

# Effect of Transfusion on the Extension of IVH in Preterm Neonates

Ali Reza Jashni Motlagh<sup>1</sup>, Azamolmolouk Elsagh<sup>2\*</sup>

1. Kamali Clinical Research and Developmental Unit, Alborz University of Medical Sciences, Karaj, Iran  
2. Faculty of Nursing, Alborz University of Medical Sciences, Karaj, Iran

## ABSTRACT

**Background:** Today, preterm birth is well known as the major risk factor for intraventricular hemorrhage (IVH). In the first week of life, some preterm infants may have grade 1 IVH extending to severe (grade 3 or 4) IVH by transfusion one or more units. Several previous studies have found that blood and blood product transfusions lead to adverse clinical outcomes in neonates. Therefore, this study aimed to explore the relationship between Red blood cell (RBC) transfusion and extension of IVH in preterm infants.

**Methods:** For the purposes of the study, an observational retrospective case-control design was utilized. Moreover, all the neonates with grade 1 IVH in our referral hospital were identified in the past 5 years. Afterward, the subjects with extended IVH were compared with those who had resolved IVH.

**Results:** In total, 1050, 36, and 24 neonates were diagnosed with grade 1, grade 3, and grade 4 IVH, respectively. The mean values of the birth weight of extended IVH and resolved IVH groups were  $1285\pm 615$  g and  $1361\pm 348$  g, respectively ( $P=0.05$ ). Moreover, extended IVH and resolved IVH groups were  $29\pm 3$  weeks and  $30\pm 2$  weeks premature, respectively ( $P=0.36$ ). The low 5-minute Apgar scores of the extended IVH and resolved IVH groups were  $5\pm 2$  and  $7\pm 2$ , respectively ( $P=0.000$ ). In addition, the low cord pH of the extended IVH and resolved IVH groups were  $7.29\pm 0.1$  and  $7.37\pm 0.1$ , respectively ( $P=0.005$ ). Administration of packed RBC transfusion before and on the day of the diagnosis of grade 1 IVH had the most significant relationship with the extension of IVH (IR, 10.602; 95% CI, 2.81-39.92). The obtained results confirmed that criteria to order the transfusions were similar in both groups, based on which they did not have any proportion of the transfusions of compliance with the guidelines.

**Conclusion:** Based on the results, there was a great association between restrictive RBC transfusion and extension of a low-grade IVH into a higher grade (3 or 4) IVH. However, the statistical explanation is unclear and more studies are needed to discover the causality of this relationship.

**Keywords:** Cerebral intraventricular hemorrhage, Infant, Low birth weight, Neonate, Transfusion

## Introduction

Today, intraventricular hemorrhage (IVH) is well known as a major complication of preterm birth that has a 25% prevalence rate in very-low-birth-weight (VLBW) infants (1). The IVH begins in the periventricular germinal matrix, the area that is exceptionally vulnerable to bleeding due to the abundant vascularity of the region which is intrinsically fragile and is associated with the paucity of pericytes in order to supply the structural integrity of the blood vessels (2, 3). It is worthwhile to mention that after the germinal matrix hemorrhage, some critical factors affecting the hemostasis are able to specify whether the

bleeding ceases rapidly or continues for some hours.

Only a small percentage of infants can have grade 3 IVH, which is represented with the intraventricular blood in dilated lateral cerebral ventricles, or grade 4 IVH, which is well known as the extension of intraventricular blood (venous infarction) into the adjacent parenchymal region, based on the Papile grading (4). However, up to 75% of the infants experience mild to severe IVH-related complications in later life (5,6). Therefore, IVH can be described as a major health concern (7) that can be either resolved or extended in

\* Corresponding author: Azamolmolouk Elsagh, Faculty of Nursing, Alborz University of Medical Sciences, Karaj, Iran. Tel: +989132204626; Email: A\_elsagh@abzums.ac.ir

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some patients; however, the reason for either outcome is not clear. In recent decades, despite the decline of the incidence rate of severe IVH (Grades 3 and 4), its morbidity rate is still high in preterm newborns, particularly extremely low birth weight (ELBW) infants (8).

It should be mentioned that in preterm infants, the pathogenesis of severe IVH might consist of vascular rupture of the germinal matrix, and is susceptible of hemorrhage. Moreover, there are several perinatal risk factors, including intrauterine infection, early gestational age, low birth weight, low Apgar score, vaginal delivery, the severity of illness, acidosis, sepsis, delivery outside a perinatal center, early use of vasopressors, elevated nucleated red blood cell (RBC) counts at the time of birth, male gender of the neonate, and finally, RBC transfusions liberally along with the pathogenesis of IVH (9, 10, 11-12). Particularly, in the germinal matrix, the association between IVH and transfusion could be due to damage and volutrauma to the weak blood vessels (13).

