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Evaluation of the Oral Propranolol Effect on Retinopathy of Prematurity: Randomized Clinical Trial

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ABSTRACT

Background: Despite rapid advances in neonatal care in both industrialized and developing countries, retinopathy of prematurity (ROP) still remains the main reason of infants' blindness and visual impairment. There is some evidence that Beta-adrenergic system may be involved in infants' ROP. Considering that few studies have been done on effects of oral propranolol on prevention retinopathy pre maturity in premature infants, we designed this clinical trial to investigate the effects of oral propranolol on infants.

Methods: This study is a clinical trial in which 27 premature infants with gestational age greater than 27 weeks and afflicted with retinopathy pre maturity grade 1 and 2 hospitalized at Shahid Sadoughi hospital of Yazd city.They were randomized to receive 0.5 mg/kg/12hours oral propranolol or control. Premature infants were controlled and hospitalized at NICU and their BP, heart rate and Hyperemesis gravidarum (H.G) were monitored.

Results: Twenty-four newborns were included, 12 in the control group and 12 in the propranolol group and 3 of infants were excluded from the study (2 of propranolol group and 1 of control group) 81.34 percent of treatment group were recovered and healed compared to 66.7 percent of control group which not significantly difference.

Conclusion: Some studies about Beta Blockers' recessive effect on ROP have been done which in most recovery was the result but some serious side effects were also reported. In this study there was no positive effect on recovery of ROP but the percent of recovery was slightly higher in propranolol group compared to control group. Fortunately there were no reports of side effects this time due to usage of lower dose propranolol. Recent studies state that propranolol cannot be used as a good alternative to other treatments but it can prevent the disease from getting worse. We can also reduce its side effects by changing the dosage.

Introduction

Despite rapid advances in infant care, in both industrialized and developing countries, ROP remains the main cause of blindness and vision impairment in infants.[1] The incidence of the disease is associated with birth weight and gestational age (GA), and, it is more prevalent in premature and very low weight newborns.[2] The risk factors associated with ROP are not fully understood, but prematurity and ROP at birth represent major factors. Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and need for transfusion are considered as relevant factors. Generally, GA, lower birth weight and sick newborns are associated with a higher risk for ROP.[3]

The pathogenesis of ROP seems to include two distinct phases, where the second phase characterized by hypoxia, which induces vascular endothelial growth factor (VEGF) and neovascularization.[4] Understanding the ROP pathophysiology has increased the use of selective therapies that target the pathway for angiogenesis. There is evidence that the beta-adrenergic system may be involved in neonatal ROP. For example, polymorphisms of the β-adrenergic (B-AR) receptor in many black infants may be responsive to their lower ROP progression compared to non-black infant**.** In addition, blocking the B-AR with propranolol (the non-selective blocker of B1-AR and B2-AR)[5] suggests the recession of infantile hemangioma,[1] the most common neonatal tumor that is often associated with ROP,[3] suggesting that B-AR blockers maybe as effective at ROP. The evidence is confirmed by experimental findings from animal studies with oxygen-induced retinopathy[6] that show increased retinal norepinephrine and B-ARs that regulate the production of VEGF and retinal neovascularization in response to hypoxia. According to these studies and the significant reduction in neovascularization with topical propranolol,[7-10] therapeutic use of B-AR blockers was proposed to counter retinal neovascularization in ROP.

Based on these observations and considering that so far, only a few studies have been conducted on the effect of oral propranolol on preventing the development of retinopathy of prematurity in preterm infants, which have not achieved a definite result regarding its efficacy and dosage, this clinical trial was designed to evaluate the effect of oral propranolol administration on premature infants and ROP.

Materials and Methods

When ethics approval was gained from the Ethics Committee of Shahid Sadoughi University of Medical Sciences and we gain IRCT code (IRCT20100520003982N1) and informed consent was obtained from the parents of infants prior to the trial. This double-blind clinical trial was conducted on premature infants with GA more than 28 weeks and birth weight of less than 1500 g, with retinopathy of prematurity stage I and II admitted to NICU at Shahid Sadoughi Hospital in Yazd, Iran. Regarding to exclusion criteria, Infants with GA less than 26 weeks, IVH grade II and III, neonates with congenital anomalies, kinds of heart diseases except PDA, congenital infections (TORCH) and acute sepsis were excluded from the study. Thirty neonates were included in each group. However, due to the short term of the study, and considering that the first ROP examination is conducted at day 28th of birth, when some neonates with ROP are discharged from NICU, to monitor the complications of the treatment, they needed to be hospitalized for at least one week and complete cardiovascular monitoring. However, their family did not allow re-admitting their infants for the study. In order to match the case and control group, the study was conducted only on infants who had a long length of stay (at least 35 days) at the hospital. Twenty-eight days after birth, all preterm infants with birth weight of less than 1500 g were examined by the retinal fellowship using indirect

ophthalmoscopy (with KEELER ophthalmoscope SL4, made in the UK), and the retinopathy stage was determined. Infants with retinopathy stage I and II were divided into A and B groups according to the randomized table. Randomization of infants was conducted by a statistic consultant by using a random number table.

