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Research Article

A SYSTEMATIC REVIEW AND META-ANALYSIS OF GOAL DIRECTED INTRA-OPERATIVE TRANSFUSION PROTOCOLS GUIDED BY VISCOELASTIC METHODS AND PERIOPERATIVE OUTCOMES IN CHILDREN [CRD 42018103163].

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ABSTRACT

Introduction: In children studies have shown that when viscoelastic hemostatic methods were used to guide blood product administration in hemorrhagic surgery, the amount of transfusion was diminished, it has not been demonstrated that morbi-mortality was improved. This study was undertaken to analyse the impact of these methods on this outcome.

Methods: A systematic review and meta-analysis of randomised and non randomised trials was realised from January to March 2019.The experimental group was where thromboleastography or rotational thromboelastometry were used to guide transfusion. The control group was where conventional coagulation tests were used to guide transfusion. Statistic analysis was realised with Rev Man 5.3 software.

Results: 9 studies with 1365 children <18 years in trauma, cardiac, craniosynostosis and liver transplantation surgery were included.

1. In more than 900 children, mortality (OR 1.02 [0.34, 3.10], p=0.97) and morbidity (OR 1.95 [0.75,5.11],p=0.17) were not different.
2. In 891 children, the number of patients transfused with packed red blood cells was not different, OR 0.44 [0.18, 1.06], p=0.07.
3. In 227 children, the number of patients transfused with platelets was not different, OR 0.90 [0.08, 9.94], p=0.93.
4. In 891 children, the number of patients transfused with fresh frozen plasma was lower in the experimental group, OR 0.06 [0.01, 0.50], p=0.01.
5. In 185 children, the number of patients who received fibrinogen or cryoprecipitate was higher in the experimental group, OR 5.46 [1.83, 16.32], p=0.002.
6. In 821 children, length of hospital stay was lower in the experimental group, p=0.005.

Conclusion: In this pediatric study, when viscoelastic hemostatic assays were used in hemorrhagic surgery to guide transfusion there was a reduction in the number of patients intraoperatively transfused with fresh frozen plasma, a reduction in length of hospital stay and an increase in the number of patients who received intraoperative cryoprecipitate or fibrinogen. There was no difference in morbi-mortality.

INTRODUCTION

Transfusion can be a necessary therapy in critically ill patients. However like any other medical treatment it can be related to some side effects in critical patients such as TRALI (transfusion related acute lung injury), TACO (transfusion associated circulatory overload)[1,2]. Studies in pediatric surgical and critical pediatric patients

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have shown that transfusion was an independent factor of morbidity [3]. Are there any means to reduce transfusion or to improve transfusion protocols in order to reduce patient exposure to blood products and thus diminish morbidity? The European Society of Anesthesiology has published previously guidelines concerning the use of viscoelastic methods to guide transfusion and reduce blood loss in hemorrhagic surgeries [4]. A recent Cochrane systematic review and meta-analysis demonstrated that when viscoelastic methods are used to guide transfusion in hemorrhagic surgery in adults, mortality and morbidity were reduced [5].

In children, studies in craniosynostosis, cardiac surgery, hepatic transplantation have shown that when blood product administration was guided by these methods, packed red blood cells, platelets units and fresh frozen plasma transfusion was reduced[6-11].

Transfusion rates in pediatric hemorrhagic interventions varie according to the type of surgery : in craniosynostosis surgery it is between 17-45% [12], in scoliosis surgery it varies between 1.7% (idiopathic scoliosis)- 36% (neuromuscular scoliosis)[13], in pediatric hepatic transplantation it is 31% [14] and in polytrauma patients 35%[15]. This study was undertaken to analyse if transfusion protocols guided with viscoelastic methods in hemorrhgic pediatric surgery reduced mortality, morbidity, blood product transfusion and length of hospital stay.

Objectives

To demonstrate whether intraoperative transfusion protocols using viscoelastic methods reduced perioperative morbi-mortality (primary outcome) (morbidity was defined as complications defined as organ failure or organ dysfunction and infections) in the pediatric surgical population.

To demonstrate whether intraoperative transfusion protocols using viscoelastic methods reduced intraoperative transfusion and the amount of intraoperative blood loss (secondary outcomes).

