

The treatment and risk factors of retinopathy of prematurity in neonatal intensive care units

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Abstract-

Purpose -The purpose of this study is to report the incidence and risk factors of ROP in neonatal intensive care unit (NICU) In maharani laxmibai medical college.

Materials and Methods-A retrospective review was performed on 250 premature infants who were consecutive ROP screened in the NICU of maharani laxmi bai medical college from september 2019 to february 2020. The single-factor analysis and the logistic multivariate regression analysis were used to detect risk factors of ROP.. The data were analyzed using SPSS programme.

Results: Total 250 premature infants were consecutive ROP screened, 80 (32.00%) were found ROP, and 68(40.00%) were treated. The single-factor analysis revealed that the incidence of ROP was associated with multiple births, gestational age, birth weight, mechanical ventilation, intravascular hemolysis, the number of operations and blood culture results. The logistic multivariate regression analysis revealed that gestational age; birth weight, mechanical ventilation, minimum SaO₂ and daily weight gain were independent risk factors for ROP onset. Twinty patients underwent retinal laser photocoagulation with recurrence 10 patients. Fifteen patients underwent anti-VEGF drug (Ranibizumab) via intraocular injection with 1 patients of recurrence.

Conclusion: The incidence of ROP in NICU of maharani laxmibai medical college will match those in middle-income countries, but higher than high-income countries. Anti-VEGF drugs could be preferred as a good treatment method for zone 1 ROP and aggressive posterior ROP.

Keywords: anti-VEGF, neonatal intensive care unit, retinopathy of prematurity

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I. Introduction

Retinopathy of prematurity (ROP) is one of the major causes of blindness in children and is the most common cause of retinal vasculopathy in premature or low-birth-weight infants [1]. The physiological process by which the retina is vascularized in human embryos is divided into two stages: vasculogenesis and angiogenesis. Vasculogenesis is the process that occurs during the early stage of retinal vascularization in which endothelial progenitor cells differentiate into endothelial cells to form blood vessels. This process begins at 12 weeks and finishes at 21 weeks of gestational age. Angiogenesis is a process that occurs in the advanced stage of retinal vascularization, during which the superficial plexuses that are responsible for the central hemal arch form. The blood vessels gradually grow and develop to surround the retina from the optic disk beginning at 16 weeks of gestational age, reaching the nasal retina at 32 weeks and the temporal retina at 36 to 40 weeks [2,3,4]. However, in premature babies the retinal blood vessels it is incomplete. With many factors, the vessels maybe grow and branch abnormally, and then ROP would develop. These abnormal blood vessels may grow up from the plane of the retina and may bleed inside the eye. When the blood and abnormal vessels are reabsorbed, it may give rise to multiple bands like membranes, which can pull, up the retina, causing detachment of the retina and eventually blindness before 6 months.

In recent years, with the development of neonatal medical technology, an increasing number of severe premature infants have survived, including cases of prematurity associated with in vitro fertilization (IVF), multiple births and infants with very low birth weight, very low gestational age, congenital dysplasia, immaturity, septicemia, severe infections and multiple surgeries after birth. The survival rates of extremely immature premature infants < 26 weeks and < 1000 g worldwide have continuously increased, and the incidence of ROP has been increasing in parallel [5,6,7,8].

This study retrospectively analyzed the screening and treatment of ROP in severe premature infants who were admitted to the Neonatal Intensive Care Unit (NICU) of Maharani laxi mediccil college, jhansi. The results revealed that ROP was common in severe premature infants with risk factors and that anti-VEGF

treatment of ROP produced a curative effect. The purpose of this study was to analyze the prevalence and risk factors of ROP in advanced neonatal care hospitals in maharani laxmi bai medical college,jhansi.

II. Method and material

Subjects:

A retrospective analysis was performed on premature infants who underwent ROP screening in the NICU of maharani laxmibai medical college,jhansi from september 2019 to february 2020.The patient-related data collected in this study include the following: name, age, and clinical diagnosis. The names were replaced by numbers, and the relevant data of the patient was encrypted and stored in the main study. We had obtained the written informed consent of the parents of the children.

Methods

The first fundus examination was performed at 4 to 6 weeks after birth or at 32 weeks of postmenstrual age (PMA). The following methods and procedures were used: (1) the primary screening was performed by binocular indirect ophthalmoscopy with appropriate mydriasis. Infants with suspected ROP were examined with Retcam (retina camera). (2) The surgeon determined the use and method of treatment based on the results and images got from the Retcam examination. (3) Examination results and treatment recommendations were recorded in detailed electronic medical records. They are location of the disease into zones (1, 2, and 3), the circumferential extent of the disease based on the clock hours (1–12), the severity of the disease (stage 1–5) and the presence or absence of “Plus Disease”. And screen or treatment information, which included follow-up, treatment methods. (4) Follow-up treatments and condition progression were recorded in detailed electronic medical records according to the international staging and classification standard for ROP [10]. They are location of the disease into zones (1, 2, and 3), the circumferential extent of the disease based on the clock hours (1–12), the severity of the disease (stage 1–5) and the presence or absence of “Plus Disease”.

