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RESEARCH

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# The impact of red blood cell transfusion in preterm neonates on germinal matrix hemorrhage: incidence and grade with correlation to outcome

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## Abstract

**Background** Germinal matrix hemorrhage affects 20 to 25% of infants with a low birth weight (less than 1500 g). About one-tenth of them progress to intra-parenchymal hemorrhage, usually during the first days after birth. Several studies have found a correlation between packed RBC transfusions and a higher frequency of severe germinal matrix hemorrhage in neonatal intensive care units.

Transcranial ultrasound is a safe, noninvasive modality that can be used repeatedly in the neonates with ability to detect different grades of germinal matrix hemorrhage.

**Objective** Was to evaluate the impact of packed RBC transfusion on the incidence and grade of germinal matrix hemorrhage, as evaluated by transcranial Doppler, and correlation to outcome.

**Methods** This prospective observational study included one hundred preterm infants admitted to NICU, suffering from GM hemorrhage throughout 9 months duration. Bedside transcranial ultrasound was done for all the patients with a correlation of the grade of hemorrhage to the onset of blood transfusion, different clinical parameters, and the outcome.

**Results** Statistical analysis showed a significant relation between the age of the first PRBC transfusion and GM hemorrhage grade. A positive relation was found between total amounts of PRBC transfusion and increasing grade of GM hemorrhage. A negative relation was found between GM hge grades and Apgar scores. GM hge patients who received PRBC transfusion had lower mean birth weight, lower gestational age, and longer duration of hospital stay than those who have not received PRBC transfusion.

**Conclusion** Close monitoring of preterm neonates receiving packed RBCs, by transcranial ultrasound, as early as possible, is mandatory to early detect GM hge and limit subsequent morbidities.

**Keywords** Transcranial ultrasound, Preterm, Germinal matrix hemorrhage, Packed RBC blood transfusion

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## Background

The most common and serious neurologic injuries in preterm infants are germinal matrix hemorrhage (GMH) and intraventricular hemorrhage (IVH). Because a premature infant's brain lacks the ability to autoregulate cerebral blood pressure, changes in cerebral blood pressure and flow can rupture primitive germinal matrix arteries

or cause infarction of the metabolically active germinal matrix. Damage to the periventricular white matter can lead to serious neurologic consequences such as cerebral palsy, mental retardation, and seizures. Injury to the germinal matrix is associated with a high rate of death and morbidity [1].

It is almost always during the first days after birth, with 95% evident by 72 h and 99% by 5 days [2].

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 [3].

Particularly, in the germinal matrix, the association between IVH and transfusion could be due to damage and volutrauma to the weak blood vessels [4].

It has been reported that up to 90% of extremely low birth weight infants and 58% of preterm infants less than 32 weeks of gestational age receive red, mainly due to iatrogenic phlebotomy losses and ventilatory requirements [5].

Therefore, infants with low birth weights are more likely to receive frequent transfusions. In this regard, some of the recent research conducted on 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) [3].

For small and ill infants with severe anemia or active bleeding, a transfusion of packed RBCs can be life-saving. However, the PRBCs lack nitric oxide synthase, quickly depleted, which is crucial for small vessel relaxation. Blood flow across sections of the microvasculature depends on this relaxation; thus, germinal matrix hemorrhage progresses due to hemodynamic changes in the growing brain's microcirculation. So, the hazards associated with transfusions must be evaluated against the possible benefits each time used [6].

Transcranial ultrasonography is the principal modality for detecting and monitoring germinal matrix hemorrhage (GMH) and intraventricular hemorrhage (IVH) in neonates. Because ultrasonography is portable, it can be used easily bedside at the neonatal critical care unit (NICU). It should be performed between the 7 and 14 days of life, and more screenings are recommended on a more regular basis in certain conditions [7].

GM-IVH is usually asymptomatic and is detected by cranial ultrasound in 25–50% of premature newborns weighing less than 1500 g and born before 32 weeks of pregnancy [8]. Hence, the suggested regimen for transcranial ultrasound in preterm infants with a gestational age below 28 weeks or low birth weight is to be performed on days 1, 3, 7, 14, 21, and 28, and then every other week until term-equivalent age [9].

## Methods

### Study population

This observational descriptive study included one hundred preterm neonates ≤ 34 weeks gestation, and weight less than 2500 g, with GM hge, admitted to the NICU of kasralainy hospital over a period of 9 months duration from February to October 2018.

Both sexes were included in our study.

We excluded other causes of bleeding as coagulation abnormalities and thrombocytopenia.

All patients were examined bedside at the NICU. Verbal consent was obtained from their legal guardians.

The study was approved by the ethical committee of the Faculty of Medicine at Cairo University on 17/4/2018.

### Clinical examination

History taking focusing on gestational age, sex, mode of delivery, birth weight, maternal clinical history, maternal drug intake, and Apgar score at 1, 5, and 10 min was included and diagnosis on admission.

Other data collected included:

- History of anemia and its severity, history, and signs suggestive of GMH/IVH (seizures, apnea, and bulging anterior fontanel) and length of hospital stay.
- PRBC transfusion data, including indication, number of transfusions, total amount of blood transfused, hemoglobin value, and hematocrit value before and after transfusion age at blood transfusion.
- Germinal matrix hemorrhage/intra-ventricular hemorrhage data, regarding onset in relation to blood transfusion, grading of GM hge.
- Outcome data, whether discharge, death, or discharge with sequel.

### Laboratory investigations

Complete blood picture including the hematocrit value and bleeding profile.

### Imaging

The examination was done bedside at the NICU using the Toshiba Aplio 500 ultrasound machine, using curvilinear and linear probes over the course of the study period, with the anterior fontanel serving as the primary acoustic window.

