Optimising diagnosis and treatment of coagulopathy in severely injured trauma patients
Balvers, K.

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ARE THERE ANY ALTERNATIVES FOR TRANSFUSION OF AB PLASMA AS UNIVERSAL DONOR IN AN EMERGENCY RELEASE SETTING?


Transfusion 2016
ABSTRACT

Introduction: AB plasma is used as the universal donor plasma product in patients requiring massive transfusion. However, currently it is a recommended policy to transfuse plasma derived from male donors only as transfusion of plasma from HLA antibody-positive female donors is associated with an increased risk for transfusion-related acute lung injury (TRALI). As a result, due to high demands, supplies of blood banks may run out of AB plasma, calling for alternatives. Therefore, the aim of this review was to investigate alternatives for emergency release of AB plasma as the universal donor.

Methods: A systematic search was conducted in Embase and Pubmed. Studies on adult patients, who were transfused with at least one unit of plasma investigating the incidence of transfusion-related complications or mortality in patients transfused with ABO identical plasma, ABO compatible or ABO incompatible plasma, were eligible for inclusion. The primary outcomes were the incidence of transfusion-related complications and mortality.

Results: In total 6 studies were included. Transfusion of ABO compatible plasma was associated with an increased incidence of lung injury and mortality (OR 1.10, 95% CI 1.04-1.15 p=0.0003) compared to transfusion of ABO identical plasma. No significant differences were observed regarding transfusion-related complications and mortality between patients transfused with ABO compatible or ABO incompatible plasma.

Conclusion: Studies are insufficient to formulate advices about alternatives for transfusion of AB plasma as universal donor plasma in the emergency setting due to the small number of studies. The results of this review underline the need for further research.
INTRODUCTION

Massive hemorrhage is a leading cause of mortality\(^1\)-\(^3\). Resuscitation of massive hemorrhage has shifted towards earlier administration of plasma to reduce mortality\(^4\)-\(^7\). Ideally, blood products from the same blood group as the recipient are transfused. However, blood group determination delays time until administration of blood products in massively bleeding patients and is therefore not practical\(^8\). Transfusion of ABO non-identical plasma may increase the risk for transfusion-related complications caused by anti-A, anti-B and anti-A,\(\text{B}\) antibodies of the donor that bind to host erythrocytes\(^9\). AB plasma does not contain anti-A and anti-B antibodies, and is compatible with A, B, AB and O blood groups. Thereby, AB plasma is frequently used as the universal donor plasma product. However, blood group AB is less prevalent than other blood groups\(^10\). Also, policies to mitigate the risk of transfusion-related acute lung injury (TRALI) by deferral of donors with a high risk of carrying HLA antibodies may further hamper supply of a specific blood type of plasma\(^11\)-\(^15\). As a result, supplies of blood banks may run out of AB plasma. Alternatives for AB plasma are ABO identical plasma and ABO-non-identical plasma, of which ABO non-identical plasma can be divided in ABO compatible and ABO incompatible plasma. However, it is unknown whether these alternatives are associated with an increased incidence of transfusion-related complications and mortality. Therefore, the aim of this review was to determine the incidences of transfusion-related complications and mortality in patients transfused with either ABO identical, ABO compatible or ABO incompatible plasma.

MATERIAL AND METHODS

The present review was reported according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses)\(^16\).

STUDY SELECTION

Sepsis [tiab]) NOT (animal [mh] NOT human [mh]). No restriction on publication date was performed. Additionally, we have assessed all citations of the studies included for full text screening. After the search, duplicates were removed and studies were assessed for eligibility.

Studies on adult patients who were transfused with at least one unit of plasma investigating the incidence of transfusion-related complications and mortality in patients transfused with ABO identical, ABO compatible or ABO incompatible plasma in an emergency setting, were eligible for inclusion. All observational studies and randomized controlled trials with adult patients (≥18 years) and transfusion-related complications or mortality as primary or secondary outcome, were eligible. Exclusion criteria were animal studies, reviews, letters to the editors, case reports and editorials. The search was conducted by two independent researchers (SS and KB). Language was limited to English, German and Dutch. The primary outcome of this analysis was the incidences of mortality and transfusion-related complications like hemolytic reactions, transfusion-related acute lung injury (TRALI), adult respiratory distress syndrome (ARDS), acute renal failure (ARF), acute liver failure and thromboembolic events.

