The effects of various platelet-transfusion thresholds in preterm infants with severe thrombocytopenia

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MANUSCRIPT CITATION

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TYPE OF INVESTIGATION

Intervention and Prognosis

QUESTION

In preterm infants less than 34 weeks gestation at birth (P), does a platelet-transfusion threshold of 50,000/mm^3 (I) compared to 25,000/mm^3 (C) reduce the risk of death and major bleeding (O) within 28 days after randomization (T)?

METHODS

- **Design:** Multicenter randomized controlled superiority trial
- **Allocation:** Concealed; 1:1 ratio
- **Blinding:** Treating clinicians, parents, and guardians were aware of the treatment assignments. Clinicians confirming each outcome were blinded.
- **Setting and time period:** Neonatal intensive care units in the United Kingdom, the Netherlands, and Ireland from June 2011 to August 2017
- **Subjects:**
    - Inclusion Criteria:
        1. Born at < 34 weeks gestation
        2. Platelet count < 50,000/mm^3
        3. Cranial ultrasound within 6 hours before randomization without major intraventricular hemorrhage
    - Exclusion Criteria:
        1. Major or life-threatening congenital malformation
        2. Major bleeding within the previous 72 hours
            - If no further bleeding, these infants were eligible for randomization 72 hours after the bleeding episode

3. Fetal intracranial hemorrhage
4. Immune thrombocytopenia
5. No administration of parenteral Vitamin K
6. Low probability of survival beyond several hours

- **Intervention:**
  - High threshold group: platelet transfusion of 15ml/kg if platelet count < 50,000/mm^3
  - Low threshold group: platelet transfusion of 15ml/kg if platelet count < 25,000/mm^3
- **Outcomes:**
  - Primary outcome: Composite of death or major bleeding up to and including day 28
  - Secondary outcomes:
    1. Survival up to day 28 after major bleeding episode
    2. Death up to day 28
    3. Rate and time from randomization to major bleeding up to day 28
    4. At least one minor bleeding episode up to day 14
    5. At least one moderate bleeding episode up to day 14
    6. Major bleeding episode after red-cell transfusion
    7. Chronic lung disease (need for oxygen or respiratory support at > 36 weeks post-menstrual age)
    8. Stage 2 retinopathy of prematurity (unilateral or bilateral)
    9. Retinopathy of prematurity leading to laser or bevacizumab
    10. Discharge by 38 weeks post-menstrual age
    11. Number of platelet-transfusion episodes per participant
    12. Receipt of at least one platelet transfusion
    13. Median platelet-count nadir before major bleeding episode
    14. Median platelet count closest to major bleeding episode
    15. New sepsis event
    16. New necrotizing enterocolitis event
    17. Serious adverse event
    18. Platelet transfusion-related adverse events
    19. Neurodevelopmental outcome at 2 years of age

- **Follow-up period:**
  - Bleeding assessment form completed daily for 14 days after randomization then weekly.
  - If an infant was transferred to another hospital before day 28, primary outcome data at least up to and including day 28 were documented.
  - Safety outcomes reporting was mandatory only at participating hospitals.
  - Neurodevelopmental follow up at 2 years of age
- **Analysis and Sample Size:**
  - It was estimated that 329 infants in each group would provide 80% power to detect an absolute difference of 8% in the event rate for the primary outcome of 12% in the high-threshold group vs. 20% in the low-threshold group, using a two-sided test at a 5% significance level.
  - 660 infants underwent randomization with 331 infants in the low-threshold group and 329 infants in the high-threshold group. Analyses were performed according to the intention-to-treat principle.
  - Prespecified subgroups analyses
    1. Excluding rectal-only bleeding
    2. Missing data
    3. Intrauterine growth restriction
    4. Gestational age

5. Postnatal age at randomization
    - Mixed logistic regression analysis of primary outcome and Cox proportional-hazards regression analysis of secondary outcomes
- **Patient follow-up:**
    - In the low-threshold group, two patients were excluded from primary outcome analysis.
    - In the high-threshold group, one patient was excluded from all analyses and five patients were excluded from primary outcome analysis.

MAIN RESULTS

Baseline characteristics of the trial population were similar between the low-threshold and high-threshold groups prior to randomization. The median birth weight was 740 grams, and the median gestational age was 26.6 weeks. Of all the infants, 37% underwent randomization or on before 5 days of life and 59% by 10 days. Thirty-nine percent of infants received at least one platelet transfusion before randomization.