However, the rate of transfusions has risen exponentially in recent years (14). In general, it has been reported that up to 90% and 58% of ELBW and preterm infants (<32 weeks of gestational age) receive RBC transfusions since the 1990s until now, respectively, due to the ventilator requirements and iatrogenic phlebotomy losses (15). Moreover, according to the statistics, 50-94% and 95% of VLBW (birth weight of <1500 g) and ELBW infants (birth weight of <1000 g) receive at least one transfusion during their hospital stay, respectively (16). Therefore, infants with low birth weights are more likely to receive frequent transfusions.

In this regard, some of the recent research conducted on the neonatal populations stated the associations between RBC transfusion and the increased risk of specific complications, including necrotizing enterocolitis (NEC), chronic lung disease (CLD), the extension of IVH, and retinopathy of prematurity (ROP) (9, 17).

This finding could be due to the loss of nitric oxide of the erythrocytes during storage. This would impair capillary vasodilation and incorporate the received erythrocytes as well as the hemorrhage blood entering the extracellular compartment, which is probably to contribute for the iron-induced oxidative damage to the cells of the developing brain (18).

Some of the invaluable factors that could reduce both the incidence and severity of IVH include antenatal glucocorticoids, sedation with

opioids or indomethacin, Vitamin K, and fresh frozen plasma (19, 20, 21-22). Santos in her/his study reported that low birth weight is associated with IVH extension (23). Furthermore, Christensen et al. in their study, which was performed in Intermountain Medical Center, hypothesized that a decrease of the transfusion rate would lead to the reduction of the rate of IVH, particularly in VLBW infants (21, 24).

According to the results of another research carried out by von Linderen et al. in Leiden, the high-grade IVH in VLBW neonates is noticeably independent of both the thrombocytopenia and platelet (PLT) count, which is involved in some cases of extension from a grade 1 to a higher grade hemorrhage (25). The present study aimed to explore the impact of RBC transfusion and PLT count on IVH. Moreover, this aforementioned issue is crucial when a consensus cannot be reached regarding the optimal trigger threshold for RBC transfusion in preterm infants as well as the main effects of RBC transfusion at various levels of anemia.

Based on the literature review, no previous research has investigated the relationship of PLT and RBC transfusion with IVH (26). Therefore, this study aimed to detect the effects of transfusion on the progression of IVH, in order to improve the neonatal intensive care and decrease IVH progression in VLBW neonates.

## Methods

This observational retrospective case-control study was performed on a study population of 15000 preterm infants who were born at  $\leq 32$  weeks of gestation and admitted to the Kamali Hospital in Karaj which is the referral hospital for high-risk pregnancies in Alborz province, Iran, during March 21, 2014-March 31, 2019. The participant neonates were delivered both by cesarean and vaginal methods; moreover, they were diagnosed with a grade I IVH by the first ultrasound evaluation.

Inclusion criteria consisted of 1) birth weight of < 1500gr, 2) preterm birth of < 32 weeks, 3) possibility of follow up, 4) no congenital anomaly, 5) the need for at least two-week hospitalization, and 6) grade I IVH.

On the other hand, the exclusion criteria were 1) term birth, 2) normal weight, 3) the impossibility of follow up, 4) congenital anomaly, 5) death of the infant in the first 12 h of life, and 6) liberal transfusion. In this regard, the neonates with no cranial sonographic data admitted within three days after the birth

and/or neonates who were transferred from other centers after three days of age were finally excluded from this study.

In total, 15000 infants were examined for the purposes of the study between March 21, 2014 to March 31, 2019, 1050 of whom were eligible. Out of these participants, 60 infants who had extended IVH ranging from Grade 1-4 were assigned to the case group. In this paper, the control group included 985 infants with resolved IVH and no extension.

All the infants of both groups underwent cranial ultrasounds regularly when they were 1, 2, 3, 7, and 14 days old, with a 2.2-5 MHz transducer, according to the clinical protocols of the neonatal intensive care unit (NICU).