In order to assess the risk of bias of the included studies, the Newcastle Ottawa scale was used, since most of the studies were observational cohort studies. Studies were scored on different categories, i.e. comparability, methods used to select study participants and determination of outcome variables. The maximum score per item within the categories was two, the maximum score overall was 10.

Review Manager (RevMan 5, The Nordic Cochrane Centre) was used to pool data from different studies in a meta-analysis. Pooling of studies was performed if homogeneity was sufficient after assessment of study population, intervention, and outcome. The Inverse Variance method was used to test for homogeneity, which was expressed by an I2 lower than 75%. Randomized controlled studies and observational studies were not combined in the same meta-analysis. Results of meta-analyses were expressed by odds ratios and 95% confidence intervals.

RESULTS

In total, 1761 studies were screened and assessed for eligibility on abstract and title. Six studies were included after applying the inclusion and exclusion criteria, with in total 88,160 patients. Of these 6 studies, 5 studies were retrospective cohort studies and 1 study was a sub study of a randomized controlled transfusion trial. Figure 1 illustrates the flowchart of the inclusion process and Table 1 the characteristics of the included
studies. Two studies compared the use of ABO identical plasma with ABO compatible plasma, whereas the other 4 studies compared the use of ABO compatible with ABO incompatible plasma in an emergency release setting. Risk for bias was moderate as scores on the Newcastle Ottawa Scale varied between the 5-8 points. The number of studies included in this study, which examined alternatives for AB plasma in the emergency setting, was insufficient. Therefore results are reported narratively rather than systematically.

Transfusion of ABO identical vs ABO compatible plasma
Two retrospective single center studies\textsuperscript{8,18} investigated the effect of ABO compatible plasma and ABO identical plasma on the incidence of transfusion-related adverse events. The first registry study\textsuperscript{18} was conducted in Sweden and included a large number of patients (n=86082). All patients transfused with at least one plasma unit were included. The incidence of transfusion-related complications was not determined, however a trend was observed towards a higher 14-days post transfusion mortality rate in patients transfused with ABO plasma (RR 1.06, 95\% CI 0.997-1.13, p=0.006). This risk was most apparent in those patients who received large numbers of ABO compatible plasma. Of note, data in this study are obtained from a blood bank registry, with limited data on patient characteristics. Therefore, differences in patient characteristics between groups were unaccounted for in this study.

The second study\textsuperscript{8} was limited to trauma patients who were matched for patient characteristics in order to adjust for confounders. Although mortality rates were similar in both groups, a significant dose dependent increase in ARDS was observed in patients receiving ABO compatible plasma compared to patients receiving ABO identical plasma. Patients receiving 4 to 6 units of ABO compatible plasma had a 3-fold higher risk of ARDS than patients receiving ABO identical plasma. Patients receiving $\geq$6 units ABO compatible plasma had a 4-fold higher risk than patients receiving ABO identical plasma. This increase in ARDS was most apparent in patients with blood group O (17.4\% vs 7.8\%, P<0.001). An explanation may be that patients with blood type O may have higher titers of anti-A and anti-B antibodies resulting in higher numbers of circulating immune complexes. However, patients with blood type A and B were underpowered in this study and data to support this hypothesis are not available.

Pooling of data from these two above mentioned studies for transfusion-related complications was not feasible due to a lack of documentation. However, pooling of data for mortality was feasible and resulted in a significant increased risk for mortality in patients transfused with ABO compatible plasma compared to ABO identical plasma (Figure 2, OR 1.10, 95\% CI 1.04-1.15, p=0.0003).
FIGURE 1: Flow diagram of the inclusion process

- Search Pubmed N=732
- Search Ebase N=1014
- 15 of additional records identified through other sources

376 of records after duplicates removed

1385 of records screened

1366 of records excluded

19 of full-text articles assessed for eligibility

13 of full-text articles excluded, with reasons

6 of studies included in qualitative synthesis

FIGURE 2: Meta-analysis; effect of transfusion of ABO identical plasma versus ABO compatible non-identical plasma on mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ABO non-identical plasma</th>
<th>ABO identical plasma</th>
<th>Odds Ratio</th>
<th>Odd Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Inaba 2010</td>
<td>96</td>
<td>284</td>
<td>100</td>
<td>284</td>
</tr>
<tr>
<td>Shanwell 2009</td>
<td>1827</td>
<td>20220</td>
<td>5353</td>
<td>65762</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>20604</td>
<td>66046</td>
</tr>
<tr>
<td>Total events</td>
<td>1992</td>
<td></td>
<td>5453</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 1.99, df = 1 (P = 0.30); I² = 8%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.72 (P = 0.0002)</td>
<td></td>
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</tr>
<tr>
<td>Year</td>
<td>Author (Origin)</td>
<td>Design</td>
<td>Participants</td>
<td>Comparison</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>2009</td>
<td>Shanwell et al (Europe)</td>
<td>Retrospective</td>
<td>86082</td>
<td>ABO compatible non-identical ABO identical plasma</td>
</tr>
<tr>
<td>2010</td>
<td>Inaba et al (United States of America)</td>
<td>Retrospective</td>
<td>568</td>
<td>ABO compatible non-identical ABO identical plasma</td>
</tr>
<tr>
<td>2013</td>
<td>Zielinski et al (United States of America)</td>
<td>Retrospective</td>
<td>254</td>
<td>Emergency release A plasma ABO compatible ABO incompatible</td>
</tr>
<tr>
<td>2014</td>
<td>Chhibber et al (United States of America)</td>
<td>Retrospective</td>
<td>385</td>
<td>Emergency release A plasma ABO compatible ABO incompatible</td>
</tr>
<tr>
<td>2015</td>
<td>Zielinski et al (United States of America)</td>
<td>Retrospective</td>
<td>191</td>
<td>Emergency release A and AB plasma ABO compatible ABO incompatible</td>
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<tr>
<td>2015</td>
<td>Novak et al (United States of America)</td>
<td>Sub analysis RCT</td>
<td>680</td>
<td>Emergency release A and AB plasma ABO compatible ABO incompatible</td>
</tr>
</tbody>
</table>

ALI = acute lung injury, TRALI = transfusion-related acute lung injury, ARDS = acute respiratory distress syndrome, PE = pulmonary embolism, ARF = acute renal failure, DVT = deep venous thrombosis

NS = not significant,
 CHAPTER 8

Transfusion of ABO compatible vs ABO incompatible plasma

Of the 6 studies in this analysis, 4 studies\textsuperscript{10, 19-21} investigated the effect of ABO compatible plasma with ABO incompatible plasma on transfusion-related complications and mortality. The first study\textsuperscript{19} was a retrospective single centre study conducted in England and included 385 patients, for whom type A plasma was issued. Of these, 325 patients had blood group A or O and therefore received compatible plasma, 11 patients did not receive any blood products or died from exsanguination and 26 patients with blood group B were not exposed to A plasma. The remaining 23 patients received ABO incompatible A plasma. In these patients, no transfusion-related complications or other adverse outcomes were observed.

The second\textsuperscript{20} study was a retrospective single center study conducted in all transfused trauma patients, who received at least one emergency release A plasma unit. In total, data from 254 patients were analyzed, of which 35 patients received incompatible plasma. No differences in the incidence of ALI, TRALI, ARDS, deep venous thrombosis (DVT), pulmonary embolism (PE), ARF and mortality were observed. However, adjustment for confounders was not performed.

