Neonatal transfusion practices

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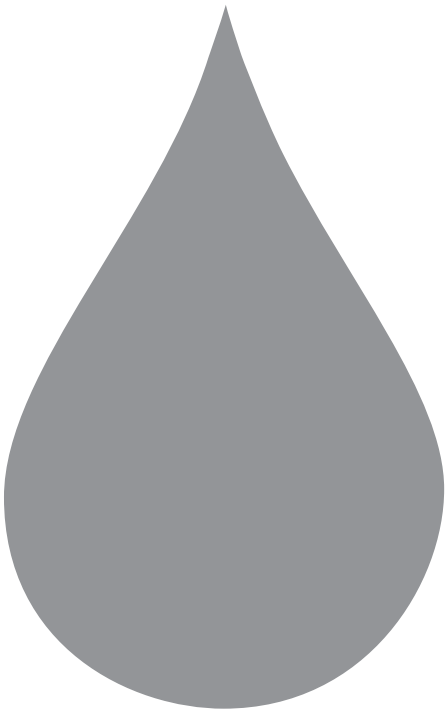
Chapter 9

Thrombocytopenia and intraventricular hemorrhage in very premature infants: a tale of two cities



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Submitted

Abstract

Objective To study whether the incidence of intraventricular hemorrhage (IVH) in very premature infants with thrombocytopenia is lower when using a liberal platelet transfusion guideline compared to a restrictive guideline.

Study design A retrospective cohort study comparing the incidence of IVH in very premature infants with thrombocytopenia (platelet count <150 x 10^9/L) admitted between 2007 and 2008 to two neonatal intensive care unit in The Netherlands. The restrictive platelet transfusion unit (N=353) transfused only in case of active hemorrhage and a platelet count <50 x 10^9/L. The liberal-transfusion unit (N=326) transfused according to predefined platelet count thresholds. Primary outcome was the incidence and severity of IVH in thrombocytopenic infants in both units.

Results The incidence of IVH in thrombocytopenic infants in the restrictive-transfusion and liberal-transfusion unit was 30% (44/145) and 29% (41/141), respectively (p=0.81). The incidence of severe IVH (grade 3 or 4) in the restrictive-transfusion and liberal-transfusion unit was 8% (12/145) and 11% (16/141), respectively (p=0.38).

Conclusion In the restrictive-transfusion unit, the rate of platelet transfusions was significantly lower, but the incidence and severity of IVH was similar to the liberal-transfusion unit.

Introduction

Thrombocytopenia, defined as a platelet count below 150 x 10^9/L, occurs in approximately 21–33% of all neonates admitted to a neonatal intensive care unit (NICU).[1-4] The incidence of thrombocytopenia in extremely low birth weight infants (≤1000 grams) is even higher and may reach 73%.[5] Various studies in premature infants have reported co-occurrence of thrombocytopenia and intraventricular hemorrhage (IVH).[2,6,7] However, the etiology of IVH in premature infants is multicausal and related to various risk factors including extreme prematurity, patent ductus arteriosus (PDA), sepsis and mechanical ventilation.[8] Whether (severe) thrombocytopenia is independently associated with an increased risk of IVH is not known. Whether platelet transfusions in premature infants with thrombocytopenia reduce the risk of IVH is not known either. The only randomized controlled trial (RCT) in this field reported similar incidences and grades of IVH when comparing prophylactic platelet transfusions with no platelet transfusion for newborn infants with moderate thrombocytopenia.[9] The paucity of data on the effects of platelet transfusions has led to multiple consensus-based platelet transfusion guidelines, some of them being liberal, whereas others are restrictive.
We analyzed the incidence and grade of IVH in very premature infants in two comparable Dutch NICUs using different platelet transfusion guidelines.

Materials and methods

Subjects studied

We included all premature infants with a gestational age <32 completed weeks born between January 1st 2007 and December 31st 2008 and admitted to the NICUs of the Leiden University Medical Center and the University Medical Center Groningen. These centers are two of the 10 neonatal tertiary care centers in the Netherlands.

Platelet transfusion guidelines

The platelet transfusion guidelines used during the study period in the two units differed significantly. One unit used a liberal transfusion guideline based primarily on platelet count thresholds, the other unit used a more restrictive guideline based primarily on signs of clinical bleeding.
Platelet transfusions in the liberal-transfusion unit were given when platelet counts fell below the following thresholds: 1) <30 x 10^9/L in clinically stable infants, 2) <50 x 10^9/L in unstable infants and/or before planned surgery, 3) <100 x 10^9/L in neonates with active bleeding and/or at the start of an exchange transfusion.