To demonstrate whether intraoperative transfusion protocols using viscoelastic methods reduced length of hospital stay (secondary outcome)

Description of the Condition

Potential hemorrhagic surgical interventions in children aged 0-18 years where viscoelastic methods or standard care are used to guide transfusion (Inclusion criteria). Exclusion criteria: patients over 18 years.

Description of the Intervention

Potential hemorrhagic surgical interventions such as scoliosis, craniosynostosis, liver transplantation, trauma and cardiac surgeries in children where blood product *administration was guided by viscoelastic methods (TEG, Thromboelastograpy or ROTEM,* Rotational thromboelastometry) and compared to the same interventions where transfusion was guided using standard protocols other than viscoelastic methods.

Types of studies included :randomised and non randomised trials were included.

Outcomes

Primary Outcome

Intraoperative and postoperative morbi-mortality.

Secondary Outcomes

- Intraoperative blood products administration
- Intraoperative blood loss
- Length of hospital stay (LOS)

Outcome measures

Primary outcomes measures were defined as the number of deaths and complications defined as organ failure or organdys function and infections in the intraoperative and postoperative period. Secondary outcomes measures were defined as :

1. Intraoperative number of patients transfused (with PRBC, FFP, CUP, fibrinogen or cryoprecipitate).
2. Intraoperative amount of blood loss.
3. Number of days spent in hospital (LOS) until discharge.

METHODS AND MATERIALS

This study was registered under the number CRD42018103163 in PROSPERO. Since this was a systematic review and meta-analysis, ethical approval from the local ethic committe was not necessary. Titles and abstracts using these keywords 'Transfusion and viscoelastic methods in children and outcome OR transfusion and TEG/ROTEM in children and outcome OR transfusion and thromboelastography in children and outcome OR transfusion and rotational thromboelastometry in children and outcome OR thromboelastography in children in hemorrhagic surgey and outcome OR rotational thromboelastometry in children and outcome and randomised OR non randomised trials in children OR viscoleastic methods in randomised and non randomised trials in children and outcome OR blood products in children and outcome or transfusion in children and outcome OR Viscoelastic methods in children and outcome OR TEG/ROTEM in children and outcome OR thromboelastography in children and outcome OR rotational thromboelastometry in children and outcome' were searched electronically in MEDLINE (133215 titles),EMBASE (2977 titles), CENTRAL (5658 titles), GOOGLE SCHOLAR (70 titles), CLINICALTRIALS.GOV (15 trials), ABSTRACT CONFERENCE (0 titles) and DARE (0 titles) from January 2019 to March 2019 without date restriction. 23 relevant abstracts were retained for which complete articles were searched. Among these 14 were excluded because of unavailable complete study data (4abstracts) and because of the absence of the inclusion criteria (10 studies). 9 studies with complete articles were finally included. See flowchart in supplemental figure 1 for the search and selection process[16]. Among the studies identified 2 were randomised, 2 were prospective non randomised and 5 were retrospective studies. See supplemental tables 1 and 2 for

the characteristics of the included trials. Statistic analysis, data collection were realised with Review Manager (RevMan) [Computer program]. Version 5.3

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.Assessment of risk of bias in included studies was realized using the tools proposed by the Cochrane Handbook for systematic reviews of interventions which is included in the Rev Man 5.3 software.

Measures of treatment effect were dichotomous for morbi-mortality and transfusion (how many patients died or how many patients presented complications or how many patients were transfused with different blood product including packed red blood cells (PRBC), fresh frozen plasma (FFP), concentrated platelet units (CUP), fibrinogen and cryoprecipitate and were presented as odds ratios (OR) with 95% confidence(CI).

Measures of treatment effect were continuous for length of hospital stay and were presented as mean differences with 95% CI.

Forest plots were used to provide visual summary of data included. I^2 statistics was used to assess for heterogeneity. Funnel plots were used to assess for publication bias.

Since some data were not always available for the intraoperative amount of blood loss meta-analysis concerning this outcome was not realised and a descriptive qualitative analysis was realised. Wilcoxon test was used to compare the two groups (experimental and control) in terms of intraoperative blood loss. This outcome was expressed in median value with the interquartile range. A p-value ≤ 0.05 was considered significative.