Every patient was evaluated for the presence or absence of germinal matrix hemorrhage. Grading of the GMH/IVH was assigned based on the earliest transcranial ultrasound. The ventriculomegaly that occurs days to weeks following GMH/IVH was not considered a grade III IVH if the original IVH grade was grade I or II as it represents post-hemorrhagic sequelae. For simplification of data presentation, we assigned the higher grade of GMH/IVH in cases of bilateral different grades of hemorrhage. Grading was done according to the commonly used system where:

- Grade 1: limited to subependymal region/germinal matrix, seen in the caudothalamic groove.
- Grade 2: Extension non-dilated ventricles and typically filling less than half of the volume of the ventricle
- Grade 3: Extension into dilated ventricles
- Grade 4: Grade 3 plus parenchymal hemorrhage

### Statistical analysis

Patients were allocated into two groups: those who had GMH/IVH with a history of PRBC transfusion and the other group were the preterm neonates who had GMH/IVH but with no history of blood transfusion. For the first group, the duration between the first transfusion and the GMH/IVH was determined and correlated to its grade. Also, the total number of transfusions was correlated to the grade of hemorrhage.

Data were tabulated and subjected to computer-assisted statistical analysis using SPSS package version 14.0. Nominal data were described as frequency and percentage and compared using Chi-square tests. Numerical data were described as mean and standard deviation and compared using a *t*-test. Non-parametric data were described as median and range. Numerical associations were tested using Pearson's correlations and potential risk factors were tested using sensitivity, specificity, and odds ratio. *P* values less than 0.05 were considered significant.

**Table 1** Gender distribution among cases

| | Frequency | Percent |
|---|---|---|
| Sex | | |
| Female | 67 | 67% |
| Male | 33 | 33% |

## Results

This prospective observational study included 100 patients, delivered between 27 and 35 weeks gestational age, recruited over a period of 9 months from the neonatal intensive care unit, and presented with germinal matrix hemorrhage. Fifty-eight percent of the patients, presenting with GMH/IVH, had PRBC transfusion while 42% of them had no transfusion. The transfusion was once in 40% of the cases and during the first week.

Sixty-seven percent were females and 33% were males (Table 1).

The mean gestational age for the cases was 30.91 + 2.23 weeks. Their mean body weight was 1473.20 + 436.149 g (Table 2).

Cesarean section was performed in 71% of the mothers of the cases and only 29% had a normal vaginal delivery.

Fifty-four percent of the mothers had no history of illness, 18% had a history of pre-eclampsia/PIH, 10% had a history of premature rupture of membranes/PROM, 5% had a history of antepartum hemorrhage, 3% had a

**Table 2** Descriptive clinical data of cases

| Descriptive statistics | Mean | SD ± |
|---|---|---|
| Gestational age (weeks) | 30.91 | 2.230 |
| Body weight (grams) | 1473.20 | 436.149 |
| Apgar score at 1 min | 2.69 | 1.650 |
| Apgar score at 5 min | 5.49 | 1.703 |
| Apgar score at 10 min | 7.55 | 1.710 |
| Duration of hospital stay (days) | 27.71 | 14.740 |

**Table 3** Maternal descriptive data of patients ($n = 100$)

| | Frequency | Percent |
|---|---|---|
| Mode of delivery | | |
| CS | 71 | 71% |
| VD | 29 | 29% |
| Maternal history | | |
| No | 54 | 54% |
| Antepartum Hge | 5 | 5% |
| DM | 3 | 3% |
| PIH | 18 | 18% |
| PROM | 10 | 10% |
| Others | 10 | 10% |
| Maternal drug intake | | |
| No | 82 | 82% |
| Aldomet | 9 | 9% |
| Aldomet/dexa | 1 | 1% |
| Antibiotics | 1 | 1% |
| Dexa/antibiotics | 7 | 7% |

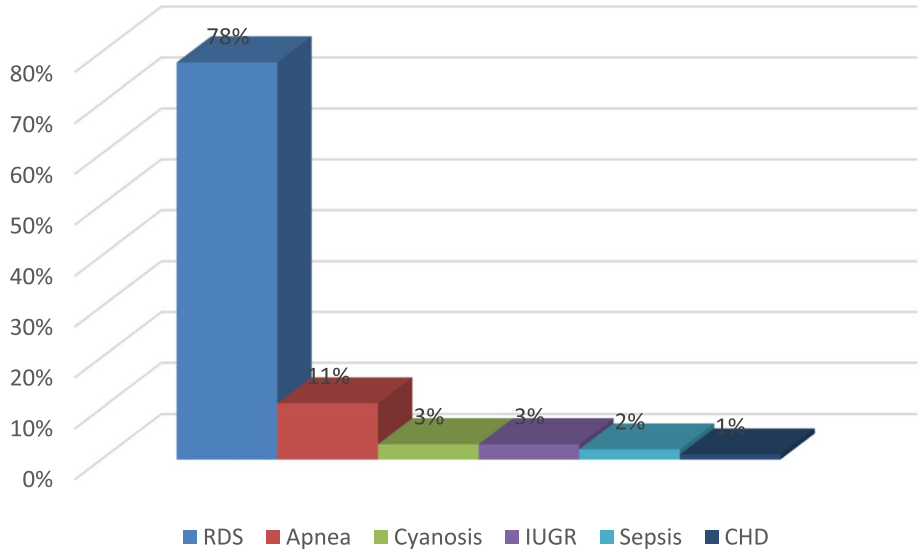


**Fig. 1** Bar graph representing the provisional diagnoses on admission

**Table 4** Clinical presentation on admission ($n=100$)

| | Frequency | Percent |
|---|---|---|
| Diagnosis on admission | | |
| RDS | 78 | 78% |
| Apnea | 11 | 11% |
| Cyanosis | 3 | 3% |
| IUGR | 3 | 3% |
| Sepsis | 2 | 2% |

**Table 5** Presence of anemia and its severity ($n=100$)

| | Frequency | Percent |
|---|---|---|
| **History of anemia** | | |
| **No** | 43 | 43% |
| **Yes** | 57 | 57% |
| **Severity of anemia according to the hemoglobin level** | | |
| **No** | 43 | 43% |
| **Mild** | 1 | 1% |
| **Moderate** | 30 | 30% |
| **Severe** | 26 | 26% |

history of diabetes mellitus/DM, and 10% had a history of other diseases (Table 3).