Platelet transfusions in the restrictive-transfusion unit were given if the platelet count fell below 50 x 10^9/L in the presence of any of the following: major bleeding, massive petechiae, bruising, need for surgery, need for invasive procedures or the need for indomethacin treatment for a patent ductus arteriosus. Premature infants with (very) severe thrombocytopenia but without clinical signs of bleeding did not routinely receive prophylactic platelet transfusions.

Cranial ultrasound guidelines

During the study period both units used a similar cranial ultrasound protocol: scans were performed on day 1, 3 and 7 of life. Ultrasound scans were repeated within 1 week if abnormalities were present. Follow-up ultrasound scans were performed until normalization or long-standing stabilization of the IVH, periventricular leukomalacia (PVL) or (post-hemorrhagic) dilatation of the ventricles. Additional ultrasound scans were performed in case of illness known to increase the risk for hemorrhage such as sepsis, necrotizing enterocolitis (NEC) or thrombocytopenia.

We recorded the platelet count and platelet transfusions in both units. Thrombocytopenia was a defined as a platelet count <150x10^9/L. The severity of thrombocytopenia was graded as mild (100–150 x 10^9/L), moderate (50–100 x 10^9/L), severe (30–50 x 10^9/L) and very severe (<30 x 10^9/L).

We recorded the rate and severity of IVH in both units. IVH was graded according to Papile.[10] In short, grade 1 is a subependymal hemorrhage, grade 2 an IVH without ventricular dilatation, grade 3 an IVH with ventricular dilatation and grade 4 an IVH with parenchymal hemorrhage.

Additional data were collected from patient files, local databases, and laboratory and transfusion records. The data included gestational age at birth, birth weight, gender, Apgar score, days on respiratory support, sepsis, NEC (≥ grade 2 according to Bell, i.e. clinically ill children with abdominal distention, gastric residuals, signs of ileus, occult or gross hemorrhage from the gastrointestinal tract, and on abdominal radiography pneumatosis intestinalis, portal vein gas or (in grade 3) presence of pneumoperitoneum)[11], mortality, and major hemorrhage defined as a pulmonary or intestinal hemorrhage or massive petechiae and bruising. Sepsis was defined as clinical symptoms of infection and a positive blood culture.

Outcome

The primary outcome was the incidence and severity of IVH in thrombocytopenic infants in both units.

Statistical analysis

SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA) was used. All variables were analyzed using the t-test for continuous variables and chi-square or Fisher's exact test for nominal variables. Logistic regression analysis was performed for potential confounding factors. A p-value of <0.05 was considered significant. Odds ratios were calculated.

Approval from the medical ethical committee was not requested for this study as anonymous data collection is part of standard care in the Netherlands.

Results

Total study population

A total of 689 infants were admitted during the study period. In 28 infants no cranial ultrasound scans were performed. Of these 28 infants, 11 died of whom 10 shortly after birth before a cranial ultrasound scan could be made. These 10 infants were not included in the analysis because several other variables (for example platelet counts) were also missing. The characteristics of the study population are presented in Table 1. There were no significant differences in demographic and clinical characteristics between the two populations in both units. There were no premature infants with fetal/neonatal autoimmune thrombocytopenia. Only one infant (in the liberal-transfusion unit) received an exchange transfusion but had a normal platelet count. For the analysis of (intraventricular) hemorrhage only those infants were included of whom a cranial ultrasound scan was made and a platelet count was known (323 infants in the liberal-transfusion unit and 330 in the restrictive-transfusion unit).

Table 1. Characteristics of all patients per unit

	Liberal transfusion unit (N=326)	Restrictive transfusion unit (N=353)	p-value
Gestational age at birth, wk[a]	28.9 (±1.9)	28.9 (±1.9)	0.91
Birth weight, g[a]	1259 (±326)	1270 (±353)	0.67
IUGR, n (%)	19 (6)	10 (3)	0.05
Male, n (%)	172 (53)	195 (55)	0.52
Apgar score 5 min [a]	7.7 (±2.0)	7.6 (±1.5)	0.54
RBC Tx, n (%)	163 (50)	159 (45)	0.20
Patent ductus arteriosus, n (%)	60 (18)	81 (23)	0.14
Sepsis, n (%)	98 (30)	89 (25)	0.16
NEC, n (%)	9 (3)	14 (4)	0.39
Mortality, n (%)	22 (7)	25 (7)	0.86
IVH, n/N (%)[b]	63/323 (20)	75/330 (23)	0.31

[a]Value given as mean ± SD; [b]N=number of infants with a cranial ultrasound scan

IUGR=intra-uterine growth retardation; RBC Tx=red blood cell transfusion; NEC=necrotizing enterocolitis

Platelet transfusions

Data on the incidence and severity of thrombocytopenia and the incidence of platelet transfusions in the two units are shown in Table 2. The overall rate and severity of thrombocytopenia was similar in both units. The percentage of thrombocytopenic patients who received one or more platelet transfusions was significantly higher in the liberal-transfusion unit than in the restrictive-transfusion unit, 31% (44/141) versus 15% (21/145), respectively (p<0.001). The mean (± SD) number of platelet transfusions per thrombocytopenic infant was significantly higher in the liberal-transfusion unit than in the restrictive-transfusion unit, 1.1 ± 3.0 SD versus 0.2 ± 0.7 SD, respectively (p=0.001).