They were randomly assigned in the case or control group. For the case group, medication therapy began in the first two days with a dose of 0.25 mg/kg/dose and then 0.5 mg/kg/dose oral propranolol (pranol 10 from OLIDARU) every 12 hours, and continued until the patient required laser therapy or intraocular injection, or, slowly or completely recovered without invasive treatment whereas The control group received no medications. Prior to starting the treatment for the case group, full heart diagnostic examination was conducted by a pediatric subspecialist to ensure that they can take propranolol safely. Following the initiation of prophylaxis treatment with propranolol, neonates underwent complete cardiovascular monitoring and BP control at NICU for at least one week (using Datascope Pasport 2 monitors, made in the United States) and hypoglycemia monitoring to stop medication in case of complications (apnea, bradycardia, hypertension, or hypoglycemia). It should be noted that due to the low birth weight of these infants, hospitalization for one week was part of the routine process of treatment for them, and some of them required more than one week to reach the desired weight for discharge. Therefore, one week monitoring imposed no additional costs on newborns in the case group. After a week, in the case of discharging newborns from NICU, they were treated as an outpatient and parents were instructed on the warning signs to refer to the Emergency Department of Shahid Sadoughi Hospital if any problem occurred; an NICU bed was booked for emergency cases, and a direct contact number was provided for parents to contact residents or physicians in case of having any questions. Other supportive and therapeutic interventions were similar in both groups and were based on the protocols of the ward. In addition, no costs were imposed to the parents for medications used in the study, and medications were provided by an assistant. The retinopathy process in neonates in both groups was monitored weekly to the end of the recovery from ROP by a retinal fellowship using indirect ophthalmoscopy, which is part of the NICU routine program, and it is conducted every 1-2 weeks in all premature infants to ensure the complete recovery of ROP. If necessary, a therapeutic intervention including laser or injection was performed in both control and case groups. To ensure blindness of the study, the retinal fellowships who examined the infants and determined the patient's recovery, as well as the statistic counselor who performed the data analysis, did not know which neonates were in the case or control group.

For all infants, all data related to independent variables including gestational age, birth weight, initial weight in the study (using the ZYKLUS med scale, made in Germany), gender, type of delivery, APGAR score at birth and at 5 minutes after birth, length of oxygen intake and how to receive oxygen, number of surfactants dosage, frequency of transfusion, previous sepsis, PDA, apnea before treatment, NEC, pneumothorax, retinopathy grade, and data related to dependent variables including Apnea, bradycardia, hypertension, retinopathy stage after starting treatment, laser therapy or injection, weight at discharge, length of stay, and complications and mortality were entered into the pre-designed questionnaire and recorded.

Statistical Analysis: Data were analyzed using SPSS software and Chi-square, T-test, Mann-Whitney and the Wilcoxon signed-rank test, where $P > 0.05$ was considered significant.

Results

Twenty seven babies participated in this study. They were divided into two groups. The experimental group received propranolol

0.25 mg/kg/dose for the first two days and then 0.5mg/kg/dose every 12 hours. The control group received no medication. The average drug intake period was 3 months. 2 babies of the experimental group (one in the third day of treatment due to BS = 35 but without any sign, resulted from daily BS monitoring, and the other one because of not continuing the treatment after discharge) and a baby of the control group (because of referring bias due to not referring to the center for the follow ups after discharge) were excluded from the study (Table 1).

There was not a significant difference between Stage ROP frequency distribution in the two control and experimental groups (P = 0.089). There was no significant difference between the average number of days for receiving free oxygen, C-PAP, and ventilator in the two control and experimental groups. Moreover, there was not a significant difference between the average weight at the beginning of the study in the two control and experimental groups (P = 0.758). Besides, there was no significant difference between gestational age in the two control and experimental groups (P = 0.446). There was a significant difference between the average drug intake period in the experimental group on the response to treatment and not responding to the treatment (P = 0.050). There was no significant difference between ROP frequency distribution in the two control and experimental groups (P = 0.640). However, the two patients in the experimental group who needed treatment were treated by laser. The 4 patients in the control group who needed treatment were all injected intravitreally (Table 1).

Discussion

This clinical trial study was related to the effect of Propranolol drug in the patients with ROP. The hypothesis was that Propranolol, as a beta blocker, can stop the increase of VEGF rate in the lesion site and decrease neovascularization in the site. The study showed that the improvement of ROP disease in the treatment receiving (experimental) group was 81.3% compared to 66.7% in the control group. According to collected data, more improvement through taking Propranolol can prevent from treating the patients by laser and bevacizumab and this can decrease the side effects of the two treatment methods that are aggressive, as well.

