Coagulopathy and plasma transfusion in critically ill patients

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Chapter 14

Low risk TRALI donor strategies and the impact on the onset of transfusion-related acute lung injury; a meta-analysis

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Abstract

Background: Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality. In the past decade blood banks have implemented low risk TRALI donor strategies, including a male only donor policy for plasma containing blood products in order to prevent onset of TRALI. We performed a meta-analysis to determine whether use of low risk TRALI donor strategies for plasma indeed reduces onset of TRALI.

Study design and Methods: We searched Medline and Cochrane Central Register of Controlled Trials from January 1995 up to January 2013. Two reviewers independently extracted data on study characteristics, methods, and outcomes. Primary endpoint was onset of TRALI. Subgroup analyses were performed for patient populations prone to develop TRALI and general patient populations.

Results: Ten articles were included. Meta-analysis using a random effects model taking into account all transfused products, showed a significant reduction for the risk of TRALI after implementation of low risk TRALI donor strategies (OR 0.61 95%CI 0.42-0.88). Data from patient populations prone to develop TRALI showed a significant reduction of TRALI risk (OR 0.51 95%CI 0.29-0.90), while data from general patient populations showed a similar non-significant trend (OR 0.66 95%CI 0.40-1.09). Results were similar when taking only plasma products into account (OR 0.62 95% 0.42-0.92).

Conclusion: The introduction of low risk TRALI donor strategies for plasma containing products results in a reduction of TRALI.
Introduction

Transfusion-related acute lung injury (TRALI) is a life-threatening complication of blood transfusion. It causes high morbidity and is the leading cause of transfusion-related mortality for the last five years in the US [1]. TRALI is a clinical diagnosis and defined as a new episode of acute lung injury (ALI) occurring during, or within 6 hours after a blood transfusion in the absence of hydrostatic edema [2,3]. TRALI can be the result of a single event (e.g. transfusion), although most TRALI cases are postulated to be a ‘two-event’ entity. The first event is related to the underlying condition of the patient (e.g., infection or surgery) that causes activation of the pulmonary endothelium, leading to the sequestration and priming of neutrophils in the lung. The second event is the transfusion of a blood product, which activates the primed neutrophils in the lung, causing endothelial damage, and subsequently TRALI [4].

The transfusion factors can be divided in antibody and non-antibody mediated TRALI. Non-antibody mediated TRALI is caused by transfusion of stored cell containing blood products. Pro-inflammatory mediators which have accumulated during storage or the aged erythrocyte and platelet themselves have been implicated in non-antibody mediated TRALI [4-7]. Antibody mediated TRALI is caused by passive infusion of antibodies which causes neutrophil activation [8]. The latter form of TRALI is the most prevalent type [9,10] and will be subject of the current meta-analysis. Antibodies are present in plasma containing blood products. Plasma from female donors has been particularly implicated in the pathogenesis of TRALI [11-13]. Donor leukocyte reactive antibodies (HLA class I and II and anti-granulocyte (HNA) antibodies) are mainly found in (multiparous) female donors. This might be explained by allo-immunization during pregnancies [14]. Therefore, plasma derived from male donors should less likely cause TRALI than plasma derived from women. In 2003, the National Blood Service (NBS) in the UK was the first to implement a precautionary measure to reduce TRALI by the preferential use of plasma from male donors for transfusion [15]. Nowadays, more blood collection organizations have taken similar measures (table 1). Most of them use only, or preferentially, plasma from male donors for single donor plasma. Some blood collection organizations also implemented a (pre-dominantly) male only donor strategy for other high volume
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plasma products such as platelet concentrates [16]. However, the implementation of these low risk TRALI donor strategies for plasma containing blood products have serious consequences for the blood supply, in particular for the availability of AB plasma. So far, effects of these high volume plasma donor policies have only been published in observational studies [15,17-25].

To quantify the impact of low risk TRALI donor strategies for plasma on the onset of TRALI, a meta-analysis of all trials on this topic since 1995 was performed.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations was used for this meta-analysis [26]. We did not register our protocol.

Study Selection Criteria

To identify and review all studies that met the following criteria: observational controlled trials of transfusion, plasma, transfusion-related acute lung injury and acute lung injury were sought.

