Transfusion-related acute lung injury in the critically ill: a translational approach
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Chapter 18

Correction of subclinical coagulation disorders before tracheotomy in the intensive care

A randomized controlled trial


Submitted
Abstract

Background: Percutaneous dilatational tracheotomy (PDT) is a simple bedside procedure in critically ill patients. Intensive care unit (ICU) patients however, frequently have coagulation disorders which could place them at higher risks for bleeding during or after PDT. In a randomized controlled trial we determined the effect of correction of mild coagulation disorders on bleeding during and after PDT.

Methods: ICU patients planned for bedside PDT with (a) prothrombin time (PT) between 14.7 – 20.0 seconds, (b) platelet count between 40–100 x $10^9$/L and/or (c) active treatment with acetylsalicylic acid were randomized to receive infusion with fresh frozen plasma (FFP) and/or platelets (“correction”) versus no transfusion (“no correction”) before PDT.

Results: We randomized 35 patients to the “correction” group and 37 patients to the “no correction” group. Nineteen patients in the “correction” group received FFP; 23 patients were transfused with platelets. In patients that received FFP, the decrease in PT was only marginal (mean decrease 0.40 ± 0.56 seconds); median increase in platelets after transfusion of platelets was 35 [11 – 47] x $10^9$/L. There were no patients with clinically significant bleeding in either group. Median blood loss in the “correction” group was 3 [IQR: 1 – 6] grams compared to 3 [IQR: 2 – 6] grams in the “no correction” group ($P = 0.96$). The duration that blood was visible in tracheal aspirates was short (a median of 1 hour) and not affected by the study intervention.

Conclusions: Bleeding during and after bedside PDT in ICU patients with mild coagulation disorders is rare in our setting. Correction of subclinical coagulation disorders by transfusion of FFP and/or platelets does not affect bleeding during or after PDT.
Introduction

Percutaneous dilatational tracheotomy (PDT) is a common surgical procedure in mechanically ventilated intensive care unit (ICU) patients, especially in those who have an (expected) prolonged duration of mechanical ventilation. One feared complication of PDT is periprocedural bleeding. Although PDT is a simple surgical procedure, the rate of periprocedural bleeding is reported to be as high as 5%. Many ICU patients have coagulation abnormalities, varying from mild lengthening of coagulation tests and/or mild thrombocytopenia, to severe coagulation disorders. In addition, a substantial number of ICU patients receive active treatment with acetylsalicylic acid. There is evidence that PDT can be safely performed in patients with severe coagulation disorders if these are carefully corrected via infusion of fresh frozen plasma (FFP) and/or platelets directly before the procedure. However, it is currently unclear whether or not PDT can be performed safely in ICU patients with uncorrected mild coagulation disorders. A recent postal survey in the Netherlands showed that the opinions regarding which coagulation disorders should be corrected before PDT varied greatly. Notably, it is common practice in many ICUs to correct even mild coagulation disorders. We performed a randomized controlled trial to determine the effect of correction of mild coagulation disorders on bleeding during and after PDT. We hypothesized that the correction of mild coagulation disorders before PDT via transfusion of FFP and/or platelets decreases the rate of bleeding, thus outweighing the costs and risks associated with transfusion.

Materials and methods

Study design and setting

Open–label randomized controlled trial in a 32–bed mixed medical–surgical ICU of a University–affiliated hospital in the Netherlands. The study was approved by the local ethics committees. Each patient or the legal representative gave written informed consent.

Inclusion and exclusion criteria

Patients planned for bedside PDT with mild coagulation disorders (prothrombin time, PT 14.7 – 20.0 seconds, and/or platelet counts 40–100 x 10^9/L) and/or active treatment with acetylsalicylic acid at any dose were included. Exclusion criteria were: a) age < 18 years; b) need for surgical tracheotomy; c) contraindications for transfusion of blood products; d) use of clopidogrel. The
patient was also excluded from participation in this trial if the attending physician insisted on the need for transfusion of FFP and/or platelets.

**Study groups**

Patients with a prolonged PT (normal values are between 11.0 and 14.7 seconds) assigned to the “correction group” received 1 or 2 units of FFP (1 unit contains 300 ml of FFP: if the PT was between 14.7–18.0 seconds the patient received 1 unit of FFP; if the PT was between 18.0–20.0 seconds the patient received 2 units of FFP). Patients with a low platelet count and/or active use of acetylsalicylic acid assigned to the correction group received 5 units of platelet concentrates prepared from 5 pooled buffy coats. Patients assigned to the “no correction” group received neither plasma nor platelets. However, FFP and/or platelets were made available for immediate transfusion in case bleeding occurred during or after PDT.