Concerning the amount of intraoperative blood products administered (PRBC, FFP, CUP, fibrinogen and cryprecipitate), meta-analysis was not realised because of some missing data concerning these outcomes.

The experimental group was defined as the group where viscoelastic hemostatic assays namely thromboelastography (TEG) or rotational thromboelastometry (ROTEM) were used to guide transfusion intraoperatively. The control group was defined as the group where standard care was used to manage transfusion intraoperatively. Standard care was defined as conventional coagulation tests i.e prothrombin time (PT), activated thromboplastin time (aPTT), fibrinogen or when no coagulation tests were used to guide intraoperative transfusion. The level of evidence was assesed using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system[17].

RESULTS

9 studies were included[6,8,9, 18-23]with 1365 children less than 18 years old. For the characteristics of the studies see supplemental tables 1 and 2. Four studies concerned 381 children in cardiac surgey[6,8,22,23], two trials with 819 children in trauma[18,20], two studies with 127 children in craniosynostosis [9,19]and one trial with 38 patients in liver transplantation[21]. 5 trials were retrospective[9,19-22],two were prospective non randomised [6,18]and two were prospective randomised[8,23].

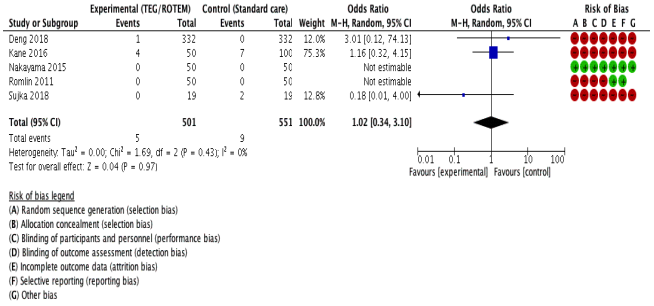

Figure 1 Forest plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for Outcome Mortality

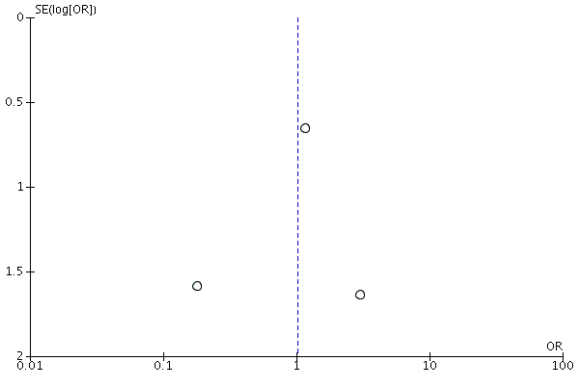

Figure 2 Funnel plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for Outcome Mortality

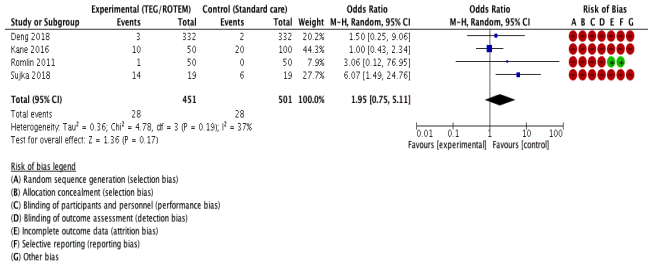

Figure 3 Forest plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for Outcome Morbidity.

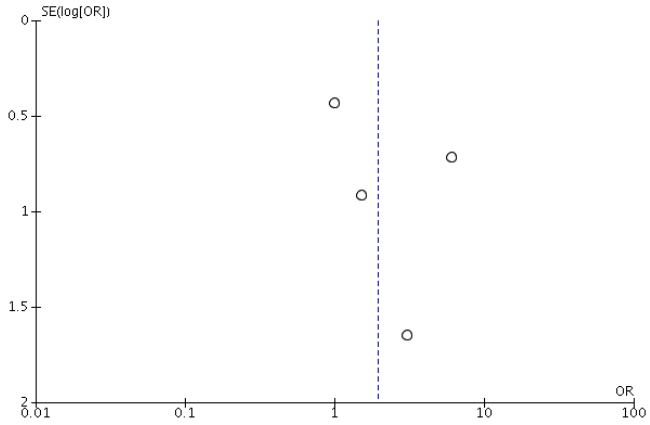

Figure 4 Funnel plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for Outcome Morbidity.