Primary Outcome

The primary outcome occurred in 26% of the infants in the high-threshold group and 19% of the infants in the low-threshold group. After adjusting for gestational age, intrauterine growth restriction and trial site, the odds ratio was 1.57 (95% CI, 1.06-2.32, p= 0.02), demonstrating significance towards the low-threshold group.

Secondary Outcomes

Infants in the low-threshold group had a lower frequency of survival with bronchopulmonary dysplasia at 36 weeks (54% vs. 63%, OR 1.54; 95% CI, 1.03-2.30). There were no differences in other secondary outcomes, including rates of minor or worse bleeding episodes, survival with retinopathy of prematurity, new sepsis event, or new necrotizing enterocolitis event.

Sensitivity Analyses

For the primary outcome, results were unchanged in a per-protocol analysis (OR 1.68; 95% CI, 1.11-2.55), analysis excluding rectal-only bleeding (OR 1.75; 95% CI, 1.14-2.67), and analysis assessing sensitivity to missing data.

Subgroup Analyses

There was no difference seen in the primary outcome with intrauterine growth restriction, gestational age, or postnatal age at randomization.

Serious Adverse Events

There was no difference in rates of serious adverse events between the high-threshold and low-threshold groups (25% vs. 22%, OR 1.14; 95% CI, 0.78-1.67).

CONCLUSION

In preterm infants with severe thrombocytopenia, use of a platelet transfusion threshold of 50,000/mm^3 resulted in an increase in death or major bleeding and bronchopulmonary dysplasia compared to use of a lower threshold of 25,000/mm^3.

COMMENTARY

Neonatal thrombocytopenia is estimated to occur in 25% of neonates admitted to the neonatal intensive care unit, with the highest risk occurring in premature infants. Currently, there is no clear relationship described between low platelet counts and major bleeding or long-term outcomes resulting in a lack of consensus on the optimal threshold for platelet transfusion (1). The Platelets and Neonatal Transfusion Study Group in the United Kingdom first performed a prospective, observational study describing outcomes for neonates with severe thrombocytopenia. They found that the majority of neonates did not develop major bleeding (2). As a follow up to this descriptive analysis, the group performed this multicenter, randomized trial to provide clinicians with neonatal outcomes associated with high and low platelet transfusion thresholds in premature infants.

A composite outcome of death or major bleeding within 28 days of randomization served as a clinically relevant primary outcome for this trial. The study was adequately powered based on the event rates observed in the group's initial descriptive analysis. The investigators hypothesized that fewer complications would occur in the high-threshold group, however, death or major bleeding occurred less frequently in the low-threshold group. Based on the observed event rates in both groups, reducing the prophylactic transfusion threshold to 25,000/mm^3 would prevent death or major bleeding in 7 of 100 premature infants with severe thrombocytopenia.

The results of this trial provide a useful guide to the management of critically ill premature infants with severe thrombocytopenia, commonly a result of late-onset sepsis or necrotizing enterocolitis. The trial population at randomization consisted of 63% of patients receiving antibiotic treatment for sepsis and 16% of patients undergoing treatment for necrotizing enterocolitis Stage 2a or higher defined by the Modified Bell's staging criteria. The distribution amongst the high and low threshold groups was similar.

This trial supports the theory that the cause of major bleeding is likely multifactorial, not simply due to low platelet counts. Additionally, targeting higher platelet counts in critically ill patients may result in worse outcomes. Some potential reasons include higher risk of thrombosis, infection, and inflammatory effects like transfusion associated lung injury. It is important to note that about 60% of infants were randomized after day of life 5, and 40% of infants received a platelet transfusion prior to randomization. Therefore, it is extremely difficult to predict the outcome if these findings were applied to extremely premature infants during the first week of life when the risk of intraventricular hemorrhage is highest.

This trial highlights the need for additional randomized trials investigating the optimal platelet threshold in premature infants. The results are reassuring as no significant adverse events occurred in those infants in the low-threshold group, however, neuro-developmental outcomes at two years of age have yet to be released. Furthermore, high-quality evidence is lacking for the optimal platelet threshold for the prevention of intraventricular hemorrhage in the setting of severe thrombocytopenia.

REFERENCES

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