Table 1. Comparing of Variables between control and case groups

Variables	Cases (n = 12)	Controls (n = 12)	P-value
Pregnancy age (weeks)	29.9 ± 3.1	29.1 ± 1.3	0.45
Birth Weight (gram)	11117.5 ± 227	1220.8 ± 234	0.28
Weight (gram)	1365.8 ± 318	1402.9 ± 261	0.75
Weight after study (gram)	1416 ± 464	1558.7 ± 254	0.36
First Apgar	6.33 ± 2.4	5.58 ± 2.1	0.49
5^{th} Apgar	8.5 ± 2.5	7.8 ± 2.1	0.43
Admission duration (days)	49.6 ± 12.6	50.5 ± 22.8	0.90
Need of Resuscitation	4(33.3)	6(50)	0.68
Corton use for mother	10(83.3)	11(91.7)	1.00
Surfactants	10(83.3)	9(75)	1.00
Transfusion	6(50)	4(33.3)	0.68
Length of oxygen intake days	9.3 ± 18.08	18.66 ± 15.1	0.93
Intake C PAP (days)	8.4 ± 10.7	7.1 ± 8.00	0.43
Ventilator usage (days)	7.4 ± 6.2	5.7 ± 4.5	0.67
Previous sepsis	6(50)	2(16.7)	0.19
Apnea before treatment	2(16.7)	2(16.7)	1.00
PDA	3(25)	0(0.00)	0.09
StageI ROP	6(50)	10(83.3)	0.08
StageII ROP	6(50)	2(16.7)	0.08

Mean ± SD

The major part of the previous studies has been related to using beta blocker for improvement of the new vascularization in the animal samples. Six studies have recently been done in the field of using Propranolol in the experimental and the control groups. In Ozturk MA and the colleague's study, which was related to the efficiency of the oral Propranolol in the infants, it was shown that taking Propranolol in 0-1 steps cannot improve the disease and change the treatment procedure; however, it can be useful in step 2 for treatment of the patients. In Filipp and the colleagues' study in the field of safety of the use and effect of the drug, it was shown that taking the drug can be useful in the decrease of the disease level and prevent from the increase of the disease to step 4 and also prevent from treating by laser and using bevacizumab in the patients, but its side effects were noticeable. Also, in Aldo Bancalari and the colleagues' study on the oral Propranolol with less dosage, it was shown that the oral Propranolol drug can prevent from the improvement of the disease and increase the need for the aggressive treatments and no important side effects were seen. In a study, Makhoul and the colleagues found that taking the Propranolol drug can decrease the patients' need for the aggressive treatment, but because of the small number of the samples, the results were not significant. This group took a less dosage of the drug, too and no specific lesion was seen. It seems that the treatment by Propranolol in the first steps of the disease is not so effective. In a study with systematic review by Buhrer and Bassler, related to the analysis of Filipp and Makhoul's studies, it was shown that 6 patients out of the 35 ones taking Propranolol needed the aggressive treatment. Meanwhile, in the control group, 14 patients out of 36 ones needed other treatments. Generally, in different studies, higher dosages were accompanied by serious side effects. This study tested the least dosage of Propranolol and the percentage of improvement in the experimental group taking the drug was more compared to the control group, but no significant relation was found between taking and not taking the drug in the patients. One of the causes for the existing different views in the studies is the small number of the patients in each experimental group and the high rate of decrease of the patients' number in the studies. The change of the retinopathy and the ocular areas of the disease in each study can be a reason for this, too.[11-15]

Because of the patient's need for drug discontinuation and more aggressive therapies, drug consumption duration is different. In this study, the difference of the drug consumption duration between the group that has shown reactions to the cure and the group without reactions has shown significant, while in Ozturk MA study, the drug consumption duration has been a variable and there has not been a significant relation between the two groups, unlike our study. In Korkmaz L and the colleagues' study, the drug consumption duration in each group has had a more significant relation and the patients in the reaction group have had longer drug consumption duration. The difference among the studies can be a result of the difference among the number of the subjects that have had a need for more aggressive actions.[14,15]

In this study, the only side effect has been one case of hypoglycemia in the third day of the cure (Bs = 35) in which the patient showed no sign of the hypoglycemia but he was let out of the study. In other similar studies including Makhoul and Aldo Bancalari studies, no side effects were seen. In Ozturk and the colleagues' study, among the 147 patients 4 ones showed a need for the ventilator and in Levent Korkmaz that included 171 patients, 5 ones were let out of the study because of apnea and hypoglycemia. In the studies without side effects, the dose for the patients has been up to 2 mg per day and in the studies without the effects, the patients received the dosage of 1.5 mg per day. In our study that was with 1 mg dosage

per day, the patents showed effects. You should pay attention that taking Propranolol can have its specific and important side effects, including hypotension, bradycardia in the patients, closure of the airways and hypoglycemia.[15-17]

Conclusion

The study shows that Propranolol cannot replace other drugs for the cure as a good one but it can stop patients' getting worse and the growth of the disease to higher levels in the short time. It requires more complementary studies to detect the capabilities and to assess its effect rate in more people.

Conflict of Interests

Authors have no conflict of interests.

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