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Prophylactic plasma transfusion for patients without inherited bleeding disorders or anticoagulant use undergoing non-cardiac surgery or invasive procedures (Review)

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[Intervention Review]

Prophylactic plasma transfusion for patients without inherited bleeding disorders or anticoagulant use undergoing non-cardiac surgery or invasive procedures

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ABSTRACT

Background

In the absence of bleeding, plasma is commonly transfused to people prophylactically to prevent bleeding. In this context, it is transfused before operative or invasive procedures (such as liver biopsy or chest drainage tube insertion) in those considered at increased risk of bleeding, typically defined by abnormalities of laboratory tests of coagulation. As plasma contains procoagulant factors, plasma transfusion may reduce perioperative bleeding risk. This outcome has clinical importance given that perioperative bleeding and blood transfusion have been associated with increased morbidity and mortality. Plasma is expensive, and some countries have experienced issues with blood product shortages, donor pool reliability, and incomplete screening for transmissible infections. Thus, although the benefit of prophylactic plasma transfusion has not been well established, plasma transfusion does carry potentially life-threatening risks.

Objectives

To determine the clinical effectiveness and safety of prophylactic plasma transfusion for people with coagulation test abnormalities (in the absence of inherited bleeding disorders or use of anticoagulant medication) requiring non-cardiac surgery or invasive procedures.

Search methods

We searched for randomised controlled trials (RCTs), without language or publication status restrictions in: Cochrane Central Register of Controlled Trials (CENTRAL; 2017 Issue 7); Ovid MEDLINE (from 1946); Ovid Embase (from 1974); Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOHost) (from 1937); PubMed (e-publications and in-process citations ahead of print only); Transfusion Evidence Library (from 1950); Latin American Caribbean Health Sciences Literature (LILACS) (from 1982); Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, from 1990); ClinicalTrials.gov; and World Health Organization (WHO) International Clinical Trials Registry Search Platform (ICTRP) to 28 January 2019.

Selection criteria

We included RCTs comparing: prophylactic plasma transfusion to placebo, intravenous fluid, or no intervention; prophylactic plasma transfusion to alternative pro-haemostatic agents; or different haemostatic thresholds for prophylactic plasma transfusion. We included participants of any age, and we excluded trials incorporating individuals with previous active bleeding, with inherited bleeding disorders, or taking anticoagulant medication before enrolment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included five trials in this review, all were conducted in high-income countries. Three additional trials are ongoing.

One trial compared fresh frozen plasma (FFP) transfusion with no transfusion given. One trial compared FFP or platelet transfusion or both with neither FFP nor platelet transfusion given. One trial compared FFP transfusion with administration of alternative pro-haemostatic agents (factors II, IX, and X followed by VII). One trial compared the use of different transfusion triggers using the international normalised ratio measurement. One trial compared the use of a thromboelastographic-guided transfusion trigger using standard laboratory measurements of coagulation.

Four trials enrolled only adults, whereas the fifth trial did not specify participant age. Four trials included only minor procedures that could be performed by the bedside. Only one trial included some participants undergoing major surgical operations. Two trials included only participants in intensive care. Two trials included only participants with liver disease.

Three trials did not recruit sufficient participants to meet their pre-calculated sample size. Overall, the quality of evidence was low to very low across different outcomes according to GRADE methodology, due to risk of bias, indirectness, and imprecision.

One trial was stopped after recruiting two participants, therefore this review's findings are based on the remaining four trials (234 participants).

When plasma transfusion was compared with no transfusion given, we are very uncertain whether there was a difference in 30-day mortality (1 trial comparing FFP or platelet transfusion or both with neither FFP nor platelet transfusion, 72 participants; risk ratio (RR) 0.38, 95% confidence interval (CI) 0.13 to 1.10; very low-quality evidence).

We are very uncertain whether there was a difference in major bleeding within 24 hours (1 trial comparing FFP transfusion vs no transfusion, 76 participants; RR 0.33, 95% CI 0.01 to 7.93; very low-quality evidence; 1 trial comparing FFP or platelet transfusion or both with neither FFP nor platelet transfusion, 72 participants; RR 1.59, 95% CI 0.28 to 8.93; very low-quality evidence).

We are very uncertain whether there was a difference in the number of blood product transfusions per person (1 trial, 76 participants; study authors reported no difference; very low-quality evidence) or in the number of people requiring transfusion (1 trial comparing FFP or platelet transfusion or both with neither FFP nor platelet transfusion, 72 participants; study authors reported no blood transfusion given; very low-quality evidence) or in the risk of transfusion-related adverse events (acute lung injury) (1 trial, 76 participants; study authors reported no difference; very low-quality evidence).