Moreover, some additional ultrasound examinations were carried out when there was clinical suspicion of bleeding, in which both sagittal and coronal planes were evaluated through the anterior fontanelle. The severity of IVH was graded based on the categories developed by Papile et al. (4,27). Therefore, the highest grade means that there was more than one report, or there was bilateral hemorrhage. It should also be mentioned that other intracranial bleeding, such as subdural, subarachnoid, and epidural hemorrhage were not investigated as IVH

Afterward, those variables that led to grade 1 IVH were detected. Furthermore, some differences were observed in the coagulation tests, complete blood counts, and also transfusions. The gestational age, birth weight, venous blood gas from the umbilical cord at birth, administration of RBC transfusion during grade I IVH (GMH), misuse of corticosteroid, genetic susceptibility, early use of vasopressors (e.g., dopamine), out-of-hospital delivery, male gender of the infant, APGAR score, use and duration of mechanical ventilation, duration of blood storage in blood bank, hematocrit of the infants, prothrombin time, partial thromboplastin time, and coagulation test results were also recorded.

The neonates diagnosed with the grade 1-4 IVH received one unit in the first week of life based on the guidelines developed by Strauss RG et al. (28). In this study, the transfused RBCs were provided by the Iranian Red Blood Cell Transfusion Organization (Tehran, Iran). It should be noted that the blood was irradiated, maintained in CPDA-1, and packed by centrifugation, while it was not washed before the transfusion. Meanwhile, the RBCs were aliquoted into a pump-compatible syringe by a sterile connecting tool and subsequently infused using a

standard clot filter. The guidelines proposed by Kamali suggested the preparation of a volume of RBCs of 10 mL/kg the body weight within a period of 3 h. For this purpose, both the time of RBC infusions and volume were carefully recorded and afterward provided in the chart of NICU patients.

In the conducted stepwise regression analysis, the considered elements included the weeks of gestation, birth weight, venous blood gas from the umbilical cord at birth, and administration of RBC transfusion during grade 1 IVH (germinal matrix hemorrhage).

Accordingly, 95% confidence intervals (CI) and odds ratios (OR) were utilized. In addition, the obtained values of the groups with normal distribution were described using means and standard deviations (SD). The statistical analysis was performed in SPSS software (version 17.0) and a p-value of less than 0.05 was considered statistically significant.

### **Ethical consideration**

The researchers referred to Kamali Hospital after receiving a written consent along with an introduction letter from Alborz University of Medical Sciences and the Research Deputy of this university. Afterward, the researchers started to gather the required data after the provision of an explanation of the research aims to the manager of the hospital. This research was also approved in the ethics committee of Alborz University of Medical Sciences (registration code: Abzums.Rec.1396.47).

### **Results**

During the five-year period of the study, 15000 preterm neonates were examined and only 1050 of them were diagnosed with Grade 1 IVH. Among them, 985 neonates were cured before reaching a higher grade, whereas 65 neonates were diagnosed with higher-grade hemorrhage over the next 2-3 weeks. On the other hand, in the case of 5, 36, and 24 participants, their disease was extended into grades 2, 3, and 4 IVH, respectively. It should be noted that the five patients with extensions to grade 2 were not assessed in this study.

Ultimately, the 60 patients with grade 3 and 4 hemorrhages were identified with bilateral hemorrhages which occurred in 36 out of the 60 (55.3%) patients. Moreover, only 24 (36.9%) cases had a unilateral hemorrhage, all of whom had grade 4 IVH. The necessary time needed for grade 1 IVH to extend into grade 3 or 4 could not be exactly specified since the ultrasound examinations were not performed on a daily basis.

**Table 1.** Neonates with and without extension of intraventricular hemorrhage  
The obtained values are provided as percent or Mean±SD.

Variable	Control group (n=985)	Case group (n=60)	p-value
Gestational age at birth (weeks)	30±2	29±3	0.360
Birth Weight (gr)	1361±348	1285±615	0.050
PH	7/37±0/1	7/29±0/1	0.009
5-minute Apgar score	7±2	5±2	0.000

**Table 2.** Experimental results of the implemented logistic regression analysis, investigating the likelihood (i.e. OR, 95% CI), in which all of the 5 listed variables have a relationship with the progression from grade 1 IVH to a severe IVH (grade 3 or 4)

Variables	Odds ratio	Lower 95%	Upper 95%
Birth weight	0.999	0.997	1.001
Weeks of gestation	1.038	0.741	1.455
Cord PH	1.146	1.010	1.284
PLT transfusion	0.414	3.121	10.418
RBC transfusion	10.602	2.815	39.923

Nonetheless, there was a delay of 2±1 weeks between the diagnosis of grade 1 and grade 3 or 4 IVH in the 60 infants.