Table 2. Rate and severity of thrombocytopenia in the 2 units and IVH and platelet transfusion practices in the thrombocytopenic infants per unit

Variable	Liberal transfusion unit	Restrictive transfusion unit	p-value
Thrombocytopenia all, n/N (%)	141/325 (43)	147/334 (44)	0.87
Mild (100-150 x 10^9/L), n/N (%)	41/141 (29)	58/147 (40)	0.06
Moderate (50-100 x 10^9/L), n/N (%)	55/141 (39)	50/147 (34)	0.38
Severe (30-50 x 10^9/L), n/N (%)	21/141 (15)	19/147 (13)	0.63
Very severe (<30 x 10^9/L), n/N (%)	24/141 (17)	20/147 (14)	0.42
Platelet Tx in thrombocytopenic infants, n/N (%)	44/141 (31)	21/145 (15)	<0.001
Platelet Tx per thrombocytopenic infant, n[a]	1.1 (±3.0)	0.2 (±0.7)	0.001
Platelet Tx per transfused infant, n[a]	3.6 (±4.6)	1.6 (±0.9)	0.05
IVH grade 1, n/N (%)	15/141 (11)	30/145 (21)	0.02
IVH grade 2, n/N (%)	10/141 (7)	2/145 (1)	0.02
IVH grade 1 or 2, n/N (%)	25/141 (18)	32/145 (22)	0.36
IVH grade 3, n/N (%)	8/141 (6)	2/145 (1)	0.06
IVH grade 4, n/N (%)	8/141 (6)	10/145 (7)	0.67
IVH grade 3 or 4, n/N (%)	16/141 (11)	12/145 (8)	0.38

[a]Value given as mean ± SD

Tx=transfusion; IVH=intraventricular hemorrhage

Intraventricular hemorrhage

The overall incidence of IVH was similar in the liberal- and restrictive-transfusion unit, 20% (63/323) versus 23% (75/330), respectively (p=0.31). The rate of IVH in thrombocytopenic infants in the liberal-transfusion and restrictive-transfusion unit is shown in Table 2. The rate of clinically significant, severe IVH (grade 3 or 4) was similar, 11% (16/141) versus 8% (12/145), in the liberal- and restrictive-transfusion unit respectively (p=0.38). We found no differences in the incidence of IVH after stratifying for severity of thrombocytopenia (data shown in Table 3). Logistic regression analysis with gestational age at birth (<28 weeks or 28–32

Table 3. Rate of intraventricular hemorrhage per unit versus severity of thrombocytopenia

Platelet count	No IVH			IVH grades 1+2			IVH grades 3+4		
x 10^9/L	Lib	Restr	p-value	Lib	Restr	p-value	Lib	Restr	p-value
>150	160/182 (88%)	157/185 (85%)	0.40	12/182 (7%)	24/185 (13%)	0.04	10/182 (6%)	4/185 (2%)	0.10
100–149	30/41 (73%)	44/58 (76%)	0.76	6/41 (15%)	12/58 (21%)	0.44	5/41 (12%)	2/58 (3%)	0.12
50–99	38/55 (69%)	32/49 (65%)	0.68	9/55 (16%)	13/49 (27%)	0.21	8/55 (15%)	4/49 (8%)	0.31
30–49	16/21 (76%)	12/19 (63%)	0.37	5/21 (24%)	4/19 (21%)	1.00	0/21 (0%)	3/19 (16%)	0.10
<30	16/24 (67%)	13/19 (68%)	0.90	5/24 (21%)	3/19 (16%)	1.00	3/24 (13%)	3/19 (16%)	1.00

Numbers are n/N (%)

IVH=intraventricular hemorrhage; Lib=liberal platelet transfusion unit; Restr= restrictive platelet transfusion unit

weeks), thrombocytopenia and severity of thrombocytopenia, sepsis, intra-uterine growth retardation (IUGR), NEC, platelet transfusion, restrictive- or liberal-transfusion unit and patent ductus arteriosus as confounders for IVH was performed. Thrombocytopenia, irrespective of the severity, was significantly related to the incidence of IVH (all grades combined (p=0.000), grade 1+2 (p=0.002) or grade 3+4 (p=0.009)). Gestational age <28 weeks was a significant causal factor for all grades of IVH (p=0.003) and IVH grade 3+4 combined (p=0.000).