**PDT procedure**

Local policy for tracheotomy included all ICU patients with respiratory failure expected to require mechanical ventilation for > 10 days. Other indications for tracheotomy included persisting Glasgow Coma Score < 8, (suspected) critical illness polyneuromyopathy (CIPNM) and/or muscle weakness, inability of the patient to maintain a patent airway, sputum retention, failed tracheal extubation, insufficient swallowing or cough reflex, indication for home ventilation and obstruction of the upper airways. Contraindications included severe coagulation disorders (e.g., disseminated intravascular coagulation) and/or anticoagulation (e.g., infusion of activated protein C), complex or abnormal anatomy, need for prone ventilation, hemodynamic instability and ventilatory instability.

PDT (Ciaglia Blue Rhino, Cook, Son, Netherlands) was the method of choice unless abovementioned contraindications required a surgical approach. PDT was performed by trained ICU physicians under fiberoptic bronchoscopy guidance. Enteral feeding was stopped 2 hours before the procedure. During PDT the blood pressure, heart rate, respiratory rate, oxygen saturation, and cardiac rhythm strip was monitored. Mechanical ventilation was maintained in a mandatory mode while the inspired oxygen fraction was increased to 100%. In the event of hypotension due to anesthetics and opioids, 500 ml of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (Voluven®, Fresenius Kabi, Den Bosch, The Netherlands) could be administered. In the event that the blood pressure remained low, norepinephrine was started or the dose adjusted.
Data collection

The volume of periprocedural blood loss was calculated by measuring the difference in weight of the gauzes before and after the procedure. The intensity of intra–tracheal periprocedural bleeding was scored by the endoscopist (“none”, “mild but not requiring intra–tracheal suction”, or “severe requiring intra–tracheal suction”). After the procedure the trachea was suctioned every hour (until a maximum duration of 12 hours) and the duration that blood was visible in the tracheal aspirates was documented.

Other data to be collected included patient demographics, admission type, reason for admission: age, gender, APACHE II score, time from ICU admission until tracheotomy, reason for mechanical ventilation, reason for tracheotomy, length of ICU stay, ICU and hospital mortality.

Definitions

Periprocedural bleeding was defined as bleeding during or within the first 12 hours post procedure. Clinically irrelevant bleeding was defined as: procedural bleeding of < 100 grams of blood that could be controlled with the application of local pressure and not requiring re–exploration or transfusion of packed red cells. Minor bleeding was defined as: blood loss > 100 grams that could be controlled with the application of local pressure and not requiring re–exploration or transfusion of packed red cells. Major bleeding was defined as the presence of blood in the airways requiring repeated suction post procedure, requiring emergency surgery, and/or transfusion of packed red cells.

Randomization

A computer–generated randomization scheme was used. Each assignment (“correction” or “no correction”) was recorded on a tri–folded piece of paper enclosed in a consecutively numbered, opaque sealed envelope.

Cost effectiveness

Costs were analyzed from a provider’s perspective. The differences in costs of transfusion of FFP, platelets and packed red cells were calculated between the study groups.

Power analysis

The power calculation was based on reviews of complications during or after PDT,6,7,18 in which the rate of bleeding was estimated to be approximately 5%. We expected a higher rate of bleeding of 20% in patients with uncorrected mild coagulopathy before tracheostomy.
coagulation disorders, and thus hypothesized a 15% absolute decrease following the correction of subclinical bleeding disorders. We calculated that in order to detect a difference, with a two–sided significance level of 0.05 and a power of 80%, 76 patients had to be included in each group.

**Statistical analysis**

Data were analyzed according to intention–to–treat analysis. Continuous normally distributed variables were expressed as mean and standard deviation, or as medians and interquartile ranges, where appropriate. Categorical variables were expressed as n (%). To test groups of continuous normally distributed variables, a Student’s t-test was used. Likewise if continuous data was not normally distributed the Mann-Whitney U test was used. Categorical variables were compared with the Chi–square test or Fisher’s exact tests when appropriate. A P–value < 0.05 was considered statistical significant. Data was analyzed in SPSS version. 16.0.