Laser photocoagulation and anti-VEGF drug (Ranibizumab) were used in 35 premature infants with ROP who reached the therapeutic threshold. Twenty with ROP in zone 2 or zone 3 underwent retinal laser photocoagulation, and 15 with ROP in zone 1 or aggressive posterior ROP (AP-ROP) were given anti-VEGF drug (Ranibizumab 0.25 mg) via intraocular injections. All patients with ROP recurrence were retreated with laser photocoagulation. Infants with ROP were monitored until 54 weeks of PMA as the study endpoint.

Inclusion Criteria:

ROP screening was performed on premature and low birth weight infants with a gestational age < 32 weeks or birth weight < 2000 g. For infants with severe illness or a clear history of oxygen intake over a long period of time, ROP screening standards were appropriately relaxed.

Exclusion Criteria:

- 1-death before the initial screen
- 2-death or loss to follow up before complete retinal vascularization was developed
- 3-incomplete screening procedure
- 4-infants who underwent ROP screening at other hospitals

Statistical Analysis

The data was entered regularly. Nominal data was presented as numbers & percentage. Data analysis & percentage calculation was done using Microsoft Office Excel.

III. Result

Two hundred fifty severely premature infants met the ROP screening criteria and completed a first ROP ophthalmological examination at which their general condition was recorded. Among these patients, 150 (60.00%) were boys, and 100 (40.00%) were girls. The incidence of all stages ROP was 20.00% (20) girls and 30.00% (45) boys. The treatment of ROP was 40.00% (08) girls and 55.55% (45) boys. There are 175 (70.00%) were single births, 50 (20.00%) were twin births, and 25 (10.00%) were gestations births. The incidence of ROP was 36.00% (63) in single births, 24.00%(12) in twin births, and 44.00%(11) in gestations births. The treatment of ROP was 42.85%(27) in single births, 50.00%(06) in twin births, and 63.63%(07) in gestations births. The average gestational age was 33.84 weeks (min 26 max 39 weeks). Overall, 140 of the patients (56.00%) had a gestational age ≤ 32 weeks, and 110 patients (44.00%) had a gestation age > 32 weeks. The incidence of ROP were 30.00% (42) in gestational age < 32 weeks and 20.00% (22) in gestational age > 32 weeks. The treatment of ROP were 47.61%(20) in gestational age < 32 weeks and 40.90%(09) in gestational age > 32 weeks. The mean birth weight was 2160.23 g (min 1015 max 3690 g). Birth weights ≤1500 g were recorded in 125 cases (50.00%), weights 1501–2000 g were recorded in 100 cases (40%), and weights > 2000 g were recorded in 25

cases (20.00%). The incidence of ROP were 40.00% (50) in birth weights ≤ 1500 g, 20.00% (20) in birth weights 1501-2000 g, and 40.00% (10) in birth weights > 2000 g. The treatment of ROP was 20.00%(10) in birth weights ≤ 1500 g, 10.00% (02) in birth weights 1501-2000 g, and 0 in birth weights > 2000 g. Eighty of the patients (32.00%) were mechanical ventilation > 96 h group, and 170 patients (68.00%) were mechanical ventilation < 96 h group.

The incidence of ROP were 50.00% (40) in mechanical ventilation > 96 h group, and 20.00%(34) in mechanical ventilation < 96 h group. The treatment of ROP were 25.00% (10) in mechanical ventilation > 96 h group, and 50.00%(17) in mechanical ventilation < 96 h group.

Among the 80 included premature infants with ROP, 68 achieved the treatment threshold, including 20 patients with ROP in zone 2 or zone 3 who underwent retinal laser photocoagulation and 15 with ROP in zone 1 or AP-ROP who were given anti-VEGF drug (Ranibizumab) via intraocular injections. Ranibizumab was injected into the vitreous with 0.25 mg per dose. In the laser photocoagulation treatment group, 10 patients exhibited recurrence of ROP. In the Ranibizumab treatment group, 1 patients had recurrence of ROP. All infants with ROP recurrence were retreated with laser photocoagulation. The conditions of all infants were controlled after retreatment until 54 weeks of PMA. No serious complications such as retinal detachment occurred in any patient in our study. The results of the analysis showed that both the number of gestational weeks and birth weight were significantly lower in the Ranibizumab treatment group than in the laser photocoagulation treatment group and the untreated ROP (+) group

IV. Discussion

In this study, all subjects were severely premature infants who underwent ROP screening in the NICU of Maharani laxmibai medical college,jhansi from september 2019 to february 2020. There was a high incidence rate of ROP in multiple births, low birth weight, low gestational age, congenital dysplasia, developmental immaturity, sepsis, mechanical ventilation, and severe infection. The overall incidence of ROP was 32.00% (80cases), and 40.00% (68 cases) of premature infants with ROP required treatment. We assumed that the differences in ROP incidence were primarily related to the following factors: (1) some pregnant women did not receive regular antenatal care, and they're maybe a significant error in the calculation of gestational age. (2) The survival rate of premature infants of very low birth weight and low gestational age was lower than that in developed countries.