Seventy-eight percent of the cases were presented with respiratory distress (RDS) on admission, 11% of the cases were diagnosed as having apnea, and one case had sepsis. Fifty-seven percent of the cases had a history of anemia (Fig. 1).

**Table 6** Clinical findings suggestive of GM/IVH ($n=100$)

| History of IVH | Frequency | Percent |
|---|---|---|
| **Seizures** | | |
| **No** | 25 | 25% |
| **Yes** | 75 | 75% |
| **Apnea** | | |
| **No** | 61 | 61% |
| **Yes** | 39 | 39% |
| **Bulging AF** | | |
| **No** | 29 | 29% |
| **Yes** | 71 | 71% |

One of them was mild, 30 cases were moderate, and 26 cases were severe (Tables 4 and 5).

The distribution of the different clinical findings suggestive of GM/IVH, including seizures, apnea, or bulging anterior fontanelle, among our study group patients, is represented in Table 6.

With the detailed descriptive data of PRBC transfusion therapy among studied cases, regarding the indication and frequency is represented in Table 7.

In our study, 30% of the patients developed GM hemorrhage within 4 days of receiving their first PRBC transfusion while 13% of them developed GM hemorrhage within 5–20 days after receiving their first PRBC transfusion (Table 8).

Regarding the GM hemorrhage grade, 17% were grade 1, 47% were grade 2, and 36% were grade 3 (Table 9) (Figs. 2, 3, 4, and 5).

**Table 7** Descriptive data of PRBC transfusion therapy among studied cases ($n = 100$)

| Descriptive data | Frequency | Percent |
|---|---|---|
| **Packed RBCs** | | |
| **Transfusion** | 57 | 57% |
| **No transfusion** | 43 | 43% |
| **Indications** | | |
| **Anemia** | 58 | 58% |
| **Frequency of transfusion** | | |
| **1 time** | 40 | 40% |
| **2 times** | 14 | 14% |
| **3 times** | 2 | 2% |
| **4 times** | 2 | 2% |
| **Age on first packed RBCs transfusion** | | |
| **During the 1st week** | 41 | 41% |
| **During the 2nd week** | 12 | 12% |
| **During the 3rd week** | 4 | 4% |
| **After 3 weeks** | 1 | 1% |

**Table 8** Onset of GM/IVH in relation to the first PRBC transfusion ($n = 100$)

| Descriptive statistics | Frequency | Percent |
|---|---|---|
| **Onset of GM hemorrhage in relation to age at first PRBC transfusion** | | |
| **No transfusion** | 42 | 42% |
| **After 1 day** | 7 | 7% |
| **After 2 days** | 13 | 13% |
| **After 3 days** | 10 | 10% |
| **After 4 days** | 5 | 5% |
| **After 5 days** | 3 | 3% |
| **After 7 days** | 2 | 2% |
| **After 8 days** | 1 | 1% |
| **After 14 days** | 1 | 1% |
| **After 19 days** | 1 | 1% |
| **IVH before PRBC** | 15 | 15% |

**Table 9** Grading of the germinal matrix hemorrhage among studied cases

| Descriptive statistics | Frequency | Percent |
|---|---|---|
| **Grading of GMH** | | |
| **Grade 1** | 17 | 17% |
| **Grade 2** | 47 | 47% |
| **Grade 3** | 36 | 36% |

Among the non-transfused GM hemorrhage patients, grade II was present in 40% of the cases, while grade III was present in 43% of the cases. On the other hand,