**Results**

Between July 2007 and October 2009, 355 patients underwent PDT, of which 72 met the inclusion criteria (see figure 1). 35 patients were randomized to the “correction” group, and 37 patients to the “no correction” group. Baseline characteristics were balanced between the study groups (table 1). After randomization PDT was

![Inclusion flowchart](image)

**Figure 1.** Inclusion flowchart
### Table 1. Baseline characteristics of the study groups

<table>
<thead>
<tr>
<th>Demography</th>
<th>Correction N = 35</th>
<th>No correction N = 37</th>
<th>P–value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, N (%)</td>
<td>22 (63)</td>
<td>16 (43)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age (years), median [IQR]</td>
<td>64 [56 – 72]</td>
<td>68 [60 – 76]</td>
<td>0.21</td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>22 ± 8</td>
<td>21 ± 7</td>
<td>0.49</td>
</tr>
<tr>
<td>Time from admission to tracheotomy (days), mean ± SD</td>
<td>9 ± 6</td>
<td>10 ± 6</td>
<td>0.62</td>
</tr>
<tr>
<td>Reason for mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post–surgical, N (%)</td>
<td>5 (14)</td>
<td>9 (34)</td>
<td>0.28</td>
</tr>
<tr>
<td>Coma, N (%)</td>
<td>3 (9)</td>
<td>4 (11)</td>
<td>0.75</td>
</tr>
<tr>
<td>Cardiac arrest, N (%)</td>
<td>4 (11)</td>
<td>4 (11)</td>
<td>0.93</td>
</tr>
<tr>
<td>Acute respiratory failure, N (%)</td>
<td>19 (51)</td>
<td>18 (49)</td>
<td>0.63</td>
</tr>
<tr>
<td>Trauma, N (%)</td>
<td>2 (6)</td>
<td>17 (46)</td>
<td>0.48</td>
</tr>
<tr>
<td>Other, N (%)</td>
<td>2 (6)</td>
<td>17 (46)</td>
<td>0.48</td>
</tr>
<tr>
<td>Reason for tracheotomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated weaning, N (%)</td>
<td>10 (29)</td>
<td>17 (46)</td>
<td>0.13</td>
</tr>
<tr>
<td>Expected prolonged duration of mechanical ventilation, N (%)</td>
<td>12 (34)</td>
<td>4 (11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Need for frequent airway suctioning, N (%)</td>
<td>3 (9)</td>
<td>2 (5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Low GCS, N (%)</td>
<td>5 (14)</td>
<td>6 (16)</td>
<td>0.37</td>
</tr>
<tr>
<td>CIPNM, N (%)</td>
<td>4 (11)</td>
<td>5 (14)</td>
<td>0.54</td>
</tr>
<tr>
<td>Other, N (%)</td>
<td>1 (3)</td>
<td>3 (8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days), median (IQR)</td>
<td>11 (7–24)</td>
<td>16 (10–21)</td>
<td>0.16</td>
</tr>
<tr>
<td>Length of stay ICU (days), median [IQR]</td>
<td>15 [8 – 29]</td>
<td>21 [14 – 26]</td>
<td>0.21</td>
</tr>
<tr>
<td>ICU mortality, N (%)</td>
<td>4 (11)</td>
<td>11 (31)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital mortality, N (%)</td>
<td>11 (31)</td>
<td>15 (41)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hematological values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged PT, N (%)</td>
<td>19 (54)</td>
<td>22 (59)</td>
<td>0.66</td>
</tr>
<tr>
<td>PT, seconds, mean ± SD*</td>
<td>16.0 ± 1.2</td>
<td>16.6 ± 1.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Low platelet count, N (%)</td>
<td>13 (37)</td>
<td>10 (27)</td>
<td>0.36</td>
</tr>
<tr>
<td>Platelet count, x 109/L, median (IQR) *</td>
<td>81 [63 – 85]</td>
<td>56 [47 – 70]</td>
<td>0.03</td>
</tr>
<tr>
<td>Active treatment with acetylsalicylic acid, N (%)</td>
<td>11 (31)</td>
<td>12 (32)</td>
<td>0.93</td>
</tr>
<tr>
<td>&gt; 1 coagulation disorder present, N (%)</td>
<td>8 (23)</td>
<td>7 (19)</td>
<td>0.68</td>
</tr>
<tr>
<td>Decrease in PT after transfusion, seconds, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 unit of plasma (N = 17)</td>
<td>0.40 ± 0.56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 units of plasma (N = 1)</td>
<td>1.4 (–)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increase in platelet count after transfusion, x 109/L, median [IQR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 units of platelets (N = 23)</td>
<td>35 [11 – 47]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Score; CIPNM, critical illness polyneuromyopathy. *Only patients that had a prolonged PT or low platelets are included in the calculation of means/medians.
not performed in 7 patients due to unexpected difficulties in the recognition of anatomical landmarks, and in 1 patient as a result of logistical problems. Although a sample size of 152 patients was considered necessary to find a difference of 15% in bleeding between groups, the study was prematurely terminated. Recognition of the small amount of observed blood loss even in the “no correction” group resulted in an increasing resistance of the physicians to transfuse FFP and/or platelets in the “correction” group. With a yearly incidence of approximately 150 PDT’s we would need approximately another 3 years to complete this study. We considered these arguments valid and decided to prematurely terminate the study.

