hour before with the instillation of eye drops, mydriatics such as cyclopentolate and phenylephrine are most commonly used for pupil dilation, although their use can cause difficulties in this vulnerable patient group. Phenylephrine can cause tachycardia and systemic hypertension in preterm infants', Hered and Gyland (2010) advocated the use of 2.5% solution to reduce the risk of adverse effects, but careful observation during and after screening is of importance. Bonthala et al (2000) reported a slowing down of gastric emptying with cyclopentolate drops which may have a direct affect on the overall condition of the preterm infant. Neonatal and ophthalmic practitioners involved

in screening should possess an awareness of these adverse effects as per NMC's (Nursing and Midwifery Council) Standards for Medicines Management (NMC, 2008), to ensure the safety of babies during and after screening.

Pain control within the preterm infant population has long been problematic, as the neonate vulnerability often limits the use of pharmacological analgesic measures. ROP screening involves using an eyelid speculum which is thought to be the main source of pain in infants', with Mitchell et al (2011) reporting a significant increase in apnoeic episodes 24-28 hours after screening. Dempsey and McCreery (2010) noted a reduction in pain scores when topical local anaesthetic drops (proparacaine) were administered 30 seconds prior to commencement of screening. The use of oral glucose has been identified as an effective means of providing comfort for infants during painful procedures (Dilen and Elseviers 2010). However, Olsson and Erikson (2011) have disputed its effectiveness in the relief of pain during ROP screening. Some centres use cotton buds instead of an eyelid speculum as a means of reducing pain levels. Mehta et al (2005) compared three different methods of screening and found that using a RetCam and the indirect ophthalmoscope with a speculum appeared to cause greater discomfort to infants than the indirect ophthalmoscope without a speculum and this method should be considered for screening particularly in sick infants. Whichever method is used, all comfort measures possible should be in place e.g. swaddling, non nutritive sucking or oral feeding.

Treatment

Treatment under sedation and analgesia plus elective ventilation in the neonatal unit seems the most popular choice for ROP. The 2008 ROP guidelines also advocated treatment in theatre under anaesthesia if time and resources allow. Topical anaesthesia on its own is

thought to be unsuitable (Smith 2012). The type of treatment given is dependent on the stage of and severity of the disease.

The development of therapy including cryotherapy and later laser photocoagulation followed detailed evaluation of stages and distribution of ROP (Committee for the Classification of Retinopathy of Prematurity, 1984). For less severe ROP laser therapy is the treatment of choice as it has the ability to target tiny vessels more precisely, burning the abnormal ones without affecting the surrounding tissue is important for subsequent vascularisation. The laser can make more refined burns on the retina, improving accuracy of treatment of the vessels. However, cryotherapy is still used in many developing countries where laser therapy is not available. Good et al (2010) state ROP laser treatment can result in extensive amounts of peripheral retinal ablation with the loss of visual field. However, it would appear the benefits of laser treatment far outweigh the risks (UK ROP Guidelines 2008).

Laser is only suitable for less severe stages of ROP with more severe stages requiring vitreoretinal surgery. This may include:

- A scleral buckle, a silicone band placed around the globe. This keeps the vitreous gel from pulling on the scar tissue and enables the retina to flatten back down onto the wall of the eye. Infants who have had a scleral buckle will require its removal as the eye grows.

- A Vitrectomy is the removal of the vitreous and replacing it with a saline solution. After the vitreous is removed, the scar tissue on the retina can be peeled back or cut away, allowing the retina to relax against the eye wall. Vitrectomy is a treatment for stage V ROP only.

Any treatment is usually given to both eyes as the severity and progression of ROP can affect both eyes. Post operative drop regimes include the administration of mydriatics, steroids and sometimes antibiotics. The eye should be re-examined 5-7 days later after laser and re treatment should be carried out 10-14 days after initial treatment if there has been a poor response.

Future of ROP

Due to the increased survival rate of premature infants there is a need to target infants who require screening in a more efficient manner. Uni-professional working should be enhanced in relation to the support of parents whose baby may have a visual morbidity for example the midwife, neonatal nurse, public health midwife. Further support for parents post screening is also required in terms of longer term health and social issues of visual impairment to the individual and society.

Eckert et al (2012) stated that the number of eye examinations performed on preterm infants could be reduced with the introduction of a scoring system. The score suggested takes into consideration other factors like co-morbidity in the infant and obstetric history, not merely deciding if an infant should be screened because of gestational age and birth weight. They argue that screening sessions are costly and demand a heavy workload. Moreover, repeated ophthalmological examinations may lead to stress and unnecessary discomfort for already vulnerable infants. However, it fails to include other predictive factor such as, insulin levels, white blood cell counts and the absence of elevated C-reactive protein. The implementation of any scoring system in the UK would need to be cognisant of all of these factors.

Some strategies in the fight against ROP are looking at replacing VEGF to prevent ROP developing. As previously discussed, VEGF levels are known to fall after premature birth, Bevacizumab is a humanized form of VEGF, has been administered via intravitreal injection

to premature infants with some degree of success in preventing ROP, but complications have occurred such as regression to neovascularisation (Neutze and Fecarotta, 2013).

Conclusion

Neonatal practitioners have a pivotal role to play in the prevention and treatment of ROP (Smith 2012). Practitioners caring for premature infants are responsible for oxygen administration and monitoring, and should therefore be fully informed of the importance of avoiding fluctuations in oxygen levels. Madden and Bobbola (2008) advocated the development of more formal practice guidelines, education, standardization of practice in oxygen administration, and greater collaboration between healthcare professionals and respiratory therapists.

ROP is a treatable disease which due to the numbers of premature infants born, will continue to be seen by ophthalmologists. Screening and treatment with laser would appear to be the most effective forms of limiting the progression of ROP, although research continues to try and find other means of prevention and treatment. There has been some development aimed at the prediction and screening of infants most at risk. However, more research and evidence is required before such a practice could be fully implemented in the UK.

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