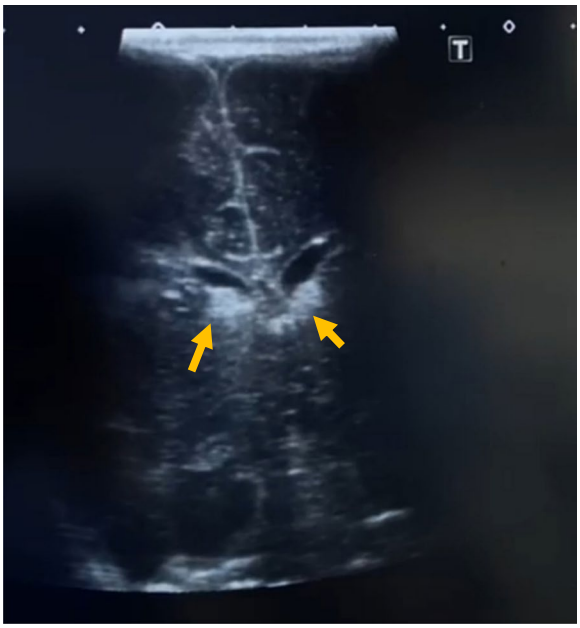

**Fig. 2** Transcranial ultrasound showing bilateral grade I GMH, yellow arrows

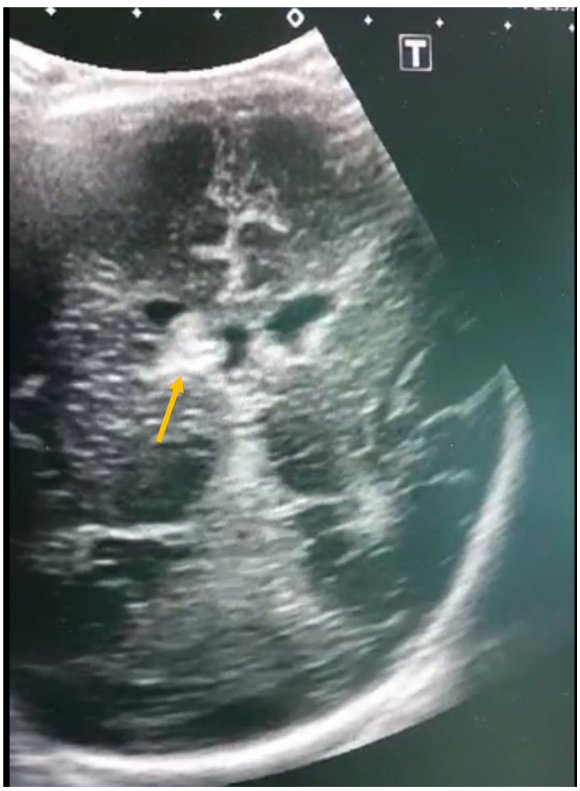

**Fig. 3** Transcranial ultrasound showing right-sided grade II GMH, yellow arrow

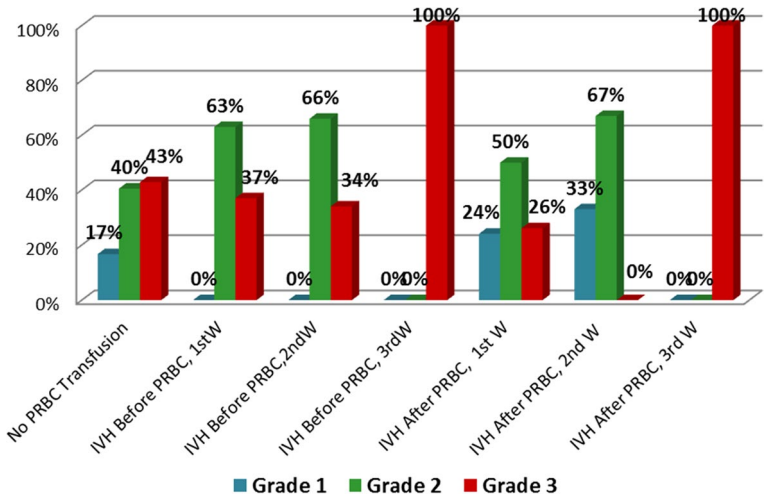


**Fig. 4** Correlation of IVH grade in relation to age on first PRBC transfusion

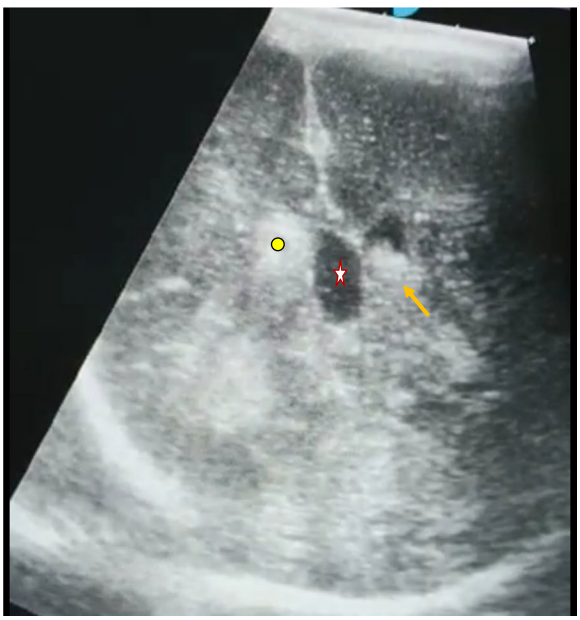

**Fig. 5** Transcranial ultrasound showing right-sided grade III GMH/IVH (yellow circle) and left-sided grade II GMH/IVH (yellow arrow) with dilated third ventricle (red asterisk)

among the PRBC transfused GM hemorrhage patients, grade II IVH was present in 52% of the cases and grade III was present in 31% of the cases.

Regarding the outcome of the GM hemorrhage, 27% of the cases died, 53% survived, and 20% survived but suffered from complications such as hypoxic-ischemic encephalopathy, hydrocephalic changes, and periventricular leukomalacia. No statistically significant association was found between the grade of GM hemorrhage and the outcome of the patients ($P > 0.05$) (Table 10).

No statistically significant correlation was found between the grade of GM hge and any of the transfusion data among the study group except for a statistically significant correlation found between the GM hemorrhage grade and the age at first PRBC transfusion ($P = 0.026$) (Table 11). However, on undergoing Spearmen's bivariate ranked correlation analysis between the GM hemorrhage groups and the various transfusion data, a statistically significant positive association was found between increased grading of GM hge and the increased total amount of PRBC transfused among the study group ($P = 0.04$) (Tables 12).

**Table 10** Correlation between the outcome and the grade of the GM hemorrhage among the study group

| Items for correlation | Categories | | Grading of IVH | | | *P*-value |
|---|---|---|---|---|---|---|
| | | | Grade 1 | Grade 2 | Grade 3 | |
| **Outcome** | **Died** | **No** | 5 | 14 | 8 | 0.722 NS |
| | | **%** | 29% | 30% | 22% | |
| | **Survived** | **No** | 9 | 23 | 21 | |
| | | **%** | 53% | 49% | 58% | |
| | **Survived with sequelae** | **No** | 3 | 10 | 7 | |
| | | **%** | 18% | 21% | 20% | |

**Table 11** Relation of GM hemorrhage grade to the transfusion data among the study group ($n=100$)

| Items | Categories | | Grading of IVH | | | *P*-value |
|---|---|---|---|---|---|---|
| | | | 1 ($n=17$) | 2 ($n=47$) | 3 ($n=36$) | |
| **History of anemia** | **No** | **No** | 8 | 17 | 18 | 0.421 |
| | | **%** | 19% | 40% | 42% | |
| | **Yes** | **No** | 9 | 30 | 18 | |
| | | **%** | 16% | 53% | 32% | |
| **PRBC transfusion** | **No** | **No** | 7 | 17 | 18 | 0.448 |
| | | **%** | 17% | 40% | 43% | |
| | **Yes** | **No** | 10 | 30 | 18 | |
| | | **%** | 17% | 52% | 31% | |
| **Frequency of PRBC transfusion** | **No** | **No** | 7 | 17 | 18 | 0.659 |
| | | **%** | 17% | 40% | 43% | |
| | **1 time** | **No** | 6 | 21 | 13 | |
| | | **%** | 15% | 53% | 33% | |
| | **2 times** | **No** | 3 | 6 | 5 | |
| | | **%** | 21% | 43% | 36% | |
| | **3 times** | **No** | 1 | 1 | 0 | |
| | | **%** | 50% | 50% | 0% | |
| | **4 times** | **No** | 0 | 2 | 0 | |
| | | **%** | 0% | 100% | 0% | |
| **Age at first PRBC transfusion** | **No PRBC transfusion** | | | | | 0.026* |
| | | **No** | 7 | 17 | 18 | |
| | | **%** | 17% | 40% | 43% | |
| | **IVH before PRBC transfusion** | | | | | |
| | **1st W** | **No** | 0 | 5 | 3 | |
| | | **%** | 0% | 63% | 37% | |
| | **2nd W** | **No** | 0 | 4 | 2 | |
| | | **%** | 0% | 66% | 34% | |
| | **3rd W** | **No** | 0 | 0 | 1 | |
| | | **%** | 0% | 0% | 100% | |
| | **IVH After PRBC transfusion** | | | | | |
| | **1st W** | **No** | 9 | 19 | 10 | |
| | | **%** | 24% | 50% | 26% | |
| | **2nd W** | **No** | 1 | 2 | 0 | |
| | | **%** | 33% | 67% | 0% | |
| | **3rd W** | **No** | 0 | 0 | 2 | |
| | | **%** | 0% | 0% | 100% | |

* Statistically significant *P*-value ($P<0.05$)

**Table 12** Bivariate analysis of GM hemorrhage grade in relation to total amounts of PRBC transfusion

| Spearman's bivariate ranked correlation | Correlation coefficient | *P*-value |
|---|---|---|
| Grading of GM hge vs total amounts of PRBCs | 0.269 | 0.041* |

* Statistically significant *P*-value ($P<0.05$)

There was no statistically significant association between the transfusion status of the cases and their outcome. In the current study, the patients who received PRBC transfusion had significantly lower mean gestational age ($P<0.001$), lower mean birth weight ($P=0.01$), and significantly longer duration of NICU stay ($P=0.001$) than those who never received a PRBC transfusion.

There was no statistically significant relation between the hemoglobin (Hb) and hematocrit (HCT) values on admission, and different GM hemorrhage grades,

**Table 13** Relation of GM hemorrhage grade to the laboratory data among the study group

| ANOVA test | IVHG | *n* | Mean | SD | Mini | Max | 95% confidence interval | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower bound | Upper bound | |
| **Hb. value on admission (*n* = 100)** | **1** | 17 | 11.5 | 3.8 | 5.9 | 19.4 | 9.5 | 13.4 | 0.233 |
| | **2** | 47 | 10.9 | 4.2 | 3.0 | 21.0 | 9.7 | 12.1 | |
| | **3** | 36 | 12.4 | 3.7 | 7.5 | 20.0 | 11.2 | 13.7 | |
| **HCT on admission (*n* = 100)** | **1** | 17 | 32.5 | 9.7 | 16.5 | 51.0 | 27.5 | 37.4 | 0.051 |
| | **2** | 47 | 32.6 | 12.8 | 10.0 | 59.0 | 28.9 | 36.4 | |
| | **3** | 36 | 38.8 | 12.2 | 22.2 | 61.2 | 34.7 | 42.9 | |

* Statistically significant *P*-value ($P < 0.05$)

**Table 14** Relation of GM/IVH grade in relation to birth weight of the patients ($n = 100$)

| Descriptive data & one way ANOVA | | Birth weight | | |
|---|---|---|---|---|
| | | Grade 1 | Grade 2 | Grade 3 |
| **N** | | 17 | 47 | 36 |
| **Mean** | | 1320.6 | 1418.7 | 1616.4 |
| **SD** | | 508.19 | 391.73 | 426.55 |
| **Min** | | 900 | 900 | 825 |
| **Max** | | 2400 | 2200 | 2320 |
| **95% confidence interval for mean** | **Lower bound** | 1059.3 | 1303.7 | 1472.1 |
| | **Upper bound** | 1581.9 | 1533.7 | 1760.7 |
| **Df** | | 97 | | |
| **F** | | 3.518 | | |
| ***P*-value** | | 0.034* | | |

* Statistically significant *P*-value ($P < 0.05$)

between the cases that received PRBC therapy and those who did not receive it. No statistically significant association was found between GM hemorrhage grade and gestational age among the study group (Tables 13 and 14).

Mean Apgar scores at 1 min and 10 min were lowest among IVH grade 3 cases ($P = 0.007$, $P < 0.001$) respectively while the mean Apgar score at 5 min was lowest among IVH grade 3 although not reaching statistical significance ($P = 0.066$) (Table 15).

On undergoing Spearmen bivariate correlation studies between GM/IVH grades and Apgar scores 1, 5, and 10 min, lower Apgar scores were significantly associated with increased grades of IVH ($P = 0.044$, $P = 0.033$, $P = 0.009$), respectively (Table 16).

Among IVH grade 1 cases, mean Apgar score at 5 min was lowest among cases who did not receive PRBC therapy ($P = 0.03$) while among IVH grade III cases, the mean Apgar score at 1 min was lowest among cases who received PRBC transfusion ($P = 0.01$) with a statistical significance (Table 17).

## Discussion

The germinal matrix is particularly prone to hemorrhage. This fragility is attributed, at least in part, to its extensive vascularity, which is naturally weak due to a lack of pericytes to support the arterial structural integrity [10].