A retrospective multicentre cohort study\textsuperscript{10} from the same research group as the previous study included 191 bleeding trauma patients. Emergency release of A plasma (n=115) was compared to emergency release of AB plasma (n=76). Patients receiving AB plasma were more severely injured and were transfused with more blood products. The incidence of transfusion-related complications like ARF, DVT, PE and mortality appeared to be higher in the AB plasma group. However, after adjustment for confounders, no difference was observed in the incidence of mortality between both groups. Controlling for confounders was not performed for other transfusion-related complications.

A sub study\textsuperscript{21} of the randomized controlled Pragmatic Randomized Optimal Platelets and Plasma ratios (PROPPR) trial included in total 680 bleeding trauma patients in 12 different hospitals. Emergency plasma blood type A, blood group A with low-titer anti-B and blood group AB were used. No transfusion-related complications were observed. The incidence of transfusion reactions in the other groups was not mentioned. However, data of this study were briefly presented.

Pooling of data of these 4 studies in a meta-analysis was not possible due to heterogeneity of the studies.
DISCUSSION

The results of this review suggest that transfusion of ABO compatible plasma is associated with an increased incidence of lung injury and mortality compared to transfusion of ABO identical plasma. However, in an emergency setting when ABO identical plasma is not available, it appears that compatibility does not affect the outcome. Nevertheless, interpretations of results found in this review are hampered by small study numbers, design, heterogeneity in patient populations and incomplete documentation.

Ideally, blood group determination is performed before transfusion in order to reduce the risk for transfusion-related complications. Previous studies observed higher incidences of hemolytic reactions after transfusion of red blood cells when no compatibility between blood groups of donor and recipient was obtained\textsuperscript{22-25}. In plasma units, high levels of antibodies can be detected\textsuperscript{26}; however, whether the same assumption between donor and recipient as in red blood cells holds for the transfusion of plasma, is unknown. The findings of this review suggest that transfusion of ABO compatible plasma is actually associated with an increased risk for ARDS and mortality. However, these results are based on a very small number of studies\textsuperscript{18, 22}, which were conducted in different patient populations (trauma vs all recipients). In particular, the study which suggested an increased risk of ARDS after transfusion of compatible ABO plasma compared to ABO identical plasma did not report differences in population in terms of plasma donor gender. Actually, 5 of the 6 studies in this review did not document sex of plasma donors. Furthermore, this study was performed before TRALI mitigation, which hampers the interpretation of these results.

Regarding transfusion of ABO non-identical plasma, no differences in the incidence of transfusion-related complications between ABO compatible and incompatible plasma were observed. All studies issued AB or A plasma in the emergency setting. Two studies reported not even one adverse event in the A plasma group. This suggests that transfusion of A plasma is potentially as safe as AB plasma and might be used as a universal donor in the emergency setting. However, the evidence found in this review for this hypothesis was very limited. The number of studies was small, designs of studies did not always control for potential confounders and different patient populations were used, which hampered pooling and interpretation of results. Additionally, low rates of incompatible transfusions were observed in the studies. This makes it impossible to draw definite conclusions.

Observational data are required comparing the incidence of transfusion-related complications and mortality in patients transfused with ABO-identical, ABO compatible
and ABO incompatible plasma. In the meantime, we recommend issuing AB plasma as universal donor plasma product initially when the blood group is unknown and switch to ABO identical plasma once the blood group has been determined. If AB plasma is not available, transfusion of A plasma seems to be a safe option and is preferable above B or O plasma as it appears that A plasma does not increase the incidence of transfusion-related complications\textsuperscript{10,19-21} and is more common than B plasma\textsuperscript{10}. O plasma is unsuitable as this plasma carries both anti-A and anti-B antibodies.

**CONCLUSION**

Presently it is unclear whether there are safe alternatives for transfusion of AB plasma as universal donor in the emergency setting. The small number of available studies in this review may suggest that ABO compatible plasma increases the risk for lung injury and mortality compared to ABO identical plasma. However, in an emergency setting when ABO identical plasma is not available, it appears that compatibility does not affect the outcome. However, interpretation of results is hampered by small study numbers, design, heterogeneity in patient populations, and incomplete documentation.
REFERENCES

REFERENCES