**Correction of mild coagulation disorders**

A total of 19 units of FFP and 23 units of platelets were transfused. Twelve patients were transfused with FFP alone, 17 patients received only platelets, and 6 patients received both blood products.

**Blood loss with PDT**

Median blood loss during PDT was similar between groups (table 2). In the “correction” group mild intra-tracheal bleeding occurred once in every 1.3 patients and in the “no correction” group once in every 1.7 patients, \( P = 0.16 \). One in every 10 patients in the “correction” group experienced a severe intra-tracheal bleed, compared to 1 in every 16 patients in the “no correction” group. The duration that blood was visible in the tracheal aspirates was not affected by correction (table 2). In 1 patient on active acetylsalicylic acid treatment bleeding was observed directly after skin incision, but before opening of the airway. Local compression was applied and the wound was sutured. Total blood loss was 17 grams which classifies as clinically irrelevant. There was no need for transfusion of packed red cells due to blood loss during or after PDT.

<table>
<thead>
<tr>
<th>Table 2. Outcome in bleeding</th>
<th>Correction N = 35</th>
<th>No correction N = 37</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (grams), median [IQR]</td>
<td>3.0 [1.0 – 6.0]</td>
<td>3.0 [2.0 – 6.0]</td>
<td>0.96</td>
</tr>
<tr>
<td>Intratracheal bleeding during procedure, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, N (%)</td>
<td>5 (14)</td>
<td>12 (32)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mild, N (%)</td>
<td>23 (66)</td>
<td>19 (51)</td>
<td>0.16</td>
</tr>
<tr>
<td>Severe, N (%)</td>
<td>3 (9)</td>
<td>2 (0.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hours until no blood aspirated (hours), median [IQR]</td>
<td>2.0 [0 – 3.0]</td>
<td>1 [0.5 – 3.0]</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Cost analysis
The cost of one FFP and 1 unit of platelet concentrates in our hospital is €172 ($252) and €484 ($709), respectively. A surplus of €14,423 ($21,104) was spent in the “correction” group compared to the “no correction” group. Consequently, a procedure that is not preceded by correction of mild coagulation disorders saves on average €465 per patient.

Discussion
ICU patients undergoing PDT frequently have mild coagulation disorders which increase their risk for bleeding during or after invasive procedures. In this study we compared bleeding in patients after correction of mild coagulation disorders to those without prior correction and found no differences. Notably, clinical significant bleeding was not present in the two study groups.

This trial has some important limitations. Firstly, this was an open label study. Hypothetically, physicians who disbelieved that correction of mild coagulation disorders would benefit patients undergoing PDT may have tried to perform PDT in such a way that blood loss was kept to a minimum in the “no correction” group, or vice versa may have acted imprudent in the “correction” group. In addition, the quantification of intra–tracheal blood loss after PDT was based upon subjective observations by nurses who were not blinded for randomization, which limits the value of this measure. Secondly, the intended inclusion of 152 patients turned out to be unrealistic.