Corticosteroid abuse by the mother, genetic susceptibility, early use of vasopressors (e.g., dopamine), out-of-hospital delivery, male gender of the neonate, use and duration of mechanical ventilation, duration of blood storage in the blood bank, and hematocrit of infants and PT, PTT coagulation tests were similar in both groups (P>0.5). Despite the fact that both groups of neonates received 10 ml/kg of PLT for thrombocytopenia, there was no difference regarding PT and PTT between the groups (P=0.75). It should be mentioned that low birth weight and a low PH of the newborns had a significant relationship with IVH extension to grade 3 or 4. As can be observed in Table 1, the IVH extension to grades 3 or 4 was related to low birth weight, birth at an earlier gestational age, low 5-minute Apgar scores, and a low cord blood PH.

### Incidence and frequency

As can be seen in Table 2, the experimental results of the conducted stepwise regression analysis revealed some of the variables associated with IVH extension, such as gestational age, PH, birth weight, and transfusion of PLTs and RBCs before the IVH extension. Moreover, the implemented regression results indicated that despite the fact that low PH values had a higher odds ratio regarding IVH extension, this factor had a significant association with the decrease of extension among other risk factors. Moreover, these results indicated that RBC transfusion (prior to the extension) had a relationship with IVH extension.

Based on Table 2, it can be concluded that grade 1 IVH extension had the lowest odds ratio regarding low birth weight, low PH, and PLT

transfusion, while its highest odds ratios were associated with RBC transfusion and low gestational age. Based on the transfusion guidelines, the proportion of RBC transfusions were considerably similar in both extended and resolved IVH groups (38% vs. 36%, P=0.80). Consequently, the neonatal qualification criteria for an RBC transfusion were similar for both groups. Particularly, before transfusion, blood hemoglobin concentrations of the resolved IVH group (10±3 g/dL) were similar to that of the extended group (10.6±4 g/dL) (P=0.15).

### Discussion

This observational retrospective analysis confirmed only two relevant individual variables. The first one was that there was a relationship between older gestational age and low odds of extension. The second one was that RBC transfusion before the conduction of IVH extension was associated with higher odds.

On the other hand, a number of critical risk factors were found regarding the extension of IVH including misuse of corticosteroid, genetic susceptibility, early use of vasopressors (e.g., dopamine), out-of-hospital delivery, male gender of the neonate, APGAR score, the use and duration of mechanical ventilation duration of blood storage in blood bank, hematocrit of infants, prothrombin time, partial thromboplastin time, and coagulation test results which were similar in both groups. No significant difference was found in this study among the aforementioned risk factors. Nevertheless, a significant association was found between RBC transfusion and low gestational age.

Santos et al. found that grades 3/4 IVH (OR,1.64; 95% CI, 1.05-2.58) was correlated with gestational age, usage of the umbilical catheter, mechanical ventilation, the parenteral nutrition,

and hospitalization longer than 60 days as a result of RBC transfusion in the preterm infants. However, based on the results of the present study, IVH was only correlated with the gestational age and RBC (29). Keir A et al. in their study also found that IVH was correlated with small amounts of RBC transfusions (10-20 ml/kg), ROP, chronic lung disease, and NEC, which is consistent with the results of this study (30).

Moreover, Christensen RD et al. observed a decrease in the early RBC transfusion rate in the first week after birth, which led to a decrease in the incidence rate of severe IVH. According to their findings, the RBC transfusion could lead to severe IVH (9, 31). Baer et al. declared that RBC transfusion on the day of grade 1 IVH detection had the most significant effect on the increase in the odds ratio of IVH extension. Besides, they found that low serum PH at birth, as well as the low birth weight, had significant effects on IVH which is also in line with the findings of the present research (21).

Bednarek et al. found that the rate of IVH, bronchopulmonary dysplasia, and NEC was independent of the RBC transfusion rate in the NICUs (20), we found this in our study too. Christensen RD et al. indicated that two transfusion risks that were unique to very low birth weight neonates were subsequent occurrence of a grade 3 or 4 intraventricular hemorrhage and NEC following transfusions on the first days after birth (32). It should be noted that this study did not assess the IVH on the day of birth. Portugal carolin et al. studied restrictive transfusions and revealed that it was an independent risk factor for pre-intraventricular hemorrhages and death (33). Similar results were also found in the present study.

Bell et al. stated that infants who received packed red blood cells (PRBC) by restriction, were more at the risk of intraparenchymal and ventricular hemorrhage, or periventricular leukomalacia (PVL). They concluded that the practice of restrictive transfusions may be hazardous to preterm infants. The present study found a correlation between transfusion and the increase of the grade of IVH (34). Furthermore, Chirico G et al. observed several side effects unique to preterm infants, such as an increased mortality rate and transfusion-related IVH. They also concluded that it was critical to decreasing the rate of RBC transfusion in critically ill neonates (35). This was in line with the findings of the present study; therefore, it can be suggested that the transfusion guidelines for preterm infants

must be revised in the future.