**Table 15** IVH grade in relation to Apgar scores at 1, 5, and 10 min, using one-way ANOVA test ($n = 100$)

| ANOVA test | IVHG | *n* | Mean | SD | Min | Max | 95% confidence interval | | df | F | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower bound | Upper bound | | | |
| **Apgar score at 1 min** | **1** | 17 | 2.53 | 1.81 | 0 | 5 | 1.60 | 3.46 | 97 | 5.30 | 0.007* |
| | **2** | 47 | 3.21 | 1.25 | 0 | 6 | 2.85 | 3.58 | | | |
| | **3** | 36 | 2.08 | 1.84 | 0 | 7 | 1.46 | 2.71 | | | |
| **Apgar score at 5 min** | **1** | 17 | 5.35 | 2.42 | 0 | 9 | 4.11 | 6.60 | 97 | 2.80 | 0.066 |
| | **2** | 47 | 5.89 | 1.40 | 3 | 8 | 5.48 | 6.31 | | | |
| | **3** | 36 | 5.03 | 1.58 | 3 | 8 | 4.49 | 5.56 | | | |
| **Apgar score at 10 min** | **1** | 15 | 6.93 | 2.19 | 3 | 9 | 5.72 | 8.14 | 90 | 10.31 | < 0.001* |
| | **2** | 42 | 8.36 | 1.38 | 5 | 10 | 7.93 | 8.79 | | | |
| | **3** | 36 | 6.86 | 1.46 | 1 | 9 | 6.37 | 7.35 | | | |

* Statistically significant *P*-value ($P < 0.05$)

**Table 16** Bivariate analysis of GM/IVH grade in relation to Apgar scores at 1, 5, and 10 min using Spearman's bivariate ranked correlation ($n=100$)

| Spearman's bivariate ranked correlation | Correlation coefficient | *P*-value |
|---|---|---|
| Grading of IVH vs Apgar score at 1 min | −0.202 | 0.044* |
| Grading of IVH vs Apgar score at 5 min | −0.213 | 0.033* |
| Grading of IVH vs Apgar score at 10 min | −0.269 | 0.009* |

* Statistically significant *P*-value ($P<0.05$)

In neonatal intensive care medicine, the transfusion of PRBCs is vital. In some cases, it can be lifesaving. Each transfusion, however, comes with its own set of risk and benefits. Some transfusion complications have been well identified, while others have been less so, and yet others may not be recognized as transfusion-related events at all, but rather as a clinical deterioration in the complex intensive care course [2].

The aim of this prospective observational study was to evaluate the impact of packed RBC transfusion on the incidence and severity of the germinal matrix hemorrhage/intra-ventricular hemorrhage. One hundred preterm neonates delivered between 27 and 35 weeks gestational age hospitalized at neonatal intensive care unit and presented with GM/IVH were examined over a period of 9 months.

Regarding demographic data and birth weight, we found that the mean gestational age of our patients was 30.91 + 2.23 weeks with the mean body weight 1473.20 + 436.15 g. Sixty-seven percent were females and 33% were males. This goes in line with the study conducted by Bordbar and Farjadnia, where 115 infants with GM/IVH and 120 infants without GM/IVH were evaluated. The neonates with and without GM/IVH had a mean age of 29.50 ± 2.9 weeks and 30.74 ± 1.9 weeks, respectively ($P=0.1$). Furthermore, neonates with GM/IVH had a lower mean weight than those without: 1978 ± 644 g GM/IVH vs 2188 ± 864 g, respectively ($P=0.2$) [11].

Regarding the peri-natal history, cesarean section was performed in the majority of our cases (71%) versus (29%) had a normal vaginal delivery); these findings are contradictory to the studies conducted by Riskin et al. and Humberg et al. who found that GM/IVH was more prevalent in the preterm neonates born by vaginal delivery, than those with planned CS [12, 13].

**Table 17** Relation of GM/IVH grade and Apgar score at 1, 5, and 10 min among the cases that received packed RBCs and those who have not received PRBC ($n=100$)

| Independent samples test | | | | | | *t*-test for equality of means | | | |
|---|---|---|---|---|---|---|---|---|---|
| IVH grade | Time of Apgar score | PRBCs trans | *n* | Mean | SD | df | *P*-value | 95% confidence interval of the difference | |
| | | | | | | | | Lower | Upper |
| **Grade 1** | **Apgar score at 1 min** | **No PRBCs** | 7 | 1.86 | 2.41 | 15 | 0.21 | −3.00 | 0.71 |
| | | **PRBCs** | 10 | 3.00 | 1.15 | | | | |
| | **Apgar score at 5 min** | **No PRBCs** | 7 | 3.86 | 2.91 | 15 | 0.03* | −4.77 | −0.32 |
| | | **PRBCs** | 10 | 6.40 | 1.35 | | | | |
| | **Apgar score at 10 min** | **No PRBCs** | 7 | 6.14 | 2.19 | 13 | 0.20 | −3.86 | 0.89 |
| | | **PRBCs** | 8 | 7.63 | 2.07 | | | | |
| **Grade 2** | **Apgar score at 1 min** | **No PRBCs** | 17 | 3.59 | 1.00 | 45 | 0.12 | −0.16 | 1.34 |
| | | **PRBCs** | 30 | 3.00 | 1.34 | | | | |
| | **Apgar score at 5 min** | **No PRBCs** | 17 | 6.29 | 1.40 | 45 | 0.14 | −0.22 | 1.47 |
| | | **PRBCs** | 30 | 5.67 | 1.37 | | | | |
| | **Apgar score at 10 min** | **No PRBCs** | 16 | 8.38 | 1.09 | 40 | 0.95 | −0.87 | 0.92 |
| | | **PRBCs** | 26 | 8.35 | 1.55 | | | | |
| **Grade 3** | **Apgar score at 1 min** | **No PRBCs** | 18 | 2.83 | 1.72 | 34 | 0.01* | 0.35 | 2.65 |
| | | **PRBCs** | 18 | 1.33 | 1.68 | | | | |
| | **Apgar score at 5 min** | **No PRBCs** | 18 | 5.33 | 1.71 | 34 | 0.25 | −0.45 | 1.67 |
| | | **PRBCs** | 18 | 4.72 | 1.41 | | | | |
| | **Apgar score at 10 min** | **No PRBCs** | 18 | 6.89 | 1.75 | 34 | 0.91 | −0.95 | 1.06 |
| | | **PRBCs** | 18 | 6.83 | 1.15 | | | | |

* Statistically significant *P*-value ($P<0.05$)

In our study, 54% of the mothers had no history of illness, 18% had a history of PIH, 10% had a history of PROM, 5% had a history of antepartum hemorrhage, 3% had a history of DM, and 10% had a history of other diseases. This is in accordance with the study results conducted by Bordbar and Farjadnia, and Linder et al. who found that the rate of GM/IVH is not related to maternal and perinatal factors such as preeclampsia, premature rupture of membranes, and chorioamnionitis [11, 14].

Regarding the clinical presentation, most of our cases (78%) were presenting with RDS, 11% of the cases were admitted by apnea, and two cases (2%) had sepsis. This was supported by Khanafer-Larocque et al.'s study which revealed that neonates in the severe GM/IVH group had more RDS and were more likely to be ventilated and to receive inhaled nitric oxide during the first 72 h of age [15].

Fifty-seven percent of our cases had a history of anemia, 1% was mild, 30% were moderate, and 26% were severe. In agreement, Rocha et al. reported a significant association between the presence of anemia on admission among their low-birth-weight neonates and high incidence of severe intra-periventricular hemorrhage [16].

On clinical examination, 75% of the cases had seizures, 39% suffered from apnea, and 71% had a bulging AF. The presence of seizures and pallor was reported to be significantly associated with GM/IVH according to a study by Egwu et al. [17].

Regarding the packed RBC transfusion, in our study, the percentage of the cases that needed packed RBC transfusion was 58% and was indicated for anemia in all these patients. Forty percent required one transfusion, 14% required twice, and 2% required either 3 or 4 transfusions. Forty-one percent of cases required transfusion during the 1st week, 12% during the 2nd week, 4% during the 3rd week, and 1% after 3rd week. The total amount of PRBC transfusion was 24.05 cc ± 7.946 cc, with a median of 20 cc. The higher percentage was noted in the first week and may be attributed to frequent blood sampling done early in life.

This is rather similar to the study done by Lee et al. who reported that infants with birth weight < 1000 g received 3.1 ± 2.2 transfusions, with a first transfusion at 22.1 ± 16.6 days. However, infants with birth weight 1000 to 1500 g received only 1.5 ± 0.8 transfusions, with a first transfusion at 32.6 ± 15.2 days. PRBC transfusions were administered significantly earlier ($P = 0.001$) and more frequently ($P < 0.001$) with smaller birth weights. Preterm infants in the NICU tend to receive more PRBC transfusions [18].

The hemoglobin level in our study group ranged from 3.00 to 20.50 g/dL with a mean hemoglobin of 10.83 + 3.58, while on discharge, it ranged from 9.90 to 17.60 with a mean of 13.08 + 1.77. For the hematocrit value on admission, it ranged from 10 to 61.20 g/dL with a mean hematocrit value of 33.08 + 11.77 while on discharge, it ranged from 30 to 55 g/dL with a mean 37.88 + 4.77. This was in accordance with the study conducted by Verhagen et al., who reported that most cases of severe GM/IVH occurred on the first day of life, corresponding with a sharp drop in hematocrit value between days 1 and 2. The low hematocrit value on the first day of life in infants with severe GM/IVH can be due to bleeding; however, a low hematocrit value can also accelerate cerebral blood flow and contribute to further bleeding. It remains uncertain whether low hematocrit value is the cause of hemorrhage or occurs secondary to it [19].

When we correlated the onset of GM/IVH with the date of the first PRBC transfusion received, 30% of the patients developed GM/IVH within 4 days of receiving their first PRBC transfusion while 13% developed GM/IVH within 5–20 days of receiving their first PRBC transfusion. Fifteen percent of the patients developed GM/IVH before PRBC transfusion. Forty-seven percent of the GM/IVH patients understudy were grade II while 36% were grade III and only 17% were grade I (Fig. 4).

Similarly, in the study by Sarkar et al., 10.5% of the very low birth weight infants surviving beyond 3 days of age had severe GH/IVH during the first 7 to 10 days of life [20].

Regarding the correlation of the GM/IVH grade to the patient's outcome, 27% of our preterm neonates with GM/IVH died, while 53% survived and 20% survived but suffered from complications. The mortalities were high among grade II GM/IVH patients (52%) followed by grade III GM/IVH patients (30%), and lastly grade I GM/IVH patients (19%) with no statistically significant association between the grade of GM/IVH and the poor outcome of the patients.

This goes in line with the study conducted by Brouwer et al., who found that grade I GM/IVH had the most minor neuro-developmental complications [21].

Our results are also in concordance with Radic et al., who found that all preterm (≤ 30 completed weeks) patients included in the study by grades 2, 3, and 4 GM/IVH were significantly associated with an increased overall mortality, primarily in the neonatal period, and the risk increased with increasing grade of GM/IVH. Grade 4 GM/IVH was significantly associated with an increased risk of disability ($P < 0.001$) [22].

In our study, no statistically significant correlation was found between the grade of GM/IVH and any of the transfusion data among the study group except for a statistically significant correlation found between the GM/IVH grade and the age at first PRBC transfusion.

This was supported by the results of the study conducted by Christensen that reported an association between "early" RBC transfusions and the subsequent occurrence of intraventricular hemorrhage, although the underlying pathophysiological mechanism of this association was not clarified [2].

Similarly, Christensen et al. observed that eliminating or reducing RBC transfusions by drawing all baseline laboratory blood tests from fetal blood in the placenta, and drawing none from the neonate, resulted in less GM/IVH [2].

However, in our study, no similar statistically significant association was observed between the status of PRBC transfusion therapy and the grade of GM/IVH ($P > 0.05$).

Similarly, Lee et al. retrospectively investigated the relationship between PRBC transfusion and short-term outcomes including GM/IVH. Forty patients had GM/IVH. In 30 patients diagnosed with GM/IVH in the transfusion group, 14 patients had been diagnosed after PRBC transfusions, and 2 patients had received PRBC transfusions within 1 week of the preceding diagnosis [18].

In our study, a statistically significant positive association was found between increased grading of GM/IVH and increased total amounts of PRBC transfused among the study group ($r = 0.269$, $P = 0.04$). A similar finding was reported by Lien et al. and Baer et al. who reported that cases who received more RBCT were at higher risk for developing a severe GH/IVH and suggested other relevant variables associated with increased GM/IVH extension including transfusion amount of RBCs [6, 23].

In disagreement with our results, a more extensive multicenter study by Kirpalani et al. showed no association between GM/IVH grade and transfusion guidelines used [24].

When correlating the GM/IVH with the mean Hb and HCT values on admission, we did not find a significant difference among the different GM/IVH grades among the cases that received packed RBCs and those who did not receive PRBC transfusion ($P > 0.05$). This is in agreement with Baer et al., who compared the blood hemoglobin (Hb) concentrations during the first 72 h that "triggered" the order for the first PRBC transfusion in each of the patients and controls. The controls had their first RBC transfusion after a Hb level of 11.1 ± 1.3 g/dL, while those who developed severe GM/IVH received their first RBC transfusion after a Hb level of 10.7 ± 1.6 g/dL ($P = 0.22$) with these results being very close to our results [6].

Also, in harmony with our study findings, Valieva et al. reported that there was no association between both HCT level at birth and HCT level immediately before the first transfusion and the severity of GM/IVH [25].

In our study, no statistically significant association was found between GM/IVH grade and gestational age among the study group ($P > 0.05$). In contrast, Swai et al. found that babies delivered before 28 weeks of pregnancy are more likely to suffer GM/IVH since the germinal matrix is entirely unsupported at this time. Furthermore, spontaneous involution of the germinal matrix usually occurs after 28 weeks of pregnancy, when the risk of hemorrhage is significantly reduced [26]. This controversy could be explained that the mean gestational age for our patients is 30.91 weeks ± 2.23, while in the other studies, the gestational age of the patients was less than 28 weeks.

In our study, an increased grade of GM/IVH was associated with statistically significant higher birth weight among the study group ($P = 0.034$). Egwu et al. did not find any association between the birth weight of neonates and grade of GM/IVH. This observation may be related to the few number of neonates with very low birth weights in both our and their study [17].

In our study, at 1, 5, and 10 min, lower Apgar scores were significantly associated with increased grades of GM/IVH ($P = 0.004$, $P = 0.033$, and $P = 0.009$, respectively).

This is in accordance with the study of Koksal et al. who reported that the prevalence of GM/IVH in very low birth weight neonates was highly associated with a low 5 min Apgar score at birth. Infants with lower Apgar scores were more likely to be subjected to procedures such as positive pressure breathing, endotracheal intubation, and chest compression, which could have resulted in a wide range of cerebral pressure fluctuations, increasing their risk of GM/IVH [27].

In our study, among GM/IVH grade 1 cases, the mean Apgar score at 5 min was lowest among cases who did not receive PRBC therapy ($P = 0.03$) while among GM/IVH grade III cases, the mean Apgar score at 1 min was significantly lower among cases who received PRBC transfusion ($P = 0.01$).

In our study, there were no statistically significant associations found between the transfusion data and any of the maternal data among the study group ($P > 0.05$). Similarly, Shanmugha Priya reported that maternal medical complications, obstetric complications, mode of delivery, multiple births, and antenatal steroid administration in mothers were not found to influence the need for transfusions statistically in their babies [28].

In our study, GM/IVH patients who received PRBC transfusion had significantly lower mean gestational age ($P < 0.001$), lower mean birth weight ($P = 0.01$), and significantly longer duration of NICU stay associated with more sampling or invasive interventions necessitating PRBC transfusion than those who never received

a PRBC transfusion ($P=0.001$). Similarly, Guzman et al. reported that statistically significant factors associated with intracranial hemorrhage were gestational age less than 32 weeks and blood transfusion [29].

In contrast, Shanmugha Priya reported that number of blood transfusions received by the preterm neonates did not make any significant difference in the length of hospital stay [28].

Limitations of our study included the absence of follow-up cranial ultrasound done at defined intervals for proper documentation of GM/IVH extension. Also, the small sample size was not enough for an accurate assessment of the problem among the targeted patient group.

## Conclusion

The focus of current medical practice should be on preventing GMH/IVH, especially in premature infants receiving PRBCs, limiting its subsequent morbidities. Multi-parametric assessment of the preterm neonates receiving packed RBC should include clinical data, perinatal history, and grade of GMH/IVH with modifications to scheduled transcranial ultrasound accordingly.

#### Abbreviations

| | |
|---|---|
| GM hge | Germinal matrix hemorrhage |
| GM | Germinal matrix |
| HB | Hemoglobin |
| HCT | Hematocrit value |
| IUGR | Intra-uterine growth retardation |
| IVH | Intraventricular hemorrhage |
| NICU | Neonatal intensive care unit |
| PIH | Pre-eclampsia |
| PRBC | Packed red blood corpuscles |
| RDS | Respiratory distress syndrome |

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We acknowledge all patients who were involved in the study.

#### Authors' contributions

DA and EM have designed this study together. SM and EM contributed to the data collection; KA and EM contributed to data analysis. DA contributed to data processing. MA is the added supervisor. KA was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

All the data are within the article. The data supporting the conclusions of this article are available upon reasonable request from the authors.

## Declarations

#### Ethics approval and consent to participate

This study was approved by the Ethical Research Committee of Faculty of Medicine Cairo University in Egypt. The ethics committee reference number is not available.

A verbal consent was taken from the legal guardians of all patients accepting to participate in our research work.

Written approval was taken from ER for asking patients by questionnaire. Also, the study was approved by ethics committee of Cairo University Children Hospital.

The study has been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its late amendments.

All methods were carried out in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

#### Consent for publications

Not applicable.

#### Competing interests

The authors declared that they have no conflicts of interest.

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## Publisher's Note