UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Experimental strategies directed at inflammation and coagulation in ARDS and TRALI

Tuinman, P.R.

Publication date
2013

Citation for published version (APA):
Tuinman, P. R. (2013). *Experimental strategies directed at inflammation and coagulation in ARDS and TRALI.*

The effect of aspirin in transfusion-related acute lung injury in critically ill patients

Pieter R. Tuinman
Alexander P. Vlaar
Jan M. Binnekade
Nicole P. Juffermans

Abstract:

Background: Aspirin has been found to improve outcomes in an animal model of transfusion-related acute lung injury. We examined the association of aspirin use before admission to the intensive care unit and the development of transfusion-related acute lung injury in critically ill patients.

Methods: We performed a post-hoc analysis of a nested case-control study that had been undertaken in a tertiary referral hospital. Transfusion-related acute lung injury cases were matched with controls (transfused patients not developing lung injury).

Results: Of these 218 patients, 66 used aspirin (30%). Use of aspirin did not alter the risk of transfusion-related acute lung injury after transfusion of platelets (OR 1.06, CI 0.59-1.91, p=0.85), plasma (OR 1.06, 95% CI 0.59-1.92, p=0.84), or red blood cells (OR 1.09, 95% CI 0.61-1.94, p=0.77). Adjustment for confounding variables using propensity scoring also did not affect the risk of acquiring transfusion-related acute lung injury (p=0.66).

Conclusion: Aspirin did not protect against transfusion-related lung injury in this cohort of critically ill patients.

Background

Transfusion is very commonly required in critically ill patients [1], however transfusion-related acute lung injury (TRALI) is a major cause of morbidity and mortality [2,3]. The pathogenesis of TRALI seems to involve a 'two hit' process. The first event is the presence of an inflammatory condition in the host, causing endothelial activation leading to neutrophil sequestration in the lungs. The second event is the transfusion of a blood product containing either antibodies or factors that accumulate during storage, providing additional signals for endothelial damage and lung injury [3,4]. The 'two hit' concept is further supported by recent clinical data which suggest that the incidence of TRALI is higher among critically ill patient populations compared to the general hospital population [5,6], contributing significantly to adverse outcome in this patient group [6].

Long considered innocent bystanders, evidence is emerging that platelets are important mediators of lung injury [7,8]. There is anatomic and functional evidence that platelets are deposited in the acutely injured lung [9]. Besides the release of a variety of cytokines, activated platelets display adhesion molecules and other factors with signalling properties on their surface, enabling them to interact not only with the pulmonary endothelium, but also with one another and with leukocytes in the pulmonary vessels. Platelets triggering neutrophils leading to vascular damage has been shown to be a plausible mechanism in the pathogenesis of acute lung injury [7,8,10]. A key molecule involved in this interaction is thromboxane-A2 [7], which is released by platelet-neutrophil aggregates [11]. Several lines of evidence suggest that aspirin (acetylsalicylic acid), which decreases thromboxane-A2 synthesis, may protect against lung injury. Both platelet depletion and treatment with aspirin protected against lung injury and reduced mortality in a two-event mouse model of TRALI, suggesting a promising novel therapeutic approach [12]. In a human population-based cohort study, pre-hospital use of anti-platelet therapy was associated with a reduced incidence of acute lung injury in at-risk patients [13], but a more recent trial did not find an association between aspirin use and a protective effect against acute lung injury [14].

Aspirin is readily available, has few side effects and is inexpensive. It would be a major breakthrough if aspirin administration could prevent or reduce adverse outcomes related to blood transfusion. This would apply in particular to pre-operative use of aspirin in cardiac surgery patients, as these patients are at particular risk of bleeding, transfusion and hence TRALI. Indeed, prolonged cardiopulmonary bypass has recently been identified as an independent risk factor for TRALI [15]. A more detailed understanding of the effect of aspirin on TRALI might alter the risk-benefit assessment regarding its' pre-operative and postoperative administration. We therefore decided to study the effect of aspirin taken before admission to the intensive care unit (ICU) on TRALI by performing a post-hoc analysis of an already published observational study [6].