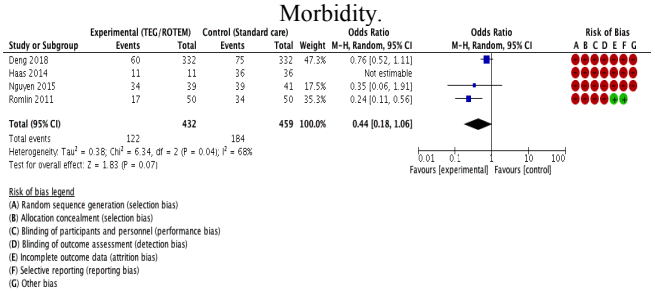

Figure 5 Forest plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for outcome Number of patients intraoperatively transfused with packed red blood cells.

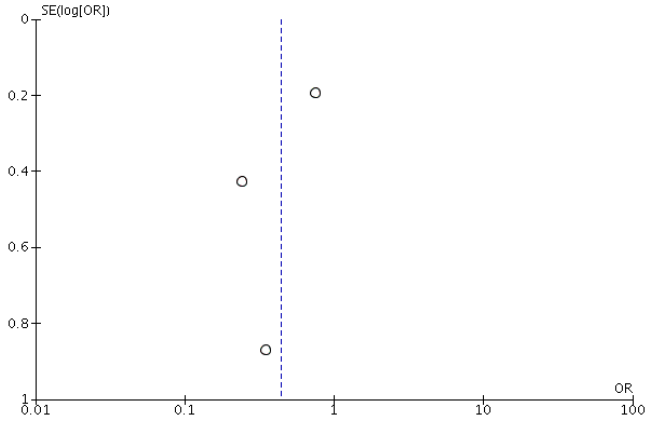

Figure 6 Funnel plot of comparison Transfusion guided by TEG/ROTEM versus Transfusion guided by standard care for outcome Number of patients intraoperatively transfused with packed red blood cells.

Mortality (figures 1 and 2)

5 studies with 1052 children analysed this outcome[6,8,20-22] Mortality was not different between the 2 groups, odds ratio (OR) 1.02 [0.34-3.10], p=0.97. Heterogeneity was low as I^2 equaled 0%. All studies had biases except the Nakayama *et al* study[8]. The risk for publication bias was low as illustrated in figure 2. With low heterogeneity, low risk of publication bias and and a great number of patients (>1000), the level of evidence (GRADE) was moderate.

Morbidity (figures 3 and 4)

4 studies with 952 children analysed this outcome[6,20-22] Morbidity, in terms of organ dysfunction and or infections (i.e acute respiratory distress syndrome, acute rejection, bleeding, reintervention for hemorrhage, thrombo-embolic events, bacteremia ; acute renal , liver , cardiac and respiratory failures) was not not different between the two groups, OR 1.95 [0.75,5.11],p=0.17. Heterogeneity was low asI2 equaled 37%. All studies had bias. Publication bias was present as illustrated in figure 4. The level of evidence (GRADE) was low (bias among the studies, publication bias) to moderate (low heterogeneity and a great number of patients).

Number of Patients who Recieved Intraoperative Packed red Blood Cells (figures 5 and 6)

4 studies with 891 children analysed this outcome[6,9,19,20] There was no difference between the two groups, OR 0.44[0.18-1.06], p=0.07. Heterogeneity was high (I^2 =68%).

All studies had bias. Publication bias was also present. The level of evidence (GRADE) was low because of high risk of heterogeneity, bias among the trials and publication bias.