ROP is a disease involving multiple factors, and its exact etiology is not known. According to many reports, gestational age and birth weight are currently recognized as the primary risk factors for ROP [31]. Our results indicate that infants with a low birth weight or small gestational age or who require extended oxygen inhalation treatment have an increased incidence of ROP. This result is consistent with many other reports [34,35,36].

We also analyzed the correlation between ROP and individual factors in this study; the results showed that the factors significantly associated with the incidence of ROP include IVH, invasive examinations, and positive blood culture. However, the mechanisms by which these factors cause ROP are not clear. We speculate that these factors may lead to vital signs instability, and long-term, high-flow oxygen absorption is usually given as a treatment method.

In a logistic regression analysis, gestational age, birth weight and unmonitored supplemental oxygen were indicated as the primary risk factors for ROP [26]. Our study identified these three risk factors too. We also found two other independent risk factors, including minimum oxygen saturation, and average daily weight gain. We suspect that low oxygen saturation will prolong the duration of oxygen inhalation treatment, thereby increasing the incidence of ROP. The average daily weight gain is affected by a variety of disease factors such as growth factor secretion, which is associated with an increased incidence of ROP [37,38].

Many studies have suggested that the up-regulated expression of VEGF plays an important role in the development of ROP [39], and anti-VEGF drugs can inhibit the over-expression of VEGF and thereby control intraocular angiogenesis and provide a good drug treatment for ROP [7,40,41,42]. In report of the developed countries, the ROP that need treatment includes zone 1, any stage with plus disease; zone 1, stage 3, with or without plus disease; and zone 2, stage 2 or 3, with plus disease. The ROP that need watch and wait includes zone 1, stage 1 or 2 without plus disease and zone 2, stage 3 without plus disease. The ROP review should be performed at the outpatient clinic until the 54 weeks endpoint of the corrected gestational age. However, sometimes the ROP outpatient review cannot be carried out in time, furthermore some infants would lost control once leave hospital. In order to prevent the rapid progress of ROP, we would like to do retinal photocoagulation for some infants with ROP of zone3, stage3, and > 1 quadrant range. So there are little bit different in our report about the standard of treatment on ROP. Retinal laser photocoagulation is a standard treatment for ROP. However, it can result in many problems, such as a wide range of retinal damage and the loss of vision in the photocoagulation area, and is not suitable for some patients, such as those with ROP in zone 1 or AP-ROP [44,45,46]. Anti-VEGF drugs may reduce complications when treating ROP. At the same time,

anti-VEGF drugs can maintain the balance of VEGF and promote the continued development of retinal blood vessels in children with ROP [7,40,41,42]. Many studies are currently ongoing to evaluate the use of anti-VEGF drugs in children with ROP [47,48]. Anti-VEGF drugs for ROP treatment include Bevacizumab and Ranibizumab. Bevacizumab is cheap and lasts long in ROP treatment, but it may have unknown systemic effects. Ranibizumab is a new anti-VEGF drug with a half-life of only 30 days and less systemic effects [51,52]. we used Ranibizumab to treat ROP in this study.

In our study, children with ROP in zone 2 or 3 were treated with traditional retinal laser photocoagulation, whereas children with ROP in zone 1 and posterior polar invasion ROP were given Ranibizumab via intraocular injections. The recurrence of ROP in the laser treatment and anti-VEGF treatment groups were 10 patient and 01, respectively. Because anti-VEGF drugs may induce systemic risks in premature infants, all infants who had ROP recurrence were retreated with laser photocoagulation. The conditions of all children were controlled after retreatment was given until 54 weeks of PMA. No serious complications such as retinal detachment occurred in any patients in our study. We speculate that may be related to the fact that children with a very low birth weight (<1000 g) and gestational age (<26 weeks) were not included in this study. An analysis of the two groups showed that the gestational age and birth weight were significantly lower in the anti-VEGF treatment group than that in the laser treatment group.

V. Conclusion

in this study, we systemically analyzed the incidence of and risk factors for ROP in severely premature infants treated in the NICU of maharani laxmibai medical college jhansi. The results of our study suggest that the incidence of ROP is 32.00% which will match those in middle-income countries, but higher than high-income countries. Anti-VEGF drugs could be preferred as a good treatment method for zone 1 ROP and aggressive posterior ROP.

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