There was an increasing resistance of the ICU–physicians to give blood products to patients in the correction group. Inclusion was restricted to patients with mild coagulation disorders and/or active treatment with acetylsalicylic acid. Severe coagulation disorders were judged as an absolute contraindication for PDT unless correction of haemostasis was carefully performed.19 Patients treated with clopidogrel were also excluded because the resulting thrombocytopathy cannot be corrected. This may have resulted in a far lower rate of bleeding than assumed beforehand. Notably, PDT was performed by physicians with extensive experience with the technique. This may also have lead to a low rate of bleeding in this population of patients. Finally, in our study population PDT was performed relatively late, namely after a mean of 10 days. Earlier PDT (within 2-3 days) may result in a shorter duration of ventilation and ICU–stay.20,21 However, there may also be higher risk of bleeding because patients often have more severe coagulation disorders within the first few days of an ICU admission. Our study does not provide answers regarding the safety of early PDT in these cases.
We exclusively used the Blue Rhino for PDT. It may be that with other techniques differences might have been found between groups, although earlier studies did not show higher complication rates with one specific percutaneous technique. In a recent survey on perioperative management of PDT in the Netherlands, we showed that it is common practice to correct for mild prolongation of PT before the procedure. Indeed, prophylactic transfusion of FFP before an invasive procedure in non-bleeding patients may often occur, although the benefits in prevention of bleeding may be low. One could argue that the dose of FFP used in this study is too low, as transfusion of 1 unit of FFP hardly influenced PT. However, the amount of FFP transfused was carried out in accordance with the hospital and blood bank policies.

Transfusion of blood products bears the risk of transfusion-related morbidity, such as infectious diseases and transfusion-associated acute lung injury (TRALI). In light of these insights one can speculate whether or not a transfusion policy such as that used in our ICU is even ethical. Unnecessary transfusion of FFP and platelets may occur too often. Education regarding the indication of transfusion, and improved identification of active bleeding may reduce transfusion rates and costs. This study supports the policy of restrictive use of blood products by showing that transfusion of blood products before PDT in case of mild coagulation disorders is not indicated and is an unnecessary expense.

Our results are in line with a large prospective observational study that evaluated risk factors associated with bleeding during and after PDT. This study showed no correlation between acute bleeding and coagulation disorders. In contrast to our results though, they did find a correlation between chronic bleeding and coagulation disorders. The risk of chronic bleeding was higher when the activated partial thromboplastin time was > 50 seconds (odds ratio (OR) of bleeding 3.7 (95% CI 1.1–12.7), the platelet count was < 50 (OR 5.0 (95% CI 1.4–17.2), or when both abnormalities were present (OR 9.5 (95% CI 2.3–34.7). Notably, the risk for bleeding was mostly present in patients with more severe bleeding disorders than the patients included in our study.

Although one patient on active treatment with acetylsalicylic acid needed subcutaneous sutures to stop the bleeding (of note, in this patient bleeding was, by study definitions, not clinically significant), we did not find a higher risk of bleeding in other patients using acetylsalicylic acid, even in those with an additional prolonged PT. The attitude towards withholding acetylsalicylic acid perioperatively has been changing over the years. Most guidelines advise the continuation of acetylsalicylic acid for non-cardiac surgery, except in patients with a low risk of thrombosis when bleeding may occur in closed spaces, or when excessive blood loss is expected. The same recommendations are made for patients taking clopidogrel or on dual anti-platelet therapy. However, we did not include patients on clopidogrel or dual
anti–platelet therapy in our study, and additional studies are needed to evaluate the safety of PDT in these cases, as well as in patients with more severe prolongation of coagulation tests. More importantly, the continuously rising costs of blood donation and transfusion in the current economic environment stress the need for studies that challenge our current practices. We should aim to abolish superfluous infusion of blood products especially in the critically ill.

**Conclusion**

Bleeding during or after bedside PDT in ICU patients with mild coagulation disorders is rare. Correction of subclinical coagulation disorders by transfusion of FFP and/or platelets does neither affect bleeding during nor after PDT.
Reference List


19. NVIC guideline: tracheostomy on the intensive care unit for adult patients [Internet]. [updated

20. Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the 

ized, study comparing percutaneous dilational tracheotomy to prolonged translaryngeal 
intubation (delayed tracheotomy) in critically ill medical patients. Crit Care Med 2004;32:1689-
94.

22. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results 
predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 

23. Vlaar AP, in der Maur AL, Binnekade JM, Schultz MJ, Juffermans NP. A survey of physicians’ 
reasons to transfuse plasma and platelets in the critically ill: a prospective single-centre cohort 

24. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients 


27. Di Minno MN, Prisco D, Ruocco AL, Mastronardi P, Massa S, Di MG. Perioperative handling of 

avascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the 
American College of Cardiology/American Heart Association Task Force on Practice Guidelines 
(Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation 
for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiog-
raphy, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular 
Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular 