

## Unknown aspects of the relationship between ABO blood group system and preterm morbidities

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### ABSTRACT

**Objectives.** Blood groups have been shown to play an important role in a lot of diseases in various studies conducted in adults. The objective was to investigate whether there is a relationship between morbidities and ABO blood groups system in preterm infants.

**Methodology.** This retrospective cohort study included preterm neonates born at <32 weeks of gestation with a birth weight <1500 g. Neonates were grouped by blood type (O, A, B, AB) and morbidities of prematurity were compared among these groups.

**Results.** Data pertaining to 1785 very low birth weight preterm neonates were analyzed. Comparison of the A and non-A blood groups revealed that infants with blood group A had significantly higher incidence of patent ductus arteriosus (PDA) (48.7 % vs. 39.7 %,  $p = 0.005$ ) and bronchopulmonary dysplasia (BPD) (27 % vs. 20.8 %,  $p = 0.04$ ), while the incidence of grade  $\geq 3$  intraventricular hemorrhage was lower (5.1 % vs. 10.1 %,  $p = 0.006$ ).

**Conclusion.** This study represents the first and biggest series examination of the relationship between blood groups and preterm morbidities. Our results show that blood group A may be a risk factor for PDA and BPD.

**Keywords:** blood group antigens, bronchopulmonary dysplasia, cerebral intraventricular hemorrhage, patent ductus arteriosus, preterm.

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### INTRODUCTION

Preterm neonatal morbidities are primarily associated with low gestational age (GA) and birth weight (BW), as well as certain postnatal risk factors (non-feeding, invasive procedures, intensive care, and long hospital stay). The incidence of these morbidities increases as GA and BW decrease.<sup>1</sup> There is believed to be a genetic component in some preterm

morbidities.<sup>2,3</sup> It is well known that the risk of indirect hyperbilirubinemia (IHB) is higher in neonates, especially those born preterm, with hemolytic disease of the newborn (maternal blood group O and neonatal blood group A or B).<sup>4,5</sup> While IHB is most recognized condition associated with neonatal blood group, there is actually enough no information in the literature concerning the relationship between preterm morbidities and blood groups.

Blood types were discovered in the early 1900s, and it was confirmed with the ABO blood group classification that blood antibodies and antigens are inheritable features.<sup>6</sup> The antigens of the ABO blood group system (referred to as A, B, and H) are complex carbohydrate molecules located on the erythrocyte cell surface. They are also highly expressed on the surface of various human cells and tissues including the epithelium, sensory neurons, platelets, and vascular endothelium.<sup>7</sup> Therefore, the importance of the ABO blood group system goes beyond blood product transfusion. Blood groups have been shown to play an important role in the development of cardiovascular, infectious, oncologic, endocrine, rheumatologic, and other diseases in various studies conducted in adults.<sup>6-19</sup>

The effect of blood group on neonatal conditions, especially preterm morbidities, has yet to be determined. The presence of blood group antigen on many cell surfaces may be related to the morbidity in premature infants. The objective was to investigate whether there is a relationship between preterm morbidities and ABO blood groups system in preterm infants.

## METHODOLOGY

### Study design and patient selection

This retrospective study was conducted on data collected between January 1, 2013 and May 31, 2018 in the neonatal intensive care unit (NICU) of the Health Sciences University Zekai Tahir Burak Women's Health Education and Research Hospital, a tertiary referral hospital serving with 130 incubators. The local hospital ethical committee approved the study protocol (ethic number: 54/2018). We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. Neonates born at GA < 32 weeks with BW < 1500 g were included in the study; those with severe congenital defects, were excluded. Data pertaining to the neonates were recorded from medical records for each patient, and their ABO blood type was recorded.

### Demographic variables of the study groups

Gender, GA, BW, 1- and 5-min Apgar scores, antenatal steroid exposure, small for gestational age (SGA) status, duration of mechanical ventilation (MV) and non-invasive ventilation (NIV), duration of oxygen support, bronchopulmonary dysplasia (BPD, moderate/severe), hemodynamically significant patent ductus arteriosus (PDA, requiring medical or surgical treatment), retinopathy of prematurity (ROP) treated with laser, intraventricular hemorrhage (IVH, grade  $\geq 3$ ), necrotizing enterocolitis (NEC, grade  $\geq 2$ ), duration of achieving to full enteral feeding, and length of hospitalization were determined for all neonates.

### Preterm morbidities

Small for gestational age was defined as BW below the 10<sup>th</sup> percentile for GA according to Lubchencho curves.<sup>20</sup> All neonates were evaluated using Doppler echocardiography (ECHO). Hemodynamically significant PDA was identified according to clinical (murmur, hyperdynamic precordium, bounding preductal pulses, worsening respiratory status, wide pulse pressure, hypotension, and metabolic acidosis) and ECHO criteria (internal ductal diameter  $\geq 1.5$  mm and left atrium (LA)/aortic root (Ao) rate  $\geq 1.5$ ). Persistent PDA was treated with drugs (ibuprofen and/or paracetamol), and infants who did not respond to medical treatment were treated with surgical ligation.<sup>21</sup> Bronchopulmonary dysplasia (moderate/severe) was recognized according to criteria including positive pressure

mechanical ventilation support or requiring > 30 % oxygen supplementation at postmenstrual age of 36 weeks (the transcutaneous oxygen challenge test).<sup>22</sup> Retinopathy of prematurity was evaluated by experienced ophthalmologists according to the revised international classification of retinopathy of prematurity.<sup>23</sup> Cranial ultrasonography examination were performed to detect IVH in the first week of life.<sup>24</sup> NEC was identified by using modified Bell's criteria.<sup>25</sup>

The neonates were grouped by blood type (O, A, B, AB) and also separated into non-O (A, B, AB) and O groups and non-A (O, B, AB) and A groups for comparison of demographic characteristics, clinical features, and preterm morbidities.

### Statistical analysis

Statistical analyses were done using the Statistical Package for Social Sciences (SPSS) (version 15 for Windows, SPSS Inc., St. Louis, MO, USA). *P* values less than 0.05 were considered significant. Non-parametric continuous variables for independent samples were analyzed by using Student's *t*-test and/or Mann-Whitney U-test, and categorical variables were analyzed using chi-square or Fisher's exact tests. Findings were expressed as median (minimum-maximum) and/or mean  $\pm$  standard deviation (SD) for continuous variables. Categorical variables and distribution of frequency were presented as percentage. ANOVA with Bonferoni adjustment was used for different comparisons. We used logistic regression to calculate odds ratio (OR)  $\pm$  95 % confidence interval (95 % CI) for the association between ABO blood groups and events such as PDA, BPD, IVH, according to corrected model for all available risk factors.

## RESULTS

A final number of 1803 preterm infants with GA < 32 weeks and BW < 1500 g were evaluated. Eighteen neonates were excluded according to the exclusion criteria, and a total of 1785 infants were eligible (Figure 1). The mean GA and BW of the entire group were  $1051 \pm 226$  g and  $28.1 \pm 1.3$  weeks, respectively. The neonates were categorized according to blood type as O, A, B, and AB (Figure 1).

Comparisons among the four blood types and between the O and non-O blood groups showed no significant differences in GA, BW, gender, 1- and 5-min Apgar scores, antenatal

steroid exposure, SGA, duration of respiratory support, PDA, BPD, ROP, IVH, NEC, full enteral feeding time, or hospital stay ( $p > 0.05$ ) (Tables 1 and 2). There were also no significant differences in GA, BW, gender, 1- and 5-min Apgar scores, antenatal steroid exposure, SGA, duration of respiratory support, ROP, NEC (grade  $\geq 2$ ), full enteral feeding time, or hospital stay between the

A and non-A blood groups ( $p > 0.05$ ). However, neonates with blood group A had a significantly higher incidence of PDA ( $n = 391$ , 48.7 %) and moderate/severe BPD ( $n = 217$ , 27 %) compared to those in the non-A blood group (PDA:  $n = 390$ , 39.7 %; moderate/severe BPD:  $n = 205$ , 20.8 %) ( $p = 0.005$ ,  $p = 0.040$ , respectively). The incidence of IVH (grade  $\geq 3$ ) was significantly lower in blood

FIGURE 1. Flow chart of patients

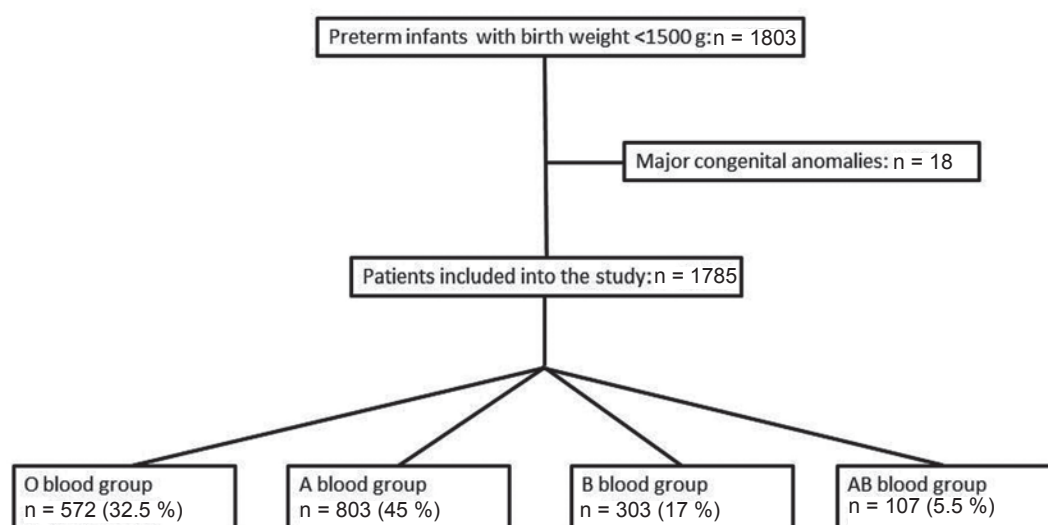


TABLE 1. Demographic variables and morbidities of infants according to all ABO blood groups

Demographic and clinical characteristics	O (n = 572, 32.5 %)	A (n = 803, 45 %)	B (n = 303, 17 %)	AB (n = 107, 5.5 %)	p
Gestational age, weeks <sup>a</sup>	28.1 $\pm$ 1.2	28.1 $\pm$ 1.2	28 $\pm$ 1.1	27.6 $\pm$ 1.1	0.179
Birth weight, g <sup>a</sup>	1042 $\pm$ 226	1079 $\pm$ 228	1031 $\pm$ 237	1018 $\pm$ 206	0.945
Male gender, n (%)	325 (56.8)	394 (49)	152 (50.1)	56 (52.3)	0.381
Apgar score at 1 min <sup>b</sup>	5 (1-7)	5 (1-8)	5 (1-7)	6 (2-7)	0.222
Apgar score at 5 min <sup>b</sup>	7 (2-9)	8 (3-10)	7 (3-9)	8 (4-9)	0.195
Antenatal steroid, n (%)	412 (72)	530 (66)	213 (70.3)	69 (64.5)	0.785
SGA, n (%)	63 (11)	83 (10.3)	37 (12.2)	14 (13.1)	0.932
Duration of MV, days <sup>b</sup>	1 (0-81)	0 (0-55)	2 (0-43)	1 (0-25)	0.257
Duration of NIV, days <sup>b</sup>	6 (1-46)	5 (1-51)	8 (1-73)	1 (1-26)	0.733
Duration of supplemental oxygen, days <sup>b</sup>	23 (2-147)	16 (2-119)	33 (4-146)	26 (9-73)	0.621
PDA, n (%)	206 (36)	391 (48.7)	131 (43.2)	53 (49.5)	0.234
BPD, (moderate or severe), n (%)	122 (21.3)	217 (27)	61 (20.7)	22 (20.5)	0.575
ROP, n (%)	74 (13)	66 (8.2)	49 (16.1)	11 (10.3)	0.106
IVH (grade $\geq 3$ ), n %	58 (10.1)	41 (5.1)	33 (10.8)	9 (8.4)	0.124
NEC (grade $\geq 2$ ), n %	12 (2.1)	17 (2.1)	7 (2.3)	3 (2.8)	0.967
Full enteral feeding, days <sup>b</sup>	14 (8-45)	14 (7-56)	14 (7-52)	15 (10-38)	0.740
Hospital stay, days <sup>b</sup>	52 (1-224)	53 (1-37)	65 (1-169)	53 (1-101)	0.611

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; MV, mechanical ventilation;

NEC, necrotizing enterocolitis; NIV, non invasive ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity;

SGA, small for gestational age.