Other major hemorrhages

In the liberal-transfusion unit 2 infants had a pulmonary hemorrhage versus 1 in the restrictive-transfusion unit. The two infants in the liberal-transfusion unit received one or more platelet transfusions. The pulmonary hemorrhage in the infant in the restrictive-transfusion unit ceased after instituting mechanical ventilation with PEEP and endotracheal xylomethazoline. In the liberal-transfusion unit 5 infants were born with extensive bruising; an expectative approach was used in these infants. In the restrictive- transfusion unit 3 infants received one or more platelet transfusions for a major hemorrhage other than IVH (gastro-intestinal (n=1), adrenal (n=1), at site of surgery after abdominal surgery (n=1)).

Discussion

This study shows that the overall incidence and severity of IVH in the NICU unit using a liberal platelet transfusion guideline was similar to the unit using a restrictive transfusion guideline. Although the number and rate (per infant) of platelet transfusions was significantly higher in

the liberal-transfusion unit, platelet transfusions did not reduce the incidence or grades of IVH in premature infants with thrombocytopenia.

The etiology of IVH is multi-factorial and related to several other factors besides a low platelet count, including gestational age, birth weight, sepsis, NEC, acidosis, patent ductus arteriosus and the fragility of the vessel wall in (extremely) premature infants.[12] In our study gestational age was the only confounding factor. Thrombocytopenia is a frequent finding in premature infants and may be due to impaired platelet production by intra-uterine factors such as placental insufficiency or postnatal factors increasing platelet consumption such as sepsis.[3,4,13] Several studies in premature infants have shown that the rate of IVH is increased in thrombocytopenic infants.[6,14,15] These data contrast with other studies, which have shown that the risk for IVH in thrombocytopenic premature infants is not related to the severity of thrombocytopenia.[2,7] Our study also shows no correlation between the severity of thrombocytopenia and IVH. The causal relationship between (severe) thrombocytopenia and IVH remains thus unclear.[16,17]

Whether restrictive platelet transfusion guidelines based on lower thresholds and/or on clinical bleeding signs are safe in premature infants is not known and international consensus is lacking. In 2008 an international forum published an article on transfusion policies and practices in various countries. Platelet transfusion thresholds varied between 20 and 100 x 10^9/L depending on disease severity and birth weight or gestational age of the infant.[18] In the previously mentioned RCT by Andrew et al. no benefit was found in terms of IVH reduction by maintaining platelet counts >150 x 10^9/L with platelet transfusions in infants with moderate thrombocytopenia (50 to 150 x 10^9/L).[9] However, in this RCT, all infants with platelet counts <50 x 10^9/L received prophylactic platelet transfusions and were excluded from analysis.

The risk of IVH in premature infants with platelet counts <50 x 10^9/L remains unclear. Despite the lack of high-quality evidence, it is intuitive to think that prophylactic platelet transfusion may prevent IVH. However, recent studies provide evidence that platelet transfusion may have potential harmful effects and even increase mortality rates.[7,19,20] In our study there was no difference in mortality rate, NEC or septicemia between the children treated with a liberal or a restrictive transfusion regimen. Moreover there was no difference in mortality rate in infants with and without a platelet transfusion in this study (data not shown). The possible causes of the detrimental effect of platelet transfusions in premature infants are not known and may be related to activation of inflammatory and coagulative necrosis, particularly in patients with sepsis or NEC.[3]

The data in our study should be interpreted with caution since bias may have been introduced by the retrospective nature of the study. Despite the large cohorts of comparable infants in both units, the incidence and grading of IVH may be center-dependent due to possible

differences in interpretation of cranial ultrasound scans. A study design using an independent reviewer evaluating all ultrasound scans would have been preferable.
Due to the multi-factorial cause of IVH more research needs to be performed to determine which factors are independently related to the risk of bleeding. Our study shows that a restrictive platelet transfusion guideline is not associated with a higher incidence of IVH or other major hemorrhage. Therefore randomized controlled trials are warranted and urgently needed to determine the safety of restrictive platelet transfusions guidelines in premature infants.

Conclusions

Liberal-transfusion guidelines in premature infants suffering from thrombocytopenia result in more platelet transfusions but do not reduce the incidence and rate of IVH compared to restrictive-transfusion guidelines.

Acknowledgements
The authors are indebted to B.A. Deelstra, data manager for collecting data for the restrictive unit.

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