Protocol TRALI-Review [1]

Title: Male-Predominant Plasma Transfusion Strategy for Preventing Transfusion-Related Acute Lung Injury (TRALI): a Systematic Review

Protocol information:
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The protocol:

Background:
Transfusion-related acute lung injury [TRALI] is a rare but potentially fatal complication of blood product transfusion. It is the leading cause of transfusion-related mortality in the US.[2] Since treatment options are very limited and mainly supportive,[3] there have been great efforts to develop effective prevention strategies.

Among all blood products, plasma-rich components such as fresh frozen plasma [FFP] and platelet concentrates carry the greatest risk of causing TRALI.[4-7] Most cases are due to donor antibodies against cognate recipient leucocyte antigens (Human Leucocyte Antigen [HLA] class I, HLA class II or Human Neutrophil Antigen [HNA]).[8-10] It has been shown that, due to exposure to fetal alloantigens during pregnancy, female donors have a higher prevalence of Anti-HLA-Ab antibodies than male donors.[11, 12] This has triggered the implementation of several TRALI risk mitigation policies during the mid to late 2000s throughout Europe and the US, in which transfusable plasma units were predominantly obtained from male donors (“male-predominant plasma transfusion strategy”).[5, 6, 13-19]

Some countries in Europe further excluded individuals with history of transfusions from their donor pool.[15] Recently, however, it has been shown conclusively that males, independent of history of transfusion, as well as females without history of pregnancy, all have approximately the same prevalence of HLA-Ab antibodies (1-2%). In contrast, a dose dependent increase in prevalence was found with increasing number of prior pregnancies (11 to 32% for 1 and 4+ pregnancies, respectively).[20, 21] These data suggest that, counter to common practice, there is no need to exclude never-pregnant females and donors with prior history of transfusion from plasma-donor pools.[13] There are many examples from observational studies in which male-predominant plasma transfusion strategies —with or without other TRALI mitigation strategies—decreased the incidence of TRALI.[2, 5, 6, 14, 17, 19]

In a study of patients undergoing cardiac surgery, however, male compared to female plasma transfusions were significantly associated with worse pulmonary function and short-term mortality, raising concerns that male-predominant transfusion strategies may not be beneficial for all patient subgroups.[22] Thus it is not clear whether this strategy should generally be adopted.[23]

A further disadvantage of this approach is the exclusion of a substantial proportion of the donor pool for plasma-rich components.[24] Thus far these policies have been feasible because in developed countries—where most studies have been undertaken—plasma is in excess of demand.[25] This may, however, not be true for less developed regions or if transfusion guidelines should change towards recommendation of higher plasma:red blood cell ratios (e.g. since 2006 US military guidelines encourages 1:1 ratio for combat-traumas).[26]

Despite its widespread adoption, the effectiveness of male-predominant plasma transfusion strategy has not been established in a systematic manner so far. The goal of our study is to fill this gap and to identify subgroups of patients in whom the effect may differ.

Objectives:
To assess the effect of male-predominant plasma transfusion strategy for preventing Transfusion-Related Acute Lung Injury (TRALI).

To assess whether the effect varies across different patient subgroups (effect heterogeneity).

Methods:

TRALI Definition:
Acute Lung Injury [ALI] within 6 hours of transfusion[27-29]

Criteria for selecting studies for this review:

Types of studies:

- Case-Control Studies
- Cohort Studies
- Randomized Controlled Trials

Types of participants:
- no restriction

Types of interventions:
- Transfusion of plasma from donor-pool mostly excluding ever-pregnant women (incl male-predominant donor-pool) compared to Transfusion of plasma from standard/unrestricted donor-pool

Types of outcome measures:
- Primary:
  - Incidence of TRALI (i.e. no. of cases/no. of units transfused during the study period)
  - Short-term all-cause Mortality (within 1 month of transfusion)
  - Long-term all-cause Mortality (> 1 month after transfusion)
- Secondary:
  - Hospital Length of Stay (HLOS)
  - Change in PaO2/FiO2 ratio within 1 day of transfusion
  - Change in Blood Pressure within 1 day of transfusion

Eligibility Ascertainment:
- by two separate reviewers blinded to each other searching through title/abstracts of retrieved articles and full-text as necessary (excluded studies + exclusion reasons will be recorded)
- discordant results will be resolved by consensus

Search methods for identification of studies:

- Searchers: FF, SS, JR, SM, CS
- Languages: English, Spanish, Italian, Greek, Hindi, German, French
- Sources – including material available until date of search in:
  - MEDLINE
  - EMBASE
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - FDA reports
  - Proceedings of AABB
  - Reference lists of eligible articles
  - Consultation of domain experts

Data collection and analysis:

Data:
- Data will be extracted by two separate investigators blinded to each other reviewing eligible full-text articles, entering abstracted data directly into a pre-designed Excel© spreadsheet. Disagreement will be resolved by consensus. Authors will be contacted in cases where insufficient data is available in the report.

