Introduction

Retinopathy of prematurity (ROP) is the most important cause of visual impairment and blindness among children worldwide [1-4]. The incidence of retinopathy of prematurity-induced blindness in one country depends on economic development and the possibility of implementing screening and treatment. The comprehensive approach to the problem of premature retinopathy implies the continuous cooperation between ophthalmologists, neonatologists and other medical personnel in neonatal units. It includes general monitoring and regular ophthalmological screening to assess the development of the blood retinal network [5]. Advances in neonatology have enabled survival of a greater number of premature newborns with lower body weight at birth and of low gestational age. However, retinopathy of prematurity still persists in spite of the continuous improvement of conditions in intensive care units [6,7].

Retinopathy of prematurity is an eye disease which affects the blood vessels of the retina during its development, whose possible consequence may be disruption of growth and development of the retina, and disorders that result in blindness [8-10].

Pathophysiologically, the ROP develops in two phases. In the first phase, hyperoxia leads to obliteration of immature retinal blood vessels, compromising the retinal perfusion. In the second phase, hypoxia induced by obliteration is a ground for the development of pathological neovascularization [11], whose clinical manifestation is obliteration of the major blood vessels which stop to grow with the resulting ischemia of peripheral retina, which provokes the process of vaso-proliferation by ischemia-induced vascular endothelial growth factor (VEGF) and enables growth of new blood vessels, and this may lead to a disruption of retinal architecture with subsequent blindness when the vitreous body is affected [12].

The development of unique anatomical International Classification of Retinopathy of Prematurity (ICROP) has enabled the standardization of criteria and diagnostics of active forms of retinopathy, timely treatment, and monitoring of treatment results. The classification includes the following entities: the stage, zone and circumferential extent of the disease (compared to the clock hours). The stage is determined by the character of consequences of developmental arrest. The gradation of complexity, and thus the severity regarding the visual function, is given through five stages. The existence of the lower stages, 1, 2 and 3 with the obligation of their early detection and timely treatment enables the development of good visual function, while stages 4 and 5 are irreversible stages. The zones represent spreading of blood vessels development from optical disc outwards, and they are shown as three circles. Zone I includes the radial diameter of growth of blood vessels towards the periphery of barely more than pupil-macular distance. If the signs of interruption of de-
development occur in this zone, they point to a high risk of development of major destructions, i.e. they suggest that the interruption of the normal process of development of the retina started very early. Circumferential extent of the disease is described by the number of hours, and it represents an arc length of the pathological events between the vascularized and ischemic peripheral retina [13-15].

There are many factors that obstruct or render impossible the normal development of retinal vascularization in premature newborns, they combine with each other and they are complementary [16,17]. These factors are: parameters of immaturity which are given by birth - weight and gestational weeks, parameters of general health and many diseases such as distress syndrome, lung atelectasis, pneumonia, intracranial hemorrhage, sepsis, enterocolitis, anemia, transfusions and other disorders of general condition. The severity of general condition of premature infants is an indication for oxygen therapy. Low weight and low gestational age imply the structural and enzymatic immaturity, which represent the conditions of poor development of blood vessels of the retina [18].

Permanent identification and monitoring of risk factors are important for the prevention of ROP, and thus the protection of the conditions for good development of the retina, i.e. visual development.

The aim of this study was to investigate the significance of the factors given by birth and the use of oxygen in relation to the development of retinopathy of prematurity.

Material and Methods

The research was prospective and it was conducted during the two years (2007-2008). The study sample included 191 premature newborns hospitalized at the Institute for Child and Youth Health Care of Vojvodina. The patients were selected according to the protocol of the American Academy of Pediatricians as well as the directives of the National Group for the ROP of Serbia. The inclusion criteria were the body weight under 2000 gr and gestational age below 37 weeks. The parental written consent had to be obtained for the participation in the research. Oxygenotherapy with saturation of up to 92% was applied in all premature newborns. The first ophthalmological examination was done three weeks after the birth, whereby the fundus oculi was examined in mydriasis (cyclopentolate drops 0.5% and 2.5% phenylephrine), using indirect binocular ophthalmoscope and magnifying glass 20 D. At this stage the study sample was divided into two groups of patients:

– The control group included the patients with regularly and completely developed retinal blood vessels

Results

During the ROP screening, the entire study sample was divided into two groups according to the presence or absence of changes of premature retinopathy (Scheme 1):

Group 1, the control group, included 104 premature newborns with normal ophthalmological findings, i.e. without signs of ROP.
Group 2, the study group, included 87 premature newborns with some forms of ROP findings. Since ROP is a dynamic disease characterized by spreading of changes in space, time and content, group 2 was divided into two subgroups.