<sup>a</sup> Mean  $\pm$  standard deviation.

<sup>b</sup> Median (minimum-maximum).

Statistical analysis: ANOVA was used for comparisons of the groups.

group A (n = 41, 5.1 %) compared to the non-A blood group (n = 100, 10.1 %) (p = 0.006) (Table 3).

We performed logistic regression analysis

that completed by one step after corrected all risk factors. The A group was significantly related to higher frequency of PDA (OR = 1.73,

TABLE 2. Demographic variables and morbidities of infants according to ABO blood groups comparing O and other blood groups

Demographic and clinical characteristics	O blood group (n = 572, 32.5 %)	Non-O blood groups (n = 1213, 67.5 %)	p
Gestational age, weeks <sup>a</sup>	28.1 ± 1.2	28 ± 1.2	0.552
Birth weight, g <sup>a</sup>	1042 ± 226	1062 ± 229	0.314
Male gender, n (%)	325 (56.8)	602 (49.6)	0.104
Apgar score at 1 min <sup>b</sup>	5 (1-7)	5 (1-8)	0.209
Apgar score at 5 min <sup>b</sup>	7 (2-9)	8 (3-10)	0.173
Antenatal steroid, n (%)	412 (72)	812 (70)	0.548
SGA, n (%)	63 (11)	134 (11.1)	0.979
Duration of MV, days <sup>b</sup>	1 (0-81)	1 (0-55)	0.629
Duration of NIV, days <sup>b</sup>	6 (1-46)	6 (1-73)	0.272
Duration of supplemental oxygen, days <sup>b</sup>	23 (2-147)	22 (2-146)	0.558
PDA, n (%)	206 (36)	575 (47.4)	0.164
BPD, (moderate or severe), n (%)	122 (21.3)	300 (24.7)	0.579
ROP, n (%)	74 (13)	126 (10.4)	0.602
IVH (grade ≥ 3), n %	58 (10.1)	83 (6.8)	0.522
NEC (grade ≥ 2), n %	12 (2.1)	27 (2.2)	0.824
Full enteral feeding, days <sup>b</sup>	14 (8-45)	14 (7-56)	0.983
Hospital stay, days <sup>b</sup>	52 (1-224)	55 (1-169)	0.267

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; MV, mechanical ventilation;

NEC, necrotizing enterocolitis; NIV, non invasive ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity;

SGA, small for gestational age.

<sup>a</sup> Mean ± standard deviation.

<sup>b</sup> Median (minimum-maximum).

TABLE 3. Demographic variables and morbidities of infants according to ABO blood groups comparing A group and non-A groups

Demographic and clinical characteristics	A blood group (n = 803, 45 %)	Non-A blood groups (n = 982, 55 %)	p
Gestational age, weeks <sup>a</sup>	28.1 ± 1.2	28.1 ± 1.2	0.926
Birth weight, g <sup>a</sup>	1079 ± 228	1042 ± 229	0.127
Male gender, n (%)	394 (49)	533 (54.2)	0.067
Apgar score at 1 min <sup>b</sup>	5 (1-8)	5 (1-7)	0.159
Apgar score at 5 min <sup>b</sup>	8 (3-10)	7 (2-9)	0.247
Antenatal steroid, n (%)	530 (66)	694 (70.6)	0.811
SGA, n (%)	83 (10.3)	114 (11.6)	0.845
Duration of MV, days <sup>b</sup>	0 (0-55)	1 (0-51)	0.289
Duration of NIV, days <sup>b</sup>	5 (1-51)	6 (1-73)	0.723
Duration of supplemental oxygen, days <sup>b</sup>	16 (2-119)	26 (2-146)	0.980
PDA, n (%)	391 (48.7)	390 (39.7)	0.005*
BPD, (moderate or severe), n (%)	217 (27)	205 (20.8)	0.040*
ROP, n (%)	66 (8.2)	134 (13.6)	0.529
IVH (grade ≥ 3), n %	41 (5.1)	100 (10.1)	0.006*
NEC (grade ≥ 2), n %	17 (2.1)	22 (2.2)	0.420
Full enteral feeding, days <sup>b</sup>	14 (7-56)	14 (7-52)	0.947
Hospital stay, days <sup>b</sup>	53 (1-37)	56 (1-224)	0.164