Analysis:
- Software: STATA 12
- Meta-Analysis [MA]
  - We intend to obtain a precise estimate of the overall effect of using male-predominant plasma as a TRALI prevention strategy
• Appropriateness of MA will be judged based on the degree of bias in - and heterogeneity between studies

• Outcome Data
  o expected primary endpoints are dichotomous (development of TRALI vs not, death vs not) reported as counts or as aggregate effect measures (Incidence rate, OR, RR)
  o expected secondary endpoints are continuous (HLOS, PaO2/FiO2, Blood Pressure)

• Choice of Effect Measure
  o For the analysis we intend to use odds ratios as effect measures due to their favorable characteristics in terms of consistency and mathematical properties as well as due to the different study designs we expect to include in the analysis (case-cohort studies!)
  o To minimize the risk of misinterpretations we will try to eventually translate results in easier-to-grasp measures as RR/RD (using a weighted average of TRALI prevalence in the control groups)
  o For secondary, continuous outcomes we will use weighted mean differences as effect measures.

• Assessment of Heterogeneity
  o Forest Plot
  o Formal Testing:
    • rather than Cochrane’s Q to test for - we will use I² to assess the extent of heterogeneity (“high” level of heterogeneity if ≥50% vs “low” level of heterogeneity if <50%)[30]
  o Weighting method for pooled estimate
    • if pooling will be deemed appropriate (semi-subjective judgment that studies are not too biased and no “high” level of heterogeneity found) a random effects model based on the DerSimonian-Laird method will be used (to be conservative)[31]

• Examining Sources of Heterogeneity
  o Using stratified Meta-Analysis and/or Meta-Regression pre-specified characteristics will be examined as sources of heterogeneity:
    • presence of other TRALI mitigation strategies
    • exact type of intervention: male-only vs male-predominant vs exclusion of ever-pregnant women
    • different TRALI case definitions (transfused ALI/possible TRALI included vs not, passive vs. active surveillance, review and diagnosis by an expert panel vs non-experts at blood centers)
    • medical specialties
    • (average) numbers of transfusions per person
    • study region
    • severity of illness (critically-ill vs “normal” hospital populations vs outpatient)
    • baseline risk of TRALI (Bayesian Meta-Analysis in BUGS software)
    • age
    • gender
  o Using L’Abbe/Galbraith plots additional characteristics may be identified as potential sources of heterogeneity and assessed in an exploratory, post-hoc analysis using stratified Meta-Analysis and/or Meta-Regression

• Evaluation of the risk of bias
  Bias in Studies
  o Bias Assessment
    • based on full text articles, two separate reviewers will independently from and blinded to each other assess the risk of bias of several components for all eligible studies as low, high or unclear risk (disagreement resolved by consensus)
    • in observational studies components will include confounding (careful adjustment?), selection ((adjustment for) censoring?) and measurement bias (standard TRALI definition used, more than one assessor, assessment blinded to exposure status?)
    • in RCTs components will include selection (sequence generation?, allocation concealment), performance (blinding of participants and personnel?), detection (blinding...
of outcome assessment?), attrition (incomplete outcome data?), reporting bias (selective outcome reporting?) for RCT’s.

- Testing robustness of results with regards to potential bias
  - Sensitivity Analysis: Meta-Analysis stratified by the risk of bias in the studies and the type of studies will be performed
  - Search for - and assessment of very influential studies

Publication Bias
- Bias Assessment
  - Funnel Plot
  - complimentary summary measure from Egger’s regression test or if studies demonstrate large treatment effects, few events per study, or all studies are of similar sizes Harbord’s test (maybe also Begg’s rank correlation test) [32-34]
  - possibly Meta-Regression
- Testing robustness of results with regards to potential bias
  - Sensitivity Analysis: Meta-Analysis excluding small studies,
  - possibly calculation of “fail safe N” (number of studies of average precision with null results that would need to be added to the meta-analysis to reduce the overall association to non-significance).

Reporting
- According to MOOSE guidelines[35]
- Considering PRISMA guidelines as appropriate (e.g. Flow Chart)[36]

References: