ORIGINAL ARTICLE, MEDICINE

The 5-minute Apgar Score as a Prognostic Factor for Development and Progression of Retinopathy of Prematurity

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Received: 08 Jun 2016

Accepted: 22 Sep 2016

Published Online: 09 Jan 2017

Published: 27 March 2017

Key words: retinopathy of prematurity, risk factors, Apgar score at 5 minutes

Citation: Marinov VG, Koleva-Georgieva DN, Sivkova NP, Krasteva MB. The 5-minute Apgar score as a prognostic factor for development and progression of retinopathy of prematurity.

Folia Medica 2017;59(1):78-83.
doi: 10.1515/folmed-2017-0011

Background: A low Apgar score at 5 minutes has been shown to be a risk factor for development of retinopathy of prematurity (ROP).

Aim: To examine the prognostic value of Apgar score at 5 minutes for development and progression of ROP.

Materials and methods: The study included 132 preterm infants who were screened from 4th week of life onward. Of these, 118 newborns were given Apgar score at 5 minutes. The prognostic significance of this index was studied as an absolute value and as a value ≤ 6 . The patients were divided into two groups: group I had no evidence of ROP ($n=82$) and group II had some signs of ROP ($n=36$). Group II was further divided into group IIA – spontaneously regressed cases ($n=22$), and group IIB with cases which progressed to treatment stages ($n=14$). We investigated 15 maternal and 20 newborn presumable risk factors for development and progression of ROP. Mann-Whitney U test, χ^2 or Fisher's exact test were used in the statistical analysis. Logistic regression was performed to find significant and independent risk factors for manifestation and progression of ROP.

Results: A low 5-minute Apgar score and an Apgar score of 6 or less at 5 minutes were not statistically significant risk factors of ROP ($p=0.191$, $p=0.191$, respectively), but were significant risk factors for the manifested ROP to progress to stages requiring treatment ($p=0.046$, $p=0.036$, respectively).

Conclusion: An Apgar score at 5 minutes of 6 or less was a significant and independent risk factor for progression of ROP to stages requiring treatment.

BACKGROUND

Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative disorder affecting prematurely born, immature infants, and infants with low (LBW) and very low birth weight (VLBW). It is among the leading causes of preventable irreversible blindness in children worldwide.¹⁻³ The disease is practically unknown in low income countries because of undeveloped neonatology. In high income countries in Western Europe, North America and Japan with highly developed neonatology care, very low birth-weight (VLBW) and extremely low birth weight (ELBW) infants survive. These countries have well functioning screening and treatment programs and the disease is under control. In middle income countries, to which Bulgaria belongs, obstetrics and gynecology, and neonatology show an undoubted progress. This makes ROP a significant problem.

Timely, continuous screening of patients at risk is the only way to preserve the vision in these babies. Finding significant and independent risk factors for the development and progression of ROP to treatment-requiring stages is extremely important for ophthalmologists and neonatologists that work with the little patients. The research on the various risk factors is extensive in literature.⁴⁻¹⁹ Finding an easily applicable and noninvasive prognostic model for the expected course of ROP is a keystone in controlling this socially significant disease. This will allow us to focus the limited human and financial resource in Bulgaria on patients at risk.

In Bulgaria, there is a national strategy for screening and treatment of ROP which was developed in 2009.²⁰

The Apgar score at 5 minutes (Apgar 5) is an indicator routinely used by Bulgarian neonatologists

to get information about how well the newborn is adapting to the environment. A low Apgar 5 has been demonstrated to be a risk factor for the development and progression of ROP either alone^{8,10,12}, or in combination with other perinatal indexes^{13,14}.

AIM

The aim of the current study was to examine the prognostic value of Apgar 5 for the development of any signs of ROP and for progression of a manifested disease to stages requiring treatment.

MATERIALS AND METHODS

Over 3 years, 132 prematurely born infants were screened in accordance with the adopted national strategy in Bulgaria for screening and treatment of ROP.²⁰

Examinations were performed by binocular indirect ophthalmoscopy (**Fig. 1**) after mydriasis and topical anesthesia. Eyelid retractors and scleral depressors were used to reach the far retinal periphery (**Fig. 2**). The screening started 4 weeks after birth and was performed every 1 or 2 weeks according to the ocular findings until complete vascularization of the retina. Treatment was administered in all cases with type 1 ROP.^{20,21}

In a specially designed questionnaire for each baby we gathered information about 15 presumable maternal risk factors (number of pregnancy, desired/undesired pregnancy, previous abortions, previous preterm births, type of conception, infections during pregnancy, bleeding during pregnancy, cervical manipulations, drug intake during pregnancy, preeclampsia/eclampsia, status of placenta, umbilical cord, amniotic sac, amniotic fluid, type of

Figure 1. Screening a premature baby.

Figure 2. Eyelid retractors and scleral depressor, used during the screening.

birth) and 20 presumable infant risk factors (birth weight, gestational age, gender, degree of prematurity, singletons/multiplets, Apgar score at 1 and 5 minutes; weight gain at 6 weeks (absolute and relative), days of intapulmonary ventilation, days of following oxygen therapy, total days of oxygen supplementation, surfactant application, respiratory distress syndrome, neonatal sepsis, number of blood and plasma transfusions, intraventricular hemorrhage, posthemorrhagic hydrocephaly, periventricular leukomalacia, clinically significant hyperbilirubinemia) for development and progression of ROP.

All 132 screened patients were divided into:

Group I – infants with no signs of ROP – 92

Group II – infants with some signs of ROP – 40

Group II was subdivided into:

Group IIA – spontaneously regressed infants - 24

Group IIB – infants progressing to stages requiring treatment – 16

Apgar 5 was calculated by a neonatologist on the basis of the indexes given in **Table 1**.

Apgar 5 score ≤ 3 indicated severe postnatal depression, Apgar 5 score between 4 and 6 showed moderate postnatal depression, and Apgar 5 score between 7 and 10 was considered optimal.

Statistical analysis was performed using MS Excel and R-statistics (www.r-project.org). Mann-Whitney U test, χ^2 or Fisher's exact test were used for comparison between groups. A p value less than 0.05 was considered statistically significant. Logistic regression was performed for finding independent

significant risk factors for either development, or progression of ROP to stages requiring treatment.

RESULTS

We had Apgar 5 score for 118 out of 132 screened premature babies. Two of them were born at home, and 12 were on intrapulmonary ventilation because of very low Apgar score at 1 minute (**Fig. 3**).

Statistical analysis showed no significant dif-

postnatal depression). In group IIA (spontaneously regressed) we had no child with Apgar 5 score ≤ 3 (severe postnatal depression).

We therefore combined the prematurely born infants with severe depression (Apgar 5 score ≤ 3) and those with moderate depression (Apgar 5 score between 4 and 6) in a common group with Apgar 5 score ≤ 6 and compared them with the infants with optimal Apgar 5 score (≤ 7). (**Fig. 4**).

Table 1. Indexes for Apgar score calculation

Index/Points	0	1	2
Color of the skin	Generalized cyanosis	Acrocyanosis	Pink
Breathing	Absent	Uneven	Normal
Heart rate	No heart beating	<100/min	>100/min
Muscular tone	Decreased	Partial flexion	Active movements
Reaction in aspiration	No reaction	Inert	Crying

ference between infants with no signs of ROP and those with some signs of ROP (group I vs group II) (Fisher's exact test, $p=0.191$). However, there was statistically significant difference between spontaneously regressed infants and those progressed to stages requiring treatment (group IIA vs group IIB) (Fisher's exact test, $p=0.046$).

Despite the borderline yet significant difference between spontaneously regressed and treated children, almost half of the treated preterm babies (group IIB) had Apgar 5 score ≤ 6 (moderate or severe

Statistical analysis again showed no statistical difference between infants with no signs of ROP and those with some signs of ROP (group I vs group II) (Fisher's exact test, $p=0.191$), but the significant difference between the spontaneously regressed and the treated infants slightly increased (group IIA vs group IIB) (Fisher's exact test, $p=0.036$).

As shown by the logistic regression analysis, Apgar 5 ≤ 6 turned out to be not only a significant risk factor, but also an independent risk factor for progression of ROP to stages requiring treatment (OR 0.174; 95% CI 0.040-0.759).

Figure 3. Distribution of screened infants by Apgar 5 score. Group I – infants with no signs of ROP; Group II – infants with some signs of ROP; Group IIA – spontaneously regressed children; Group IIB – treated children.

Figure 4. Distribution of screened children by Apgar 5 score. Group I – infants with no signs of ROP; Group II – infants with some signs of ROP; Group IIA – spontaneously regressed children; Group IIB – treated children.

DISCUSSION

Birth weight and gestational age are currently considered the most important risk factors for development of ROP; they determine the screening criteria all over the world.^{2-5,11,20} Survival of more immature and prematurely born children leads to increasing number of patients who need regular ophthalmological screening. Early determination of high risk patients that develop ROP requiring treatment will result in having an adequate therapeutic approach to them. Thus unnecessary examinations of low risk patients can be avoided. The Apgar score in 5 minutes was examined in this study as it is routinely used in Bulgarian neonatology units, it is noninvasive and easily applicable.

In a study of 957 patients, Ke et al.⁸ also found the low Apgar score at 5 minutes to be a significant risk factor for the development and progression of ROP to stages requiring treatment. The subsequent logistic regression though did not find it to be an independent factor.

Fortes Filho et al.¹³ showed that SNAPPE – II score was a significant risk factor for development of any signs of ROP, as well as for severe ROP in 304 prematurely born children. One of the parameters of this score was Apgar 5 score ≤ 7 (i.e. any or no depression 5 minutes after birth, nevertheless severe (Apgar 5 ≤ 3), or moderate (Apgar 5 between 4 and 6)). Authors compared infants with no signs of ROP with children with any stage ROP, and babies with no signs of ROP with babies with severe ROP (requiring treatment). No comparison between spontaneously regressed and progressed to treatment patients was performed.

Garcia-Serrano et al.¹² examined different risk factors for development of “plus” disease among prematurely born multiplets and found low Apgar 5 score to be a significant and independent risk factor after logistic regression. They did not examine prematurely born singletons. There have been speculations in literature about different reasons leading to premature birth in singletons and multiplets, suggesting preterm born multiplets being generally healthier than preterm born singletons.²² Again authors compared children with no signs of ROP with treated children (“plus” disease is an indication for treatment worldwide).

In retrospective analysis of 252 very low birth weight (VLBW) children (birth weight < 1500 g), Yang et al.¹⁰ also found low Apgar 5 score to be a significant factor for development of ROP requiring

treatment. Again comparison between children with no signs of ROP and treated children was performed.

Despite the presence of international classification of ROP^{21,23}, we found considerable terminological diversity in current literature. This made it difficult for us to interpret and compare the results of other researchers. Some used terms such as mild and severe ROP, others – treatment requiring ROP and ROP requiring no treatment, or threshold ROP. There were different criteria among the compared groups as well. Infants with no signs of ROP were compared with treated infants (equal to comparison between our group I with group IIB).^{5,10,12,13,15} Patients with no signs of ROP were compared with patients with any signs of ROP (equal to comparison between our group I with group II).^{5,13,15} Relatively small number of authors compared spontaneously regressed babies with patients progressed to stages requiring treatment (as we did in the current study).^{8,11,15} Possible explanation of that fact could be the natural course of the disease. Not every prematurely born child will show any signs of ROP. Most of the children with manifested disease show spontaneous regression. This leads to difficulties in gathering sufficiently large groups of patients and makes us recommend careful interpretation of the results.

CONCLUSION

The undoubted advances in neonatology lead to survival of more and more immature and prematurely born children. Finding significant and independent noninvasive prognostic factors to timely discriminate patients who will progress to stages requiring treatment from spontaneously regressing patients is pivotal in controlling ROP. This will reduce the unnecessary ophthalmological examinations without missing patients at risk. The Apgar score at 5 minutes of 6 or less is noninvasive, routinely used index in neonatology, and in the current study proved to be significant and independent risk factor for progression of manifested ROP to stages requiring treatment.

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Оценка по шкале Апгар на 5-ой минуте в качестве прогностического фактора развития и прогрессирования ретинопатии недоношенных

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Дата получения: 08 июня 2016

Дата приемки: 22 сентября 2016

Дата онлайн публикации: 09 января 2017

Дата публикации: 27 марта 2017

Ключевые слова: ретинопатия недоношенных, факторы риска, оценка по шкале Апгар на 5-ой минуте

Образец цитирования:

Marinov VG, Koleva-Georgieva DN, Sivkova NP, Krasteva MB. The 5-minutes Apgar score as a prognostic factor for development and progression of retinopathy of prematurity. Folia Medica 2017;59(1):78-83. doi: 10.1515/foimed-2017-0011

Введение: Доказано, что низкая оценка по шкале Апгар на 5-ой минуте является фактором риска развития ретинопатии недоношенных (РН).

Цель: Исследовать прогностическое значение оценки по шкале Апгар на 5-ой минуте в отношении развития и прогрессирования РН.

Материалы и методы: Исследование охватило группу из 132 недоношенных детей, наблюдение над которыми началось с 4-ой недели со дня рождения. 118 новорожденным из этой группы была проведена оценка по шкале Апгар на пятой минуте. Прогностическое значение данного индикатора было исследовано в качестве абсолютной величины и в качестве величины ≤ 6 . Пациенты были разделены на две группы: группа 1 без наличия данных о РН ($n=82$), а группа 2 с наличием отдельных признаков РН ($n=36$). Группа 2 была дополнительно разделена на 2А – случаи спонтанного регрессирования ($n=22$), а группа 2Б – случаи, прогрессирующие до этапа лечения ($n=14$). Нами было исследовано 15 предполагаемых факторов риска для матери и 20 для новорожденного в отношении развития и прогрессирования РН. Для проведения статистического анализа были выбраны U-тест Манна-Уитни, χ^2 или тест Фишера. Был проведен регрессионный анализ на предмет обнаружения значимых и независимых факторов риска проявления и прогрессирования РН.

Результаты: Низкая оценка по шкале Апгар на пятой минуте или оценка по шкале Апгар в 6 баллов или ниже на пятой минуте не являются статистически значимыми факторами риска для развития РН ($p=0.191$, $p=0.191$, соответственно), но являются значительными факторами риска, чтобы проявленная РН прогрессировала до стадии, требующей лечение (соответственно $p=0.046$, $p=0.036$).

Заключение: Оценка по шкале Апгар на пятой минуте в 6 баллов или ниже является значимым и независимым фактором риска прогрессирования РН до стадии, требующей лечения.