Mercer et al. found that elimination or reduction of the early RBC transfusions by delayed cord clamping resulted in a lower incidence rate of IVH; however, it did not have any effects on the rates of bronchopulmonary dysplasia (BPD) or NEC (36). The present research also found that transfusion could exacerbate the severity of IVH. Based on the results of a study carried out by Goodarzi et al., IVH had a significant relationship with blood transfusion in preterm neonates. However, according to them, IVH was not significantly associated with gender, gestational age, and birth weight in preterm infants (37). This was consistent with the findings of this research, except that there was a relationship between cord PH and IVH in the present study.

Hosono S et al. observed that neonates with high hemoglobin level and high blood pressure during the first 24 h had a lower risk of IVH, compared to those neonates with low hemoglobin levels ( $\leq 15$  gr%) who required blood transfusion which was in line with the results of the present study (38). Based on the results of a study conducted by Banerjee J et al., the primary outcomes of IVH, BPD, ROP, NEC, and death before discharge were significantly associated with hemoglobin levels at birth. They observed that 58% of the infants with low hemoglobin levels at birth had increased odds of receiving blood transfusion (39). The present study also found that transfusion had great effects on the progression of IVH; however, we did not study other complications associated with transfusion.

Pegoli M et al. declared that the excellent outcome in patients with aneurysmal subarachnoid hemorrhage was associated with the good clinical condition after resuscitation, no evidence of infarction in brain imaging, lack of intracerebral hemorrhage based on the presentation, and lack of blood transfusion during hospitalization, which was in accordance with the findings of this study (40).

Contrary to the results of the present research, several studies have found no association between blood transfusion and the extension of IVH. According to the results of a research performed by Chen et al., higher levels of transfusion did not result in severe IVH. In their study, the infants were divided into two groups. One group consisted of subjects who received a large PRBC transfusion volume, while the other one included recipients of restrictive transfusion for over 30 days. They did not find any significant differences in the proportion of severe IVH, patent ductus

arteriosus, respiratory distress syndrome, ROP, and CLD between the two studied groups (41). In this regard, Mukhopadhyay et al. in their study found that the frequency of transfusions had no statistically significant relationship with sepsis, IVH, and ROP (42).

In contrast to the findings of this study that indicated a significant relationship between IVH extension and transfusion, those of the study performed by Valieva revealed no association between the hematocrit level before the first transfusion and IVH; however, their research did not mention the effects of RBC transfusion on IVH (43). Nevertheless, the present research found a connection between RBC transfusion and IVH. Rabe, H et al. found that the delay in cord clamping reduced the need for transfusions due to anemia and as a result led to the decrease of the incidence rate of low grade (1 and 2) IVH, while the incidence rate of severe (grade 3 and 4) IVH and PVL remained unchanged (44). However, this study revealed that low-grade IVH extended into high-grade IVH following the transfusion.

In a clinical study performed by Ferguson et al. the fresh RBCs were compared with the standard blood bank practice, did not enhance the outcomes of IVH in premature, VLBW infants requiring RBC transfusions (45). It should be noted that the present study exploited the standard pack cells and detected a progression of IVH due to transfusion. Moreover, it was confirmed that the related retrospective studies are flawed due to their poor ability to distinguish the underlying mechanisms and failure to recognize confounding variables. Furthermore, the retrospective investigations revealed the associations that could create some new hypotheses; however, they seldom proved a causal relationship (46).

The present study did not investigate any extended IVH in the database since in many cases, the first head ultrasound indicated that the patient previously had a grade 3 or 4 hemorrhage. Moreover, severe IVH might have begun in the uterus and then extended over the following days; however, since an earlier ultrasound was not obtained, the opportunity to have such patients was lost in this research. In addition, this paper found no differences between the extended IVH group and the resolved group regarding the criteria used for the transfusion. Nonetheless, it is ambiguous whether the observed relationship between IVH and RBC transfusion was due to the transfusions or the underlying disorders.

## Conclusion

The experimental results of this paper revealed a significant association between IVH and RBC transfusion. Based on these findings, it is suggested to design new restricted guidelines for RBC transfusions in preterm infants. Certainly, further investigation is needed to specify whether RBC transfusion plays any causative role in IVH development or its extension. If any such roles are detected, some new guidelines should be developed to either prevent or decrease the severity of IVH and as a result, to potentially improve neurodevelopmental outcomes in infants.

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## Conflicts of interest

The authors declare that there was no conflict of interest in this study.

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