Search Strategy

To identify literature in electronic databases, MEDLINE from January 1, 1995, through January 1, 2013 was searched, by using the following medical subject heading (MeSH) terms: blood transfusion, plasma, ARDS and ALI. The following text words were used: TRALI and transfusion related acute lung injury. To identify observational studies, the MeSH terms case-control study and retrospective study were added.

Table 1 Overview of different low risk TRALI donor strategies [44].

<table>
<thead>
<tr>
<th>Low risk TRALI donor strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor deferral based on antibody screening</td>
</tr>
<tr>
<td>Screening all donors for HLA and/or HNA antibodies</td>
</tr>
<tr>
<td>Screening previously alloexposed donors for HLA and/or HNA antibodies</td>
</tr>
<tr>
<td>Donor deferral based on history of pregnancy or history of transfusion</td>
</tr>
<tr>
<td>Deferral of all female donors</td>
</tr>
</tbody>
</table>

Table 1 Overview of different low risk TRALI donor strategies [44].
The Cochrane Library (2012), which contains the CENTRAL Database of Controlled Trials, the Database of Abstracts of Review Effectiveness, and the Cochrane Database of Systematic Reviews, was also searched. In addition, the related articles feature of PubMed, which identifies related articles by using a hierarchical search engine that is not solely based on MeSH headings, was used. This search was completed with articles selected by 2 of the authors (AV and MM). Although search was also for non–English-language citations, subsequent article review involved only English-language publications.

**Study Selection**
After all citations based on our search strategy were identified, 2 of the authors (AV and MM) independently reviewed each abstract to confirm eligibility. Eligible studies evaluated use of low risk TRALI donor strategies for plasma and onset of lung injury and mortality. Low risk TRALI donor strategies were defined as predominantly or male only donor policy for plasma products, plasma from donors screened for absence of HLA/HNA antibodies and plasma from female donors without history of pregnancy. Both controlled and observational trials were considered eligible. If an abstract was selected as eligible, the same authors independently reviewed the respective article, if available, to confirm that it met inclusion criteria. To resolve discrepancies, the 2 reviewers either had to reach consensus, or use a third reviewer (JB). Inter-observer agreement for study selection was determined by κ, with a value above 0.80 indicating good agreement.

**Data Extraction**
Using a predefined data collection form, data from the studies to describe patient characteristics, study methods, and study findings were extracted. All data were abstracted independently by each of the 2 primary reviewers and verified for accuracy by the third reviewer, again with discussion used to resolve differences among reviewers. Both primary reviewers were physicians with formal training in clinical epidemiology and biostatistics. Corresponding authors of included studies were requested by email to provide missing data for the meta-analysis.
**Data Synthesis and Analysis**

Primary endpoint was the effect of the introduction of a low risk TRALI donor strategy for plasma containing products on occurrence of TRALI. Secondary endpoint was the effect of the introduction of a low risk TRALI donor strategy for plasma containing products on mortality among TRALI patients. Two subsets were analyzed: 1) the group of studies with data from local registries (patients prone to develop TRALI); 2) the group of studies with data from nationwide registries (general patient population). As patients often receive different types of blood products we analysed the effect of TRALI risk reduction strategies for all transfused products (denominator: total number of transfusions and numerator: all TRALI cases), in addition we assessed the effects of TRALI risk reduction strategies on plasma-induced TRALI (denominator: total number of plasma transfusions and numerator: plasma-induced TRALI cases).

The percentage of agreement before discussion among reviewers in study selection, study design, and data abstraction was measured. For data synthesis, evidence tables were constructed, to present data separately for the primary outcome variable: onset TRALI per transfused blood product and the secondary outcome variable: 30 day mortality. Furthermore data were presented based on study population e.g. at risk patients (ICU and surgery) or general hospital/region population.

The study design was classified as a randomized clinical trial, cohort study (prospective, retrospective, or historical control), case-control study, or outcomes study (cross-sectional).