When plasma transfusion was compared with other pro-haemostatic agents, we are very uncertain whether there was a difference in major bleeding (1 trial; 21 participants; no events; very low-quality evidence) or in transfusion-related adverse events (febrile or allergic reactions) (1 trial, 21 participants; RR 9.82, 95% CI 0.59 to 162.24; very low-quality evidence).

When different triggers for FFP transfusion were compared, the number of people requiring transfusion may have been reduced (for overall blood products) when a thromboelastographic-guided transfusion trigger was compared with standard laboratory tests (1 trial, 60 participants; RR 0.18, 95% CI 0.08 to 0.39; low-quality evidence). We are very uncertain whether there was a difference in major bleeding (1 trial, 60 participants; RR 0.33, 95% CI 0.01 to 7.87; very low-quality evidence) or in transfusion-related adverse events (allergic reactions) (1 trial; 60 participants; RR 0.33, 95% CI 0.01 to 7.87; very low-quality evidence).

Only one trial reported 30-day mortality. No trials reported procedure-related harmful events (excluding bleeding) or quality of life.

Authors' conclusions

Review findings show uncertainty for the utility and safety of prophylactic FFP use. This is due to predominantly very low-quality evidence that is available for its use over a range of clinically important outcomes, together with lack of confidence in the wider applicability of study findings, given the paucity or absence of study data in settings such as major body cavity surgery, extensive soft tissue surgery, orthopaedic surgery, or neurosurgery. Therefore, from the limited RCT evidence, we can neither support nor oppose the use of prophylactic FFP in clinical practice.

PLAIN LANGUAGE SUMMARY

Plasma transfusions before major surgery (other than heart surgery) or invasive procedures, to prevent bleeding

Review question

Human plasma, a blood component, is often transfused to people before undergoing surgery or other procedures (such as inserting a chest drainage tube) when blood tests show that their blood may not clot adequately. Aims of this review were to assess how effective this practice is in reducing subsequent bleeding or need for blood transfusion, and whether this approach increases risk of death or other significantly harmful effects. The review excluded people with inherited bleeding disorders and those taking medication that reduces their blood's clotting ability.

Background

Human plasma is obtained from blood donors. It contains many factors that help blood to clot. Although plasma may be transfused to people based on blood tests suggesting that their blood may not clot adequately, these tests have limitations. A person's blood may clot adequately despite abnormal test results. Abnormal test results also do not clearly predict those people who will go on to bleed. Furthermore, plasma transfusion corrects abnormal blood tests to varying degrees.

Plasma is also expensive, and some countries have issues with blood product shortages, donor reliability, and incomplete screening for infections that could be transmitted through blood product transfusion. Given the potential for life-threatening complications from plasma transfusion, its use in this setting carries risk of harm without clear evidence of benefit.

Study characteristics

We included five trials which were all conducted in high-income countries.

Our search is current up until 28 January 2019. One trial compared plasma transfusion with no transfusion given. Another trial compared plasma or platelet transfusion or both with neither plasma nor platelet transfusion given. One trial compared plasma transfusion with alternative products given to help blood clot. Another trial compared different blood tests to trigger a plasma transfusion, and still another trial compared different transfusion triggers using the same blood test.

Four trials involved adult participants over 18 years old, and the fifth trial did not specify age of participants. In four trials, participants underwent bedside procedures. Only one trial involved some participants undergoing major surgical operations. Two trials included only participants in intensive care, and two trials included only participants with liver disease.

One trial recruited only two participants. Therefore review results include the remaining four trials, incorporating 234 participants. Three further trials are ongoing.

Key results

When plasma transfusion was compared with no transfusion given, we are very uncertain whether there was a difference in major bleeding, number of blood transfusions per participant, or harmful effects from the transfusion (1 trial; very low-quality evidence). When plasma or platelet transfusion or both were compared with neither plasma nor platelet transfusion, we are very uncertain whether there was a difference in mortality within 30 days, or in the number of individuals requiring a transfusion (1 trial; very low-quality evidence).

When plasma transfusion was compared with other haemostatic agents, we are very uncertain whether there was a difference in major bleeding or in harmful effects from the transfusion (1 trial; very low-quality evidence).

When different triggers for plasma transfusion were compared (1 trial; 60 participants), we are very uncertain whether there was a difference in major bleeding or in harmful effects from the transfusion due to very low-quality evidence for these outcomes. The number of people requiring blood products may have been reduced overall, although this is based on low-quality evidence.

No trials reported procedure-related harmful events or quality of life as an outcome.

Quality of the evidence

The overall quality of the evidence was predominantly very low over a range of clinically important outcomes due to combinations of issues within the studies, such as potential for bias, limited clinical settings, and imprecise estimates of intervention effects.

Authors' conclusions

We are very uncertain of the effectiveness and safety of the use of plasma in non-cardiac operations or invasive procedures due to very low-quality evidence. Furthermore, as trials do not cover a wide range of surgical contexts, our confidence in applying study results to the wider surgical setting is limited. Overall limited evidence for the utility of plasma transfused to people within this context is of insufficient quality to support or oppose its use.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Prophylactic plasma transfusion before surgery/invasive procedures compared to no prophylactic plasma transfusion before surgery/invasive procedures (colloid, crystalloid, placebo, or no treatment) for patients undergoing non-cardiac surgery or invasive procedures

Prophylactic plasma transfusion before surgery/invasive procedures compared to no prophylactic plasma transfusion before surgery/invasive procedures (colloid, crystalloid, placebo, or no treatment) for patients undergoing non-cardiac surgery or invasive procedures					
Patient or population: patients undergoing non-cardiac surgery or invasive procedures **Setting:** individuals in ICU undergoing invasive procedures. Studies conducted in The Netherlands **Intervention:** prophylactic plasma transfusion before surgery/invasive procedures **Comparison:** no prophylactic plasma transfusion before surgery/invasive procedures (colloid, crystalloid, placebo, or no treatment)					
Outcomes	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**			**Certainty of the evidence (GRADE)**
		Without prophylactic plasma transfusion before surgery/invasive procedures	**With prophylactic plasma transfusion before surgery/invasive procedures**	**Difference**	
All-cause mortality up to 30 days № of participants: 72 (1 RCT)	RR 0.38 (0.13 to 1.10)	Study population			⊕⊖⊖⊖ Very low[a,b]
		297 per 1000	113 per 1000 (39 to 327)	184 fewer per 1000 (259 fewer to 30 more)	
Major bleeding within 24 hours № of participants: 148 (2 RCTs)	Two studies; reported separately[c] FFP group events 0/38; no FFP group events 1/38; RR 0.33, 95% CI 0.01 to 7.93 (Müller 2015) FFP or platelets or both group events 3/35; no transfusion group events 2/37; RR 1.59, 95% CI 0.28 to 8.93 (Veelo 2012)				⊕⊖⊖⊖ Very low[b,d,e]
Number of transfusions per participant within 7 days № of participants: 76 (1 RCT)	Study authors reported no difference ("P = 0.91 (RBC), P = 0.06 (FFP), P = 0.43 (PLT)") between the 2 groups (76 participants; Müller 2015). See Table 1				⊕⊖⊖⊖ Very low[d,f,g]
Number of individuals requiring a transfusion within 7 days № of participants: 72 (1 RCT)	Study authors reported "no... transfusion of packed red cells for blood loss during or after [the procedure]" (72 participants; Veelo 2012)				⊕⊖⊖⊖ Very low[d,g,h]

Serious adverse events measured by plasma transfusion-related complications within 24 hours № of participants: 76 (1 RCT)	Study authors reported that a difference between the 2 groups "did not reach statistical significance" (Müller 2015). See Table 1			⊕⊖⊖⊖ Very low[d,f,i]
Serious adverse events measured by surgery or procedure-related complications within 30 days - not reported	-	-	-	-
Quality of life - not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; FFP: fresh frozen plasma; ICU: intensive care unit; PLT: platelet; RBC: red blood cell; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two points due to indirectness (single trial, ICU setting, single bedside procedure; Veelo 2012).
[b]Downgraded one point due to imprecision (wide confidence intervals, which cross the line of no difference).
[c]Given only two studies, small numbers of participants, low event count, and very poor-quality evidence by GRADE assessment with heterogenous groups and wide confidence intervals that cross the line of no difference, we have not pooled the results, as doing so would be neither statistically nor clinically meaningful.
[d]Downgraded one point due to high risk of bias over multiple domains.
[e]Downgraded one point due to indirectness (2 trials, ICU setting, participants undergoing bedside procedures).
[f]Downgraded one point due to indirectness (ICU setting, participants undergoing bedside procedures; Müller 2015).
[g]Downgraded one point due to imprecision (low or absent event incidence).
[h]Would be downgraded two points due to very serious indirectness. However downgraded only one point as already downgraded two points in other domains (maximum 3 downgrade points allowed by GRADE method).
[i]Downgraded one point for imprecision (single study, 76 participants, terminated early, likely under-powered to demonstrate an effect; Müller 2015).

Summary of findings 2. Prophylactic plasma transfusion before surgery/invasive procedures compared to alternative haemostatic agents for patients undergoing non-cardiac surgery/invasive procedures

Prophylactic plasma transfusion before surgery compared to alternative haemostatic agents for patients undergoing non-cardiac surgery or invasive procedures

Patient or population: patients undergoing non-cardiac surgery/invasive procedures
Setting: individuals with chronic liver disease undergoing liver needle biopsy. Study conducted in Italy