7

Methods

We previously undertook a nested case-control study [6] in all patients > 18 years of age admitted to a 30-bed mixed medical-surgical intensive care unit (ICU) of a university hospital in the Netherlands. The ICU is a "closed format" department in which patients are under the direct supervision of intensivists during their admission. A waiver for informed consent was approved by the Institutional Review Board. Patients who were re-admitted to the ICU were excluded from study. The exposure of interest was use of aspirin at the time of ICU admission. This was determined using the electronic medication system used in our hospital, and was checked with the medical notes. The average dose of aspirin was 80 or 100 mg once a day, which is the standard dose for primary and secondary prevention of cardiovascular disease used in The Netherlands and is comparable with international guidelines [16]. Additional predictor variables included patient-related risk factors for TRALI as previously identified [6], including emergency coronary artery bypass grafting, sepsis, haematologic malignancy, acute physiology and chronic health evaluation-II score, mechanical ventilation and massive transfusion. Information about risk factors for acute lung injury due to other causes were also recorded, including alcohol abuse, smoking, liver failure, diabetes, trauma, lung contusion, aspiration, pancreatitis, drug overdose, near drowning and pneumonia [17-22]. Risk factors had to be present at the time of ICU admission to be considered. Manual review of the medical notes by a trained investigator was used to determine the presence of the variables of interest. TRALI-cases were matched with controls (transfused patients not developing lung injury) on gender, age (within ten years) and admission diagnosis.

During the study, all transfused red blood cells were leukoreduced (buffy coat removed and the erythrocyte suspension was filtered to remove the leukocytes ($< 1x10^6$)), which is standard practice in the Netherlands [23]. Massive transfusion was defined as transfusion of more then ten units of blood products (red blood cells, fresh frozen plasma or platelets) within a 24-hour period [24]. It was assumed that each unit of fresh frozen plasma contained 325 ml of plasma, and each pool of platelet concentrate 250 ml of plasma.

TRALI was defined using the 2004 consensus definition (new-onset hypoxaemia or deterioration demonstrated by a PaO_2/FiO_2 <40 kPa, with bilateral pulmonary changes occurring within six hours of transfusion, in the absence of cardiogenic pulmonary oedema) [25]. Cardiogenic pulmonary oedema was identified when pulmonary arterial occlusion pressure was > 18 mmHg, or by the presence of at least two of the following; central venous pressure > 15 mmHg, a history of heart failure or valve dysfunction, ejection fraction < 45% as estimated by an echocardiogram, and a positive fluid balance [26]. Chest radiographs were scored for the presence of new onset bilateral interstitial abnormalities by two independent physicians, who were blinded to the predictor variables. When interpretation differed, the chest radiograph and the report given by the radiologist were reviewed again in order to achieve a consensus [6,26].

The design of the study was a post-hoc analysis in a cohort of TRALI patients. Comparisons between groups were made with the student's T-test or the Mann-Whitney rank-sum test, depending on distribution. Categorical variables were compared with the Chi-square test. For multivariate analysis, logistic regression analysis was performed. In a crude model, the risk of TRALI after transfusion with red blood cells, fresh frozen plasma or platelets was investigated. Then, we analysed whether the use of aspirin influenced the crude risk per amount of blood product, by effect modification and confounding. Effect modification was defined as a significant p-value for the interaction term. Confounding was defined as a change of > 10% in the beta-value of the crude relationship between aspirin and TRALI after adding covariates. Furthermore, a propensity score was determined for each patient, using predicted probabilities for use of aspirin. This was generated through a regression model treating the exposure factor, i.e. aspirin, as the dependent variable and selected possible confounding variables as predictor variables. Multiple linear regression was used to determine the association between use of aspirin and TRALI, after adjusting for the propensity score. Statistical analysis was performed using were SPSS (version 18.1, IBM SPSS, Chicago, IL, USA).

7

Results

Out of 5208 ICU admissions, 2024 patients were screened, of which 109 patients were diagnosed with TRALI [6], and then matched with controls (n=109). Of these (n=218), 66 used aspirin (30%). TRALI cases were more severely ill than controls, exemplified by a higher acute physiology and chronic health evaluation-II score [6]. There was also inequality between cases and controls for the amount of platelets and plasma transfused, emergency coronary bypass grafting, sepsis, mechanical ventilation, massive transfusion and hematologic malignancies (Table 1). There was no difference in other acute lung injury risk factors.

In a crude model, the risk of TRALI after transfusion was assessed. Platelet transfusion increased the risk of TRALI (Table 2). Transfusion of red blood cells and fresh frozen plasma per se did not increase the risk of TRALI; however, the total volume of plasma infused was significantly associated with TRALI.

Table 1 Aspirin use and baseline characteristics of cases of transfusion-related acute lung injury (TRALI) and transfused controls (no TRALI). Values are mean (SD) or number (proportion).

	TRALI (n=109)	No TRALI (n=109)	p-value
Aspirin use	34 (31%)	32 (29%)	0.77
Primary ICU admission category			
Medical	44 (41%)	40 (37%)	0.62
Surgical	33 (27%)	33 (30%)	1.00
Cardiovascular or cardiac surgery	32 (31%)	36 (33%)	0.63
Covariates used in propensity score			
APACHE-2 score	22 (8)	19 (8)	0.002
Emergency CABG	8 (7%)	1 (1%)	0.02
Sepsis	36 (33%)	20 (18%)	0.01
Mechanical ventilation	94 (86%)	80 (73%)	0.02
Massive transfusion	37 (34)	16 (15)	0.001
Amount of RBCs , units	1.8 (0.3)	1.9 (0.2)	0.70
Amount of PLTs , units*	0.4 (±0.1)	0.2 (±0.1)	0.03
Amount of FFP, units*	1.3 (0.2)	0.9 (0.2)	0.20

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; RBCs, red blood cells; FFP, fresh frozen plasma; PLTs, platelets; CABG, coronary artery bypass graft surgery.

Table 2 The risk of transfusion-related acute lung injury, stratified per blood product.

Covariate	OR (95% CI)	p-value
RBCs	0.98 (0.87 - 1.10)	0.74
PLTs	2.07 (1.07 - 4.00)	0.03
FFP	1.40 (0.80 - 2.60)	0.23
Total amount of plasma	1.50 (1.39 - 1.63)	0.04

RBCs, red blood cells; FFP, fresh frozen plasma; PLTs, platelets.

The use of aspirin did not differ between patients developing TRALI compared to transfused controls. Only two patients, also on aspirin, were taking clopidogrel. Use of aspirin did not alter the risk of acquiring TRALI after transfusion of red blood cells, fresh frozen plasma, platelets or total volume of plasma transfused (Table 3). The covariates described in Table 1 were used to calculate the propensity score. The relationship between aspirin and TRALI was then adjusted by this propensity score (Table 3). This confirmed that aspirin did not exert a protective effect on the development of TRALI. The absence of this effect cannot be explained by effect modification or confounding of the amount of blood products. Furthermore, we found no influence of other covariates that could have affected the relationship between aspirin and TRALI.

Table 3 The effect of aspirin use on the incidence of transfusion-related acute lung injury, adjusted for blood products and propensity score (the propensity score is the probability of a risk factor being associated with aspirin use).

Covariate	OR (95% CI)	p-value
Aspirin	1.09 (0.61 - 1.94)	0.77
Aspirin adjusted for amount of RBCs	1.09 (0.61 - 1.94)	0.77
Aspirin adjusted for amount of RBCs and FFP	1.06 (0.59 - 1.92)	0.84
Aspirin adjusted for amount of RBCs, FFP and PLTs	1.06 (0.59 - 1.91)	0.85
Aspirin adjusted for propensity score	0.91 (0.49 - 1.69)	0.66

RBCs, red blood cells; FFP, fresh frozen plasma; PLTs, platelets.

Discussion

We have not shown a protective effect of aspirin administration on the development of TRALI. Despite the use of the latest consensus definition of TRALI [2,26], the incidence of the condition in this study was higher compared to studies in the general hospital population [21], but in agreement with previous studies in critically ill patients [5,27]. These studies have identified risk factors for TRALI [5,6,28], including emergency cardiac surgery, sepsis and hematologic malignancies. Despite matching cases and controls, the incidence of risk factors for TRALI were unequal in the two groups. We corrected for sepsis and coronary artery bypass grafting in the propensity score, however this also failed to show a protective effect of aspirin. Correction for hematologic malignancy was not possible, as none of the patients with hematologic malignancies used aspirin. However, as the use of aspirin was the same in TRALI cases and controls, it is very unlikely that any possible protective effect of aspirin may have been off-set by a potential benefit due to the presence of hematologic malignancy.

Our finding is in contrast with results from a murine model of TRALI, in which it was shown that treatment with aspirin substantially reduced the incidence of the condition [12]. There may be several explanations for this discrepancy. First, the mouse model that was used was an immune-mediated model; mice primed with lipopolysaccharide were challenged with major histocompatibility Class I antibodies. However, lipopolysaccharide may not represent a clinically relevant trigger, and the infusion of antibodies may not have the same effect as blood transfusion. It is possible that the injury invoked in the immune-mediated model may have been the result of a direct interaction of the antibodies with the endothelial wall. Second, the dose of aspirin used in the mouse model is equivalent to around 5-8 times the dosage used in humans [29]. A dose of 30 mg aspirin per day results in virtually complete suppression of platelet Thromboxane A2 production via inhibition of cyclooxygenase-1 [30,31], which is sufficient to account for the antithrombotic effect of the drug. Anti-inflammatory effects of aspirin occur via inhibition of cyclooxygenase-2, whose expression

is up-regulated by cytokines, inflammatory stimuli, and a number of growth factors [32]. As aspirin is approximately 150 – 200-fold more potent as an inhibitor of cyclooxygenase-1 than cyclooxygenase-2, this explains the difference in dosage requirements of aspirin between its action as an antithrombotic and as an anti-inflammatory drug. Therefore, the preventative effect seen in the mouse model may have been due to the anti-inflammatory effect. This fits in with the observation that prostanoids such as prostaglandin-E_2, generated by the cyclooxygenase-2 enzyme, are present in high concentrations in the lung of animals and humans with sepsis and acute respiratory distress syndrome [33-35]. Third, patients with cardiovascular disease may be resistant to aspirin [36]. Although it is controversial whether laboratory evidence of aspirin resistance is clinically significant, we can not exclude the possibility that a high number of weak responders to aspirin in this study may have accounted for the absence of a protective effect on TRALI we have demonstrated. Lastly, it should be remembered that the number of circulating platelets is higher and the number of polymorphonuclear neutrophils is lower in mice compared to humans, rendering the platelet/neutrophil ratio in circulating blood substantially different in the two species [37,38].

Platelets have been shown to play a pivotal role in models of acute lung injury due to other causes [7,8]. There are data indicating aspirin protects against onset of acute lung injury in a population-based cohort study [13]. A more recent study found no association between pre-hospitalisation aspirin therapy and acute lung injury [14]. In line with this, our study did not demonstrate a protective effect of aspirin in terms of mediating lung injury in the clinical setting. One possible reason for this contrast between the results may be related to differences in patient population and in study design, as we analysed patients who actually fulfilled TRALI consensus criteria, as opposed to patients who were at risk for development of acute lung injury [13].

This analysis has important limitations. It should be noted that our study was not designed to look at the effect of aspirin in TRALI, thereby carrying a potential for bias and confounding. Even with the use of propensity matching, designed to eliminate confounding, we cannot exclude the possibility that there were other confounders that were unaccounted for, and that these may have contributed to the results. Therefore, this study does not rule out a protective effect of aspirin on TRALI. Furthermore, critically ill patients are more often diagnosed with "possible TRALI" compared to a general hospital population. This applies, by consensus definition, to patients who have other acute lung injury risk factors besides transfusion. Therefore, our results can not be extrapolated to a general hospital patient population. Despite these limitations, we think it is important to report the results of this analysis of aspirin and TRALI, since this was conducted in one of the largest TRALI cohorts to date.

In conclusion, aspirin did not protect against TRALI in this cohort of critically ill patients. The results of this study may contribute to the design of prospective studies on the association between aspirin and lung injury.

Reference List

1. Rao MP, Boralessa H, Morgan C, Soni N, Goldhill DR, Brett SJ *et al.*: **Blood component use in critically ill patients.** *Anaesthesia* 2002, **57:** 530-534.

2. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA: **Proceedings of a consensus conference: towards an understanding of TRALI.** *Transfus Med Rev* 2005, **19:** 2-31.

3. Barrett NA, Kam PC: **Transfusion-related acute lung injury: a literature review.** *Anaesthesia* 2006, **61:** 777-785.

4. Silliman CC: **The two-event model of transfusion-related acute lung injury.** *Crit Care Med* 2006, **34:** S124-S131.

5. Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB *et al.*: **Transfusion-related acute lung injury in the critically ill: prospective nested case-control study.** *Am J Respir Crit Care Med* 2007, **176:** 886-891.

6. Vlaar AP, Binnekade JM, Prins D, van SD, Hofstra JJ, Schultz MJ *et al.*: **Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study.** *Crit Care Med* 2010, **38:** 771-778.

7. Zarbock A, Ley K: **The role of platelets in acute lung injury (ALI).** *Front Biosci* 2009, **14:** 150-158.

8. Bozza FA, Shah AM, Weyrich AS, Zimmerman GA: **Amicus or adversary: platelets in lung biology, acute injury, and inflammation.** *Am J Respir Cell Mol Biol* 2009, **40:** 123-134.

9. Heffner JE, Sahn SA, Repine JE: **The role of platelets in the adult respiratory distress syndrome. Culprits or bystanders?** *Am Rev Respir Dis* 1987, **135:** 482-492.

10. Hidalgo A, Chang J, Jang JE, Peired AJ, Chiang EY, Frenette PS: **Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury.** *Nat Med* 2009, **15:** 384-391.

11. Zarbock A, Singbartl K, Ley K: **Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation.** *J Clin Invest* 2006, **116:** 3211-3219.

12. Looney MR, Nguyen JX, Hu Y, Van Ziffle JA, Lowell CA, Matthay MA: **Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury.** *J Clin Invest* 2009, **119:** 3450-3461.

13. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ: **Pre-hospitalization anti-platelet therapy is associated with a reduced incidence of acute lung injury: A population-based cohort study.** *Chest* 2010.

14. Kor DJ, Erlich J, Gong MN, Malinchoc M, Carter RE, Gajic O *et al.*: **Association of prehospitalization aspirin therapy and acute lung injury: Results of a multicenter international observational study of at-risk patients.** *Crit Care Med* 2011, **39:** 2393-2400.

15. Vlaar AP, Hofstra JJ, Determann RM, Veelo DP, Paulus F, Kulik W *et al.*: **The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study.** *Blood* 2011, **117:** 4218-4225.

16. Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC *et al.*: **AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute.** *Circulation* 2006, **113:** 2363-2372.

17. Benson AB, Austin GL, Berg M, McFann KK, Thomas S, Ramirez G *et al.*: **Transfusion-related acute lung injury in ICU patients admitted with gastrointestinal bleeding.** *Intensive Care Med* 2010, **36:** 1710-1717.

18. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R *et al.*: **Diabetic patients have a decreased incidence of acute respiratory distress syndrome.** *Crit Care Med* 2000, **28:** 2187-2192.

19. Moss M, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Burnham EL *et al.*: **Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock.** *Crit Care Med* 2003, **31:** 869-877.

20. Iribarren C, Jacobs DR, Jr., Sidney S, Gross MD, Eisner MD: **Cigarette smoking, alcohol consumption, and risk of ARDS: a 15-year cohort study in a managed care setting.** *Chest* 2000, **117:** 163-168.

21. Wallis JP, Lubenko A, Wells AW, Chapman CE: **Single hospital experience of TRALI.** *Transfusion* 2003, **43:** 1053-1059.

22. Ware LB, Matthay MA: **The acute respiratory distress syndrome.** *N Engl J Med* 2000, **342:** 1334-1349.

23. van Hilten JA, van de Watering LM, van Bockel JH, van de Velde CJ, Kievit J, Brand R *et al.*: **Effects of transfusion with red cells filtered to remove leucocytes: randomised controlled trial in patients undergoing major surgery.** *BMJ* 2004, **328:** 1281.

24. Sihler KC, Napolitano LM: **Massive transfusion: new insights.** *Chest* 2009, **136:** 1654-1667.

7

25. Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S *et al*.: **Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel.** *Transfusion* 2004, **44:** 1774-1789.

26. Gajic O, Gropper MA, Hubmayr RD: **Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury.** *Crit Care Med* 2006, **34:** S109-S113.

27. Benson AB, Moss M, Silliman CC: **Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill.** *Br J Haematol* 2009, **147:** 431-443.

28. Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L *et al*.: **Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors.** *Blood* 2003, **101:** 454-462.

29. Reagan-Shaw S, Nihal M, Ahmad N: **Dose translation from animal to human studies revisited.** *FASEB J* 2008, **22:** 659-661.

30. Patrignani P, Filabozzi P, Patrono C: **Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects.** *J Clin Invest* 1982, **69:** 1366-1372.

31. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C: **Low-dose aspirin for the prevention of atherothrombosis.** *N Engl J Med* 2005, **353:** 2373-2383.

32. Schror K: **Aspirin and platelets: the antiplatelet action of aspirin and its role in thrombosis treatment and prophylaxis.** *Semin Thromb Hemost* 1997, **23:** 349-356.

33. Adawi A, Zhang Y, Baggs R, Finkelstein J, Phipps RP: **Disruption of the CD40-CD40 ligand system prevents an oxygen-induced respiratory distress syndrome.** *Am J Pathol* 1998, **152:** 651-657.

34. Fulkerson WJ, MacIntyre N, Stamler J, Crapo JD: **Pathogenesis and treatment of the adult respiratory distress syndrome.** *Arch Intern Med* 1996, **156:** 29-38.

35. Fukunaga K, Kohli P, Bonnans C, Fredenburgh LE, Levy BD: **Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury.** *J Immunol* 2005, **174:** 5033-5039.

36. Ben-Dor I, Kleiman NS, Lev E: **Assessment, mechanisms, and clinical implication of variability in platelet response to aspirin and clopidogrel therapy.** *Am J Cardiol* 2009, **104:** 227-233.

37. Mestas J, Hughes CC: **Of mice and not men: differences between mouse and human immunology.** *J Immunol* 2004, **172:** 2731-2738.

38. Tsakiris DA, Scudder L, Hodivala-Dilke K, Hynes RO, Coller BS: **Hemostasis in the mouse (Mus musculus): a review.** *Thromb Haemost* 1999, **81:** 177-188.