The methodological quality of eligible studies was assessed using the modified Newcastle-Ottawa scale, a validated instrument designed to evaluate the quality of observational studies in systematic reviews and meta-analyses [27]. The quality of cohort studies and case control studies were assessed separately. Methodology was evaluated in three domains: selection of study population, comparability of study groups and the quality of outcome assessment. The kappa (κ) statistic was used to assess inter-observer agreement on study quality and a value above 0.80 was defined as good agreement [28].

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Statistical analysis
The meta-analysis was performed with a random effects model [29]. A random effect model, instead of a fixed effect model, was chosen to take into account heterogeneity of the studies. The common study characteristics are the incidence of TRALI cases for the total number of blood products transfused. Effect sizes are expressed as Odds ratio and their 95% confidence intervals. The odds is the number of TRALI cases by the number of transfused products in a defined context. An Odds ratio lower than one expresses a protective effect of a low risk TRALI donor strategy for plasma products to prevent onset of TRALI. An Odds Ratio higher than one shows a protective effect against TRALI of transfused products in the period before the introduction of a male only donor policy. Heterogeneity was expressed by the CHI² test. A cut-off value $p < 0.10$ was used to consider heterogeneity. A high $p$ value suggests that the heterogeneity is insignificant.
Analyses were performed in R: A language and environment for statistical computing. R Core Team (2013) [30].

Results

Study selection
Our pre-defined search strategy identified 118 records after removal of duplicates. After title review 53 citations were excluded and an additional 28 were excluded based on the abstract. Of 37 full text articles, 10 studies were considered eligible (table 2) and 27 studies were excluded after detailed review. An overview of the search is presented in figure 1. Inter-observer agreement for study selection was good ($\kappa = 0.84$).
Table 2: Overview of studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study and inclusion</th>
<th>Population</th>
<th>Country</th>
<th>Study year</th>
<th>Endpoint</th>
<th>Reported type of cases*</th>
<th>Plasma or/and Platelets</th>
<th>Percentage male donors after implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright[25]</td>
<td>retrospective active</td>
<td>surgery</td>
<td>UK</td>
<td>1998-2006</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Male only plasma and platelets</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Chapman[15]</td>
<td>retrospective passive</td>
<td>national</td>
<td>UK</td>
<td>1999-2006</td>
<td>onset TRALI</td>
<td>Non mixed cases</td>
<td>Predominantly male only plasma and platelets</td>
<td>80-90%</td>
</tr>
<tr>
<td>Vlaar[23]</td>
<td>retrospective active</td>
<td>ICU</td>
<td>Netherlands</td>
<td>2004-2007</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Male only plasma, platelet strategy not applicable</td>
<td>100%</td>
</tr>
<tr>
<td>Eder[18]</td>
<td>retrospective passive</td>
<td>national</td>
<td>US</td>
<td>2008-2011</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Predominantly male only plasma, platelet strategy not applicable</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Wiersum[24]</td>
<td>retrospective passive</td>
<td>national</td>
<td>Netherlands</td>
<td>2002-2009</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Male only plasma, platelet strategy not applicable</td>
<td>100%</td>
</tr>
<tr>
<td>Nakazawa[21]</td>
<td>prospective active</td>
<td>surgery</td>
<td>Japan</td>
<td>2008-2008</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Male only plasma, platelet strategy not applicable</td>
<td>100%**</td>
</tr>
<tr>
<td>Lin[20]</td>
<td>retrospective passive</td>
<td>national</td>
<td>Canada</td>
<td>2001-2009</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Predominantly male only plasma and platelets</td>
<td>86-100%</td>
</tr>
<tr>
<td>Funk[19]</td>
<td>retrospective passive</td>
<td>national</td>
<td>Germany</td>
<td>2006-2010</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>Male only plasma and plasma from female donors without history of pregnancy or without WBC antibodies, Platelet strategy not applicable</td>
<td>NA</td>
</tr>
<tr>
<td>Reference</td>
<td>Type of study and inclusion</td>
<td>Population</td>
<td>Country</td>
<td>Study year</td>
<td>Endpoint</td>
<td>Reported type of cases*</td>
<td>Plasma or/and Platelets</td>
<td>Percentage male donors after implementation</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------</td>
<td>------------</td>
<td>---------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Arinsburg[17]</td>
<td>retrospective passive</td>
<td>hospitals</td>
<td>US</td>
<td>2006-2008</td>
<td>onset TRALI</td>
<td>Non mixed cases</td>
<td>Predominantly male only plasma, platelet strategy not applicable</td>
<td>95-100% NA</td>
</tr>
<tr>
<td>Toy[22]</td>
<td>prospective active</td>
<td>hospitals</td>
<td>US</td>
<td>2006-2009</td>
<td>onset TRALI</td>
<td>Mixed cases</td>
<td>1 center male only plasma and predominantly male only platelets and 1 center male or never pregnant female donors for plasma and platelets</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

*for analysis non-mixed cases were converted to mixed cases in order to compare TRALI cases per total number of products transfused/distributed.
** during the study period (October 2007- January 2008)
Non mixed cases = a single product has been identified causing TRALI, mixed cases = all products within the 6 hours prior onset of TRALI have been taken into account.
NA = not applicable
BC = buffy coat
PLT = platelet
**Figure 1:** Inclusion flow. Number of articles identified and process for inclusion in the meta-analysis.

- **Additional records identified through other sources:** N=6
- **Records identified from databases:** 
  - Pubmed N=113
  - Cochrane N=1
- **Records after duplicates removed:** N=118
- **Records screened:** N=118
- **Excluded after title review:** N=53
- **Abstracts screened for eligibility:** N=65
- **Excluded after review of abstracts:** N=28
- **Full-text articles assessed for eligibility:** N=37
- **Excluded after review of full-text article:** N=27
- **Studies included in qualitative synthesis:** N=10
Study characteristics

No randomized controlled trials were found on the effect of a low risk TRALI donor strategy for plasma products on the onset of TRALI. Therefore we only included observational studies. Of these, two studies were prospective [21,22]. The remaining 8 studies had a retrospective design. Five studies were carried out within national registries using passive reporting of TRALI [15,18-20,24]. Four studies were carried out in various high-risk TRALI populations (e.g. intensive care and surgery patients) and in these studies TRALI was actively screened for [21-23,25]. One study was carried out in the general hospital patients, but using passive reporting [17]. All authors used Canadian Consensus Criteria to diagnose TRALI [2,31] In four studies data were also collected before 2004, the year of establishment of the Canadian Consensus Criteria [15,20,24,25]. Of these studies, one used American-European consensus criteria for ALI within 6 hours of transfusion [25] and the second defined TRALI cases as “acute dyspnea with hypoxia and bilateral pulmonary infiltrates occurring during or in the 24 hours after transfusion, with no other apparent cause” [15]. The remaining two studies retrospectively applied the Canadian Consensus Criteria [20,24]. Majority of the included studies were able to implement a 95 to 100% male only plasma donation policy. Two studies used, in addition to male only plasma, plasma from female donors without history of pregnancy or without HLA/HNA antibodies [19,22]. Four studies reported implementation of a male only donor strategy for PLTs products, in addition to a male only donor strategy for plasma products, as this are high plasma volume products as well [15,18,20,25]. Detailed characteristics of included studies are shown in tables 2, 3a and 3b.
Table 3a: Transfusion data of cohort studies reporting transfused units.

<table>
<thead>
<tr>
<th>Reference</th>
<th>TRALI cases</th>
<th>Total units transfused</th>
<th>Plasma transfused</th>
<th>Platelets transfused</th>
<th>Red blood cells transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Wright[25]</td>
<td>37</td>
<td>14</td>
<td>2917</td>
<td>1750</td>
<td>1026</td>
</tr>
<tr>
<td>Vlaar[23]</td>
<td>17</td>
<td>6</td>
<td>1350</td>
<td>485</td>
<td>174</td>
</tr>
<tr>
<td>Nakazawa[21]</td>
<td>3</td>
<td>2</td>
<td>1596</td>
<td>1480</td>
<td>467</td>
</tr>
<tr>
<td>Arinsburg[17]</td>
<td>9</td>
<td>1</td>
<td>227913</td>
<td>233685</td>
<td>47756</td>
</tr>
<tr>
<td>Toy[22]</td>
<td>23</td>
<td>10</td>
<td>89321</td>
<td>123731</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA=not available

Table 3b: Transfusion data of cohort studies reporting distributed units.

<table>
<thead>
<tr>
<th>Reference</th>
<th>TRALI cases</th>
<th>Total units distributed</th>
<th>Plasma distributed</th>
<th>Platelets distributed</th>
<th>Red blood cells distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Chapman[15]</td>
<td>58</td>
<td>12</td>
<td>16550000</td>
<td>5897000</td>
<td>1874000</td>
</tr>
<tr>
<td>Eder[18]</td>
<td>58</td>
<td>127</td>
<td>8320437</td>
<td>33810762</td>
<td>1664598</td>
</tr>
<tr>
<td>Wiersum[24]</td>
<td>68</td>
<td>31</td>
<td>4067000</td>
<td>1377000</td>
<td>545000</td>
</tr>
<tr>
<td>Lin[20]</td>
<td>105</td>
<td>31</td>
<td>7633560</td>
<td>2364400</td>
<td>1648400</td>
</tr>
<tr>
<td>Funk[19]</td>
<td>44</td>
<td>4</td>
<td>12170000</td>
<td>6200000</td>
<td>2360000</td>
</tr>
</tbody>
</table>
**Figure 2:** Meta-analysis for the onset of TRALI expressed over all products transfused before and after introduction of a low risk TRALI donor strategy for plasma containing products.

Effect sizes are expressed as Odds ratio and their 95% confidence intervals. The Odds is the number of TRALI cases by the number of transfused products. An Odds ratio lower than one expresses a protective effect against TRALI of products transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.

**Methodological quality**

The methodological quality of cohort studies is summarized in table 4 and of case-control studies in table 5. Quality assessment revealed that risk of bias of patient selection was low. However, included studies were heterogeneous regarding TRALI surveillance, using passive or active reporting. In addition, in studies carried out within national registries possibly not all transfused patients were observed for the minimum of 6 hours, which may have resulted in underreporting of TRALI. How-
Table 4. Quality of included cohort studies based on modified Newcastle-Ottowa Scale [27].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort representative?</td>
<td>Non-exposed cohort adequate?</td>
<td>Ascertainment of exposure clear?</td>
</tr>
<tr>
<td>Toy[22]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chapman[15]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eder[18]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wiersum[24]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lin[20]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Funk[19]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arinsburg[17]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 5. Quality of included case control studies based on modified Newcastle-Ottowa Scale [27]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort representative?</td>
<td>Non-exposed cohort adequate?</td>
<td>Ascertainment of exposure clear?</td>
</tr>
<tr>
<td>Wright[25]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vlaar[23]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nakazawa[21]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ever, this possible disadvantage was applicable for both periods, before and after implementation of TRALI risk reduction strategies. None of the nationwide studies corrected for confounding that may have been a possible source of bias. Blinded endpoint assessment was carried out in 7 studies, leaving the possibility of interpretation bias in the other 3 studies [15,18,19]. Inter-observer agreement for the quality assessment was good (median $\kappa = 0.89$ (range 0.40 to 1.0)). Heterogeneity was assessed using $I^2$ test. Heterogeneity was high ($p<0.01$) for all studies combined and low for pre-defined subgroup analysis ($p>0.10$).
Meta-analysis on the risk of TRALI

All TRALI cases
The effect of a low risk TRALI donor strategy for plasma containing products on the occurrence of TRALI for all transfused products in all studies is summarized in figure 2. Figures 3 and 4 show the effect of a low risk TRALI donor strategy for plasma containing products for high-risk populations and from nationwide registries respectively. Four studies showed an association between the introduction of a low risk TRALI donor strategy for plasma and a reduction of TRALI risk [17-19,22]. In five studies there was a trend to TRALI risk reduction after introduction of a low risk TRALI donor strategy for plasma [15,20,21,23,25] TRALI risk was unaffected in one study [24]. Pooled data of all studies showed a significant reduction for the risk of TRALI after implementation of a low risk TRALI donor strategy for plasma containing products (OR 0.61 95%CI 0.42-0.86).

Subgroup analysis revealed that data from local registries showed a significant reduction of TRALI risk (OR 0.51 95%CI 0.29-0.90). Patients in local registries consisted of critically ill patients [23] and patients undergoing major surgery [21,25]. As confirmed by one of the included studies [22] these patients are more prone to develop a TRALI reaction compared to a general patient population that also includes outpatients. Data from nationwide registries (general patient population) showed only a tendency towards protection of a low risk TRALI donor strategy for plasma containing products against TRALI (OR 0.66 95%CI 0.40-1.09) (figure 4).
Figure 3: Meta-analysis for the onset of TRALI in at risk patient populations expressed over all products transfused before and after introduction of a low risk TRALI donor strategy for plasma containing products.

Effect sizes are expressed as Odds ratio and their 95% confidence intervals. The odds is the number of TRALI cases by the number of transfused products. An Odds ratio lower than one expresses a protective effect against TRALI of products transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.
Figure 4: Meta-analysis for the onset of TRALI in general patient populations expressed over all products transfused before and after introduction of a low risk TRALI donor strategy for plasma containing products.

Effect sizes are expressed as Odds ratio and their 95 % confidence intervals. The odds is the number of TRALI cases by the number of transfused products. An Odds ratio lower than one expresses a protective effect against TRALI of products transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.
Plasma-induced TRALI

Included studies implemented different TRALI risk reduction strategies which also affected TRALI risk associated with other products than plasma. Therefore we performed an additional subgroup analysis to assess the effect of risk reduction strategies on plasma-induced TRALI. Nine of ten included studies provided data on plasma-induced TRALI [15,17-21,23-25]. The pooled effect of a low risk TRALI donor strategy on occurrence of TRALI per transfused unit of plasma is shown in figure 5. Figures 6 and 7 summarize the effect of low risk TRALI donor strategy on plasma-induced TRALI in for high-risk populations and from nationwide registries respectively. Data for plasma-induced TRALI showed a similar pattern as the data for all transfused products. Plasma-induced TRALI was significantly reduced after introduction of a low risk donor strategy (OR 0.62 95% CI 0.42-0.92). Patients from local registries (prone to develop TRALI) experienced a significant risk reduction (OR 0.51 95% CI 0.31-0.83), while data from nationwide registries (general patient population) showed a tendency to reduced risk of plasma-induced TRALI (OR 0.69 95% CI 0.42-1.13).

Meta-analysis on mortality

Data on 30-day mortality of the total cohort were only available from two studies [23,25]. Both studies showed a non-significant reduction of mortality of the cohort of transfused patients after implementation of a low risk TRALI donor strategy for plasma products (43% before vs. 35% after and 43% before vs. 23%, N.S. respectively). As there were only two studies no meta-analysis was performed on these data points. As antibody mediated TRALI is suggested to be the most severe form of TRALI it can be hypothesized that reducing antibody mediated TRALI would also result in a reduction of mortality among TRALI patients. Data on 30-day mortality among TRALI patients were available from four studies [22-25]. None of the studies showed a significant reduction of 30-day mortality among TRALI patients after the introduction of a low risk TRALI donor strategy for plasma containing products. Pooling of data from these four studies showed a trend to a reduction of mortality among TRALI patients after introduction of a low risk TRALI donor strategy for plasma containing products (OR 0.69 95%CI 0.27-1.75). An overview of the effect of introduction of a low risk TRALI donor strategy for plasma containing products on mortality among TRALI patients is given in figure 8.
**Figure 5:** Meta-analysis for the onset of plasma-induced TRALI expressed over all units of plasma transfused before and after introduction of a low risk TRALI donor strategy for plasma.

Effect sizes are expressed as Odds ratio and their 95% confidence intervals. The odds is the number of plasma-induced TRALI cases by the number of transfused units plasma. An Odds ratio lower than one expresses a protective effect against TRALI of plasma transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.
Figure 6: Meta-analysis for the onset of plasma-induced TRALI in at risk populations expressed over units of plasma transfused before and after introduction of a low risk TRALI donor strategy for plasma.

Effect sizes are expressed as Odds ratio and their 95 % confidence intervals. The odds is the number of plasma-induced TRALI cases by the number of transfused plasma. An Odds ratio lower than one expresses a protective effect against TRALI of plasma transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.
Figure 7: Meta-analysis for the onset of plasma-TRALI in general patient populations expressed over units of plasma transfused before and after introduction of a low risk TRALI donor strategy for plasma.

Effect sizes are expressed as Odds ratio and their 95 % confidence intervals. The odds is the number of plasma-induced TRALI cases by the number of transfused plasma. An Odds ratio lower than one expresses a protective effect against TRALI of plasma transfused in the period after the introduction of a low risk TRALI donor strategy for plasma.
Figure 8: Meta-analysis for mortality among patients developing TRALI before and after introduction of a low risk TRALI donor strategy for plasma containing products.

Effect sizes are expressed as Odds ratio and their 95% confidence intervals.
Discussion

This study is the first meta-analysis on the impact of low risk TRALI donor strategies for plasma on the onset of TRALI. The main findings of this study are; 1) implementation of a low risk TRALI donor strategy for plasma containing products, mainly male only donor policies, results in a significant reduction of onset of TRALI (OR 0.61, 95%CI 0.42-0.88). 2) introduction of a low risk TRALI donor strategy for plasma containing products results into a trend towards a reduction of 30-day mortality among TRALI-patients (OR 0.69, 95%CI 0.27-1.75). 3) at risk patient populations seem to benefit most of an introduction of a low risk TRALI donor strategy for plasma products.

Our study is able to confirm that the use of a low risk TRALI donor strategy such as a male only donor policy for plasma indeed results in a reduction of TRALI. The majority of TRALI cases, up to 89%, is thought to be antibody-mediated TRALI, caused by the passive infusion of donor leukocyte reactive antibodies, present in plasma containing blood products [10]. These antibodies are mainly induced by pregnancies and blood transfusions [14]. This was the basis for the hypothesis that the use of plasma from non-transfused male donors would minimize the antibody-mediated TRALI. Although this precautionary measure is effective it has serious consequences for the blood supply as the number of (potential) plasma donors is decreased by half, leading to a shortage of donors. In particular, a shortage in the availability of group AB plasma for transfusion is a serious concern [18,20]. From this point of view some countries introduced a preferentially male plasma donor strategy, as it was not feasible to use male-only plasma [15]. It should be noted that using a male only donor plasma policy does not totally prevent antibody mediated TRALI. First of all approximately 1% of the male donor population have antibodies [32]. Second, platelet products are also high plasma volume products. The plasma added to the pooled plasma does not originate from male only plasma in all countries. Third, red blood cells (RBCs) are suspended in an additive solution. Although the final product contains only a mean volume of 10 - 20 mL of plasma, RBCs are also known to be implicated in TRALI [13,33]. Fourth, not all countries exclude male donors who have a previous history of blood transfusion themselves from donating blood [34]. Of note, an association between previous transfusions and the development of allo-reactive
antibodies has not unequivocally been demonstrated [32]. Abovementioned reas-
ons also partly explain residual TRALI cases in included studies [15,17-21]. In addi-
tion, residual TRALI cases were reported to be caused by the use of group AB plasma 
from female donors [18,20].

Theoretically, to completely minimize the risk of antibody-mediated TRALI, all 
donors should be screened for HLA or HNA antibodies and positive donors should be 
excluded for all blood products containing plasma, regardless the amount of plasma. 
Indeed, some blood collection organizations have implemented antibody screening 
for all donors or all female donors [35]. This results in less donor loss, but accounts 
for higher costs and is very labour intensive. In addition, the occurrence of HNA 
antibodies may not be linked to pregnancy or gender. Therefore, further research is 
warranted before donor antibody-screening can be advocated.

There are alternatives that might be equally effective. Other countries (e.g. Norway, 
Finland, France) use pooled solvent/detergent plasma (SD plasma) instead of single 
donor plasma. Pooling has the advantage that it reduces the possible antibody load 
by dilution and by neutralizing antigens in the plasma pool, which minimizes the risk 
of TRALI [36]. The countries that use pooled SD plasma claim that they do not see 
TRALI reactions associated with this product. Another approach could be to ask the 
donors for a history of pregnancies and blood transfusions and subsequently test 
these donors for HLA and HNA antibodies. This method is a reliable predictor of 
HLA allo-immunisation [37]. However, it has been suggested that this method may 
eglect potential HLA and/or HNA positive donors as many pregnancies end in the 
first weeks after conception, while women weren’t even aware of a pregnancy. Of 
note, no association was found between early miscarriages and occurrence of allo-
immunisation of donors [32]. Also, donors are not always aware of receiving blood 
transfusions as they are sometimes given during an operation without notification 
afterwards.

The introduction of a low risk TRALI donor strategy for plasma containing products 
seemed to reduce 30-day mortality among patients developing TRALI. However, the 
observed reduction in mortality was only a trend that can possibly be explained 
by small number of studies and patients included. An explanation for mortality 
reduction among TRALI patients is tempting. Antibody mediated TRALI is reported 
to induce a more severe form of TRALI compared to non-antibody mediated TRALI
We hypothesize that as a result of a low risk TRALI donor strategy for plasma containing products, the frequency of antibody induced TRALI is reduced hereby contributing to a reduction in mortality among TRALI patients. Data from our meta-analysis showed that the implementation of a low risk TRALI donor strategy for plasma had the highest impact among at risk patient populations such as critically ill and surgery patients. This may be well explained by the threshold model of TRALI [40]. In this model a threshold must be overcome to induce a TRALI reaction. Factors that determine the threshold are the predisposition of the patient that determines priming of the lung neutrophils and the ability of the mediators in the transfusion to cause activation of primed neutrophils. A strong antibody-mediated response can cause severe TRALI in an otherwise “healthy” recipient. When activation status is too low, it is possible that priming factors in the transfusion are not strong enough to overcome the threshold. This concept has been proven in animal models [41-43]. This model explains why a low risk TRALI donor strategy for plasma has limited effect in the general patient population as they have no severe underlying condition to overcome the threshold. In this population a high volume of antibodies or a strong antibody antigen match is needed to overcome the threshold for onset of TRALI [22].

Our study has several limitations. First of all there are no randomized controlled trials on the effect of a low risk TRALI donor strategy for plasma on the onset of TRALI. It is also not expected that after the implementation of a low risk TRALI donor strategy for plasma in many countries a randomized controlled trial will follow. The observational nature of the studies and reliance on spontaneous reporting to the blood collection organizations or the nationwide registries (which may be far from complete) may have introduced bias. However, this bias would apply equally to the before and after period.

Second, implemented donor policies were not fully equal among all studies. Not all studies were able to achieve a 100% male only donor policy for plasma due to scarcity of products with a certain blood group. Some studies reported the implementation of a male only PLT policy in addition to a male only donor plasma policy. Others also report the introduction, next to male only plasma, of plasma from female donors without a history of pregnancy or without HLA/HNA antibodies. However, all
implemented policies assume the same underlying mechanism of excluding (potential) HLA or HNA positive plasma donors to prevent antibody mediated TRALI.

Third, some of the studies included TRALI patients before the consensus criteria for TRALI from the Canadian Consensus Conference in 2004 were established [2,31]. Before that year there were no universal criteria for TRALI and TRALI was most likely underreported. However, this will rather give an underestimation of the effect of the low risk TRALI donor strategy for plasma, as the period before 2004 is included in the before group. Fourth, heterogeneity was high for all studies combined and low for subgroup analysis. This can be explained by differences in population and observation period of included studies. The random effects model used in our study provides an average effect and in this way controls for variation in studies included. From this perspective we believe that the higher heterogeneity in the total group analysis has no or limited impact on our results and conclusions.

**Conclusion**

This is the first meta-analysis on the effect of implementation of a low risk TRALI donor strategy mainly based on a male only donor policy for plasma containing products to prevent TRALI. This study shows that introduction of a low risk TRALI donor strategy for plasma containing products reduces the onset of TRALI, especially in high risk patient populations. Furthermore there is a tendency that reduction of antibody mediated TRALI results in a lower mortality rate among TRALI patients.
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