Subgroup 1 - spontaneous regression - included 58 premature infants with the lower stages of ROP (1 and 2), in whom the process regressed spontaneously and the blood vessel network continued to develop normally thus enabling the normal development of visual function.

Subgroup 2 - active ROP – included 29 premature newborns, who were treated with laser in order to stop the process and enable the normal development of visual function.

This study sample had no cases of serious progression towards stages 3 and 4 of ROP.

The parameters observed in this study are those recommended by the National Group for ROP, including the weight, gestational age and Apgar score as factors given by birth, and parameters of oxygen therapy - the number of days on oxygen therapy, days of mechanical ventilation. The fundus oculi was also examined.

Table 1 compares the results obtained for the control and study group by the parameters of body weight, gestational age, Apgar scores, number of days of oxygen therapy and days of mechanical ventilation, as calculated by T-test. T-test showed that there were differences in characteristics between the parameters of premature newborns with non-developed retinal blood vessels and premature infants having completely developed retinal blood vessels. In order to determine which of the studied factors contributed most to the differences between these two groups, the coefficient of discrimination was calculated for each measured parameter. Table 2 shows the values of coefficient of discrimination between the groups. The examined characteristics are given in horizontal rows, with the order of the size of the coefficient of discrimination, i.e. level of significance difference.

MANOVA multivariate statistical procedure was applied to obtain the characteristics which are given in Graph 1, where the ellipse fields represent categories of oxygen therapy duration and the contents of the ellipse fields represents the number of examined newborns, depending on the body weight and gestational age.

### Table 2. Coefficient of discrimination between the control and study group (quantitative)

<table>
<thead>
<tr>
<th>Control group</th>
<th>ROP</th>
<th>Coefficient of discrimination/k.disk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG</td>
<td>32.13; 33.18</td>
<td>29.90; 30.93</td>
</tr>
<tr>
<td>MV</td>
<td>1.94; 3.75</td>
<td>4.66; 10.29</td>
</tr>
<tr>
<td>AS 2</td>
<td>7.24; 7.91</td>
<td>6.85; 7.47</td>
</tr>
<tr>
<td>AS 1</td>
<td>5.65; 6.50</td>
<td>4.83; 5.69</td>
</tr>
<tr>
<td>BRDK</td>
<td>13.00; 18.13</td>
<td>18.46; 25.22</td>
</tr>
<tr>
<td>TM</td>
<td>1691.81; 1886.94</td>
<td>1289.77; 1461.95</td>
</tr>
</tbody>
</table>

**Legend:**
- NG – week of gestation/nelđa gestacije; AS 1 – Apgar skor u prvom minutu; AS 2 – Apgar skor u petom minutu; BRDK – broj dana na kiseoniku; MV – broj dana na mehaničkoj ventilaciji; Kont. gr – kontrolna grupa/kontrolna grupa ispitanika; ROP – grupa/ispitivana grupa prematurusa; k.disk. – koeficijent diskriminacije

Graph 1. Number of days oxygenotherapy according to birth weight and weeks of gestation

Grafikon 1. Broj dana na oksigenoterapiji u odnosu na telesnu masu i nedelju gestacije

**Legend:**
- 1,2,3,4 – number of days oxygenotherapy/ grupe broja dana na kiseonik; 1 – 0-7 days/danas; 2 – 8-15 days/danas; 3 – 16-30 days/danas; 4 – više od 30 dana/days; Telm 1- birth weight less than 1250 grams/telesna masa manji od 1250 grama; Telm 2 – birth weight between 1251-1750 grams/telesna masa od 1251 do 1750 grama; Telm 3 – birth weight more than 1751 grams/telesna masa viša od 1751 grama; nege-1 - gestation weeks less than 28 de te među od 29 nedelje gestacije; nege-2 - gestation weeks between 29-32/de te starosti od 29 do 32. nedelje gestacije; nege-3 - gestation weeks more than 33/de te starosti više od 33. nedelje gestacije

**Table 1. The importance of differences between control and examined group**

<table>
<thead>
<tr>
<th>Study sample Uzorak</th>
<th>Mean value for control group/Srednja vrednost kontrolne grupe</th>
<th>Mean value for study group/Srednja vrednost isp. grupe T-test</th>
<th>p value</th>
<th>T - test value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TM</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>1789.375</td>
<td>1375.862</td>
</tr>
<tr>
<td>NG</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>32.654</td>
<td>30.414</td>
</tr>
<tr>
<td>BRDK</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>15.567</td>
<td>21.839</td>
</tr>
<tr>
<td>MV</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>2.846</td>
<td>7.471</td>
</tr>
<tr>
<td>AS 1</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>6.077</td>
<td>5.264</td>
</tr>
<tr>
<td>AS 2</td>
<td>Controls group/Kontrolna grupa</td>
<td>ROP</td>
<td>7.577</td>
<td>7.161</td>
</tr>
</tbody>
</table>

**Legend:**
- TM – birth weight/telesna masa; NG – week of gestation/nelđa gestacije; AS 1 – Apgar skor u prvom minutu; AS 2 – Apgar skor u petom minutu; BRDK – broj dana na kiseonik; MV – broj dana na mehaničkoj ventilaciji; kont. gr – kontrolna grupa/kontrolna grupa ispitanika; ROP – grupa/ispitivana grupa prematurusa; k.disk. – koeficijent diskriminacije

**Graph 1.**

**Table 2.** Coefficient of discrimination between the control and study group (quantitative)

**Legend:**
- NG – week of gestation/nelđa gestacije; AS 1 – Apgar skor u prvom minutu; AS 2 – Apgar skor u petom minutu; BRDK – broj dana na kiseonik; MV – broj dana na mehaničkoj ventilaciji; Kont. gr – kontrolna grupa/kontrolna grupa ispitanika; ROP – grupa/ispitivana grupa prematurusa; k.disk. – koeficijent diskriminacije
Discussion

The study was aimed at assessing the interdependence of the factors given by birth and oxygenotherapy affecting the development of ROP in premature newborns hospitalized at the Institute for Child and Youth Health Care of Vojvodina.

The mean weight of newborns in the control and study group was 1789 gr and 1376 gr, respectively. The mean gestational age in the premature newborns with normally developed blood vessel network of the retina and in those with some forms of ROP was 32.13-33.18 weeks and 29.9-30.93 weeks, respectively.

The mean values of body weight and weeks of gestation obtained in this study are in accordance with the criteria for ROP screening in under-developed countries. In developed countries, these values are within the range of 737-763 gr and 25 weeks of gestation. Thus, the criteria for ROP in low and high income countries vary considerably and are determined by complex and multifactorial influences such as the development of neonatal care, the rate of surviving of premature infants, as well as adequate and timely implementation of screening [19], and they determine the body weight and week of gestation, i.e. the inclusion criteria for ROP screening in accordance with ICROP criteria [20].

According to the National group for ROP of Serbia, the screening criteria are 2000gr and 37 weeks of gestation, and since the screening is to be adapted to each region, the region of Vojvodina, i.e. the study sample, requires the screening criteria to be lowered to 1750gr and 33 gestational weeks, as demonstrated by the tests performed at the same institution in the period from 1995 to 2001 [21].

In Denmark, which is a developed country with adequate infrastructure, the overall criteria for screening used to be less than 32 weeks of gestational age and birth weight 1750gr; however, they have been reduced to less than 30 gestational weeks and body weight below 1500gr [22-24].

In order to determine which of the factors given by birth is the most prominent in the differences between premature infants with properly developed retinal blood vessels and premature infants with ROP, the coefficient of discrimination has been determined. As shown in Table 2, the highest value of the coefficient of discrimination is for gestational age, which means that the largest contribution to the difference between the groups is given by this parameter, its contribution to the difference being three times higher regarding mechanical ventilation and Apgar score values in the first and fifth minute. Therefore, the gestational age is the most significant risk factor for development of ROP and emphasizes the importance of ROP prevention [25,26].

It is known that the embryological development takes place by weeks of gestation. Each week of gestation involves a certain level of development of individual organs and organ systems. The lower number of gestational weeks at birth means the greater immaturity of organs and organ systems, and thus the greater vulnerability during further development [27].

Multivariate analysis of variance (MANOVA) has resulted in ellipses whose fields describe the number of days of oxygenotherapy administration, and the contents of these fields represent the number of subjects by their body weight and week of gestation. Spatial presentation of these relationships shows that the ellipses 1 and 2 are close, whereas the ellipses 3 and 4 are far away from each other. The ellipse 1 field represents the use of oxygen therapy up to 7 days, including a part where the sample is dominated by body weight over 1750gr and more than 33 weeks of gestation. Ellipse 2 shows oxygen therapy from 8 to 15 days, including a part where the sample is dominated by body weight over 1750gr and more than 29 weeks of gestation. Ellipse 3 represents oxygen therapy from 16 to 30 days, there is neither clearly distinguished body mass nor gestational age, although they incline towards lower values. The longest use of oxygen therapy includes the part of the sample which is dominated by body weight below 1250 gr and less than 29 weeks of gestation, as shown by the ellipse 4.