Number of Patients who Received Intraoperative Fresh frozen Plasma (Supplemental figures 2 and 3)

4 studies with 891 children analysed this outcome[6,9,19,20]The number of patients who recieved intraoperative fresh frozen plasma was significantly lower in the TEG/ROTEMgroup, OR 0.06 [0.01-0.50], p=0.01. Heterogeneity was high (I^2 =92%). All studies had bias. Publication bias was also present. The risk of heterogeneity, bias among the studies and publication was high. The level of evidence (GRADE) was low (high risk of bias and heterogeneity) to moderate (great number of patients, more than eight hunderd patients).

Number of Patients who Recieved Intraoperative Platelets (Supplemental figures 4 and 5)

3 studies with 227 children analysed this outcome[6,9,19] There was no difference, OR 0.90 [0.08, 9.94], p=0.93.
Heterogeneity was present (supplemental figure 4). All studies had bias. Publication bias was present. The level of evidence (GRADE) was low.

Number of Patients who Received Intraoperative Fibrinogen or Cryoprecipitate (supplemental figures 6 and 7)

3 studies with 185 children analysed this outcome[6,9,21]The number of patients who recieved intraoperative fibrinogen or cryoprecipitate was higher in the TEG/ROTEM group, OR 5.45 [1.83,16.32],p=0.002.

Heterogeneity was low. All studies had bias and publication bias was present. The level of evidence (GRADE) was low (only 185 children included) to moderate (low risk of heterogeneity).

Length of hospital, LOS (supplemental figures 8 and 9)

3 studies with 821 children analysed this outcome[18-20] LOS was lower in the TEG/ROTEM group, p=0.005. Heterogeneity was low. All studies had bias and publication bias was present.The level of evidence was low (high risk of bias) (GRADE) to moderate (low risk of heterogeneity and great number of patients).

Amount of intraoperative blood loss (supplemental table 3)

Four studies with 196 children analysed this outcome[9,19,21,23] There was no difference between the two groups, p=0.13. The level of evidence (GRADE) was low, only 196 children were included.

DISCUSSION

This systematic review and meta-analysis revealed several points. Mortality was not different in the two groups. This finding is new because a prior meta-analysis[5] concerning adults and children showed a reduced mortality in the TEG/ROTEM group in adults but not in children, there were only two pediatric studies included. Mortality was not different in our meta-analysis because this outcome could be explained by other factors than transfusion[3]. This was also an evidence that conclusions concerning clinical practice in adult studies cannot always be extrapolated to children[24].

Morbidity in terms of organ dysfunction and infections was not different. This outcome as for mortality could be explained by other factors than transfusion (the severity of illnes for instance) as it has been shown previously that morbi-mortality was predicted by multiple factors[3].

The number of patients who recieved intraoperative PRBC and platelets was not different.The number of patients who received intraoperative fresh frozen plasma was lower in the TEG/ROTEM group.

The number of patients who received intraoperative fibrinogen or cryoprecipitate was higher in the TEG/ROTEM group. These findings are not suprising since viscoelastic hemostatic assays help to detecte coagulation alterations in case of hemorrhage[25].

LOS was lower in the TEG/ROTEM group, it has been shown elsewhere that blood product transfusion increased length of hopsital stay[3]. Implementing patient blood management programs can help to reduce the rate of transfusion of some blood products i.e FFP and reduce LOS. Reducing LOS has been proven to reduce morbidity in surgical pediatric patients [26].

Concerning the presence of high risk biases in the studies : most of the studies included (8 among 9) had biases except from one[8], since situations where a critical condition like hemorrhage can occur, conducting randomised controlled blinded studies can be delicate and not always clinically practical and easy to realise. So we have to cope and manage with existing evidence that is to say retrospective or prospective trials in order to optimse patient outcome. The ideal utopic world is a place where everything is perfect, perfection does not exist but we can always do our best to come close to it.

CONCLUSION

This systematic review and meta-analysis in this pediatric setting has demonstrated that when TEG/ROTEM are integrated into patient blood management programs in hemorrhagic surgeries i.e trauma, cardiac, craniosynostosis and liver transplantation, the number of patients intraoperatively transfused with fresh frozen plasma and LOS were reduced. The number of patients who received intraoperative fibrinogen or cryoprecipitate was increased.

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Declarations of interest

There were no conflicting or competing interests

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