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; MV, mechanical ventilation;

NEC, necrotizing enterocolitis; NIV, non invasive ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity;

SGA, small for gestational age.

\* Statistically significant p values are highlighted.

<sup>a</sup> Mean ± standard deviation.

<sup>b</sup> Median (minimum-maximum).



95 % CI = 1.14–2.69,  $p = 0.01$ ), as well as BPD (OR = 1.59, 95 % CI = 1.11–2.36,  $p = 0.03$ ) according to the model with corrected risk factor including GA, BW, gender, Apgar score at 1 and 5 minutes, antenatal steroid administration, being SGA, duration of MV, duration of NIV, duration of oxygen supplementation, time of hospitalization and other morbidities. The non-A group was significantly associated with higher prevalence of IVH (grade  $\geq 3$ ) (OR = 1.92, 95 % CI = 1.26–3.53,  $p = 0.001$ ) which was true for model corrected for all risk factors involving Apgar score at 1 and 5 minutes, GA, gender, BW, antenatal steroid administration, being SGA, duration of MV, duration of NIV, duration of oxygen supplementation, time of hospitalization and other morbidities.

## DISCUSSION

In the recent study, the association between neonatal morbidities and blood groups were evaluated in preterm infants. We found that preterm infants with blood group A had a higher incidence of PDA and BPD and lower incidence of IVH compared to the other blood groups. It is unclear why the prevalence of certain morbidities varies among preterm infants born at the same GA and BW. Genetic predisposition has been implicated in this phenomenon.<sup>2,3</sup> We believe that our results may offer insight into the effect of blood group on preterm morbidities. In addition, the frequencies of the four blood types in our study was similar to rates in the Turkish population (A>O>B>AB).<sup>16</sup>

Following the discovery of blood groups, the relationship between these groups and transfusion reactions was described. After that, numerous adult studies were conducted to evaluate possible relationships between blood groups and various human diseases.<sup>10,13,26,27</sup> As in adult lung diseases, there is also genetic predisposition in BPD. However, BPD is a disease of the developing lung unlike adults.<sup>28</sup> Although the duration of respiratory support, GA, BW for BPD were similar in 4 different blood groups, the frequency of BPD was higher in A blood group than in other blood groups. The reason for this may be that ABO antigens are identified as a locus for inflammatory biomarkers. Different blood groups have different biochemical functions in the pathogenesis of BPD and may result in different outcomes as well.<sup>1,29</sup> In other words, the effect of ABO blood group genome on biochemical functions may be related to the

biochemical process in BPD pathogenesis.<sup>22,30</sup> Furthermore, because of the effect of blood groups on genetic inherited and inflammatory processes, the relationship with biochemical functions in premature infants with A blood group may be riskier for BPD due to genomic difference.

In a study on blood groups and neonatal diseases which was conducted by El-Ferzli et al., demonstrated that response to inhaled nitric oxide was less effective in improving oxygenation in those with blood group A in neonates with pulmonary hypertension.<sup>29</sup> These results were attributed to the genetic association of the ABO gene locus on the chromosome 9q34 with its genetic association with other genes regulating vasoconstriction, vasodilation, or vascular tone. Since these factors were developmentally regulated, they might cause different vascular responses in the fetal / neonatal period compared to children and adults.<sup>30</sup> Furthermore, ABO antigens could have many functions that affect vascular tone (such as calcium channels) and were developmentally regulated.<sup>31</sup> Calcium ion had an important function in the closure of the patent ductus arteriosus.<sup>32</sup> Therefore, in our study, the high frequency of PDA in the blood group A may be due to the difference in both the genetic locus and calcium ion transport associated with the ABO blood group regulating vascular tone.<sup>29,32</sup> Supporting this hypothesis, it was noted in our study that frequency of PDA was higher in infants who had A and AB blood group carrying 'A allele' compared to other groups (O and B blood group).