The longer use of oxygen therapy may point to a severe health condition of premature infants, having a great number of accompanying diseases. Oxygen therapy may have an impact on the development of prematurity retinopathy if it is given in the first four weeks of life. However, if it is properly implemented, oxygen therapy is an independent factor. Higher body weight and higher gestational age are predictors for better development of organs and organ systems [28].

Conclusion

By analyzing the factors given by birth and the duration of oxygenotherapy in relation to the development of retinopathy of prematurity, it can be concluded that there are differences between premature infants with developed retinopathy of prematurity and those with normally developed blood vessel network of the retina. The most important factor given by birth which causes the development of retinopathy of prematurity is gestational age. In other words, the most important risk factor for the development of retinopathy of prematurity is prematurity birth.
Olujić M, et al. Retinopathy of Prematurity

Sažetak

Prematurena retinopatija je oboljenje oka koje zahvata krvne sudove retine i predstavlja najvažniji uzrok slepila i slabovidosti u dečijem uzrastu širom sveta. Mnogi su faktori rizika zadati rođenjem i parametri opšteg zdravstvenog stanja koji mogu da utiču na ovo oboljenje. Cilj ove studije je bio da se ispita značajnost faktora zadatih rođenjem i primene kiseonika u odnosu na pojavu prematurene retinopatije.

Materijal i metode

Urađena je prospektivna studija u trajanju od dve godine u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine. Ispitani su parametri koje je Nacionalna grupa za premature retinopatiju iznela u svojim preporukama. To su telesna masa i gestacionalna starost, te broj dana na oksigenoj terapiji i broj dana mehaničke ventilacije.

Rezultati

Rezultat ispitivanja je da je najvažniji faktor rizika za pojavu prematurene retinopatije gestaciona starost.

Zaključak

Najvažniji faktor rizika je gestaciona starost.

Uvod

Prematurena retinopatija je oboljenje oka koje zahvata krvne sudove retine i predstavlja najvažniji uzrok slepila i slabovidosti u dečijem uzrastu širom sveta. Mnogi su faktori rizika zadati rođenjem i parametri opšteg zdravstvenog stanja koji mogu da utiču na ovo oboljenje. Cilj ove studije je bio da se ispita značajnost faktora zadatih rođenjem i primene kiseonika u odnosu na pojavu prematurene retinopatije.

Materijal i metode

Urađena je prospektivna studija u trajanju od dve godine u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine. Ispitani su parametri koje je Nacionalna grupa za premature retinopatiju iznela u svojim preporukama. To su telesna masa i gestacionalna starost, te broj dana na oksigenoj terapiji i broj dana mehaničke ventilacije.

Rezultati

Rezultat ispitivanja je da je najvažniji faktor rizika za pojavu prematurene retinopatije gestaciona starost.

Zaključak

Najvažniji faktor rizika je gestaciona starost.

References


Ključne reči: Prematurena retinopatija; Faktori rizika; Kiseonik + terapijska primena; Gestaciona starost; Prevremeno rođeno dete

Rad je primljen 23. XII 2011.

Prihvaćen za stampanje 30. XII 2011.

Sažetak

Prematurena retinopatija je oboljenje oka koje zahvata krvne sudove retine i predstavlja najvažniji uzrok slepila i slabovidosti u dečijem uzrastu širom sveta. Mnogi su faktori rizika zadati rođenjem i parametri opšteg zdravstvenog stanja koji mogu da utiču na ovo oboljenje. Cilj ove studije je bio da se ispita značajnost faktora zadatih rođenjem i primene kiseonika u odnosu na pojavu prematurene retinopatije.

Materijal i metode

Urađena je prospektivna studija u trajanju od dve godine u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine. Ispitani su parametri koje je Nacionalna grupa za premature retinopatiju iznela u svojim preporukama. To su telesna masa i gestacionalna starost, te broj dana na oksigenoj terapiji i broj dana mehaničke ventilacije. Ispitani su parametri koje je Nacionalna grupa za premature retinopatiju iznela u svojim preporukama. To su telesna masa i gestacionalna starost, te broj dana na oksigenoj terapiji i broj dana mehaničke ventilacije, te je ispitivan na lavaz na očnom dnu.

Rezultati

Rezultati ispitivanja je da je najvažniji faktor rizika za pojavu prematurene retinopatije gestacionalna starost.

Zaključak

Najvažniji faktor rizika je gestacionalna starost.