Some studies declared that no relationship was observed between blood groups and intracranial hemorrhage or hemorrhagic stroke.<sup>33,34</sup> In our study, the incidence of IVH was lower among preterm infants with A blood group. In a related article conducted with a small number of newborns were reported that no relationship was found between the blood groups and neonatal IVH.<sup>35</sup> PDA is an important risk factor for IVH in preterm infants.<sup>21</sup> Furthermore, there is an increased risk of IVH due to dysregulation of cerebral blood flow in premature infants. Calcium ions that regulate vascular tone also have an important role on cerebral vascular tone. ABO gene locus may have an effect on IVH due to its regulation of vasoconstriction or vasodilation and its effect on ion channels (calcium).<sup>29,31</sup> Based on this mechanism, A blood group may increase the susceptibility to PDA, and have a protective effect

on IVH, and may be related to different central and peripheral effects. Supporting this theory, our findings determined that the frequency of IVH in the AB blood group which had 'A alleles' was less than that of O and B blood groups. In a study by Thomson et al., the risk of NEC-related mortality was higher in the AB blood group than in the other groups. This result was attributed to the iso-agglutinin hypothesis, due to the anti-A and anti-B antibodies in the O group blood used for transfusion given to the infants having AB blood group.<sup>36</sup> According to our results, no blood group was found to be a risk factor for the development of NEC.

Although the main risk factors for preterm neonatal morbidity are low GA and BW, the causes are multifactorial.<sup>1-3</sup> The role of blood group among the causes of preterm morbidity is still unknown. In our study, there was no significant difference between the blood groups in terms of GA and BW, which are the most important risk factors for morbidity. However, it was a noteworthy finding that blood group A was associated with higher incidence of PDA and BPD and lower incidence of IVH. Our results suggested that blood type might in fact be among the underlying factors affecting preterm morbidity. Furthermore, these results were difficult to interpret for a number of reasons. With over 20 different subgroups, the ABO blood group system is highly polymorphic. Studies generally investigate the association between disease and ABO phenotype, but are rarely related to ABO genotype, secretory status, and Lewis phenotype. In addition, data obtained from experimental animal models are unsatisfactory, since, the antigen glycosylation differs from that in humans.<sup>6</sup>

Antigen A has higher antigenicity than B antigen. Thus, anti-A hemolysins have a higher prevalence than anti-B hemolysins.<sup>37</sup> The antigenicity of antigen A decreases in the AB blood group including A and B antigens together. This is reflected in the haemolytic disease of the newborn (HDN). HDN is the highest in newborns with A blood group compared to newborns with AB blood group. In addition, the risk of developing severe HDN depends on several factors, including immunoglobuline G class, specificity of the red cell alloantibodies, and level of expression of the involved blood group antigen on the fetal red cells and other tissues.<sup>38</sup> In our results, the highest rate of PDA and BPD in the A blood group was lower in the AB blood

group, and IVH rate was the lowest in the A blood group which could be due to the above-mentioned reasons.

There were some limitations in our study. Because of the retrospective nature of our study, the relation of ABO blood groups with genome, alleles, secretory status and biochemical parameters could not be evaluated.

## CONCLUSIONS

Our study was the first and biggest series to show that blood groups might be a risk factor for some preterm morbidities with a huge number of patients. In our study, it was found that preterm infants with blood group A had a higher incidence of PDA and BPD and lower incidence of IVH compared to the non-A blood groups. Although, all biological functions of A and B antigens are not clear, recognition of their role in the morbidity of preterm infants may warn the attending physicians for potentially negative clinical outcomes. Further researches are needed to elucidate the relationship between preterm neonatal morbidities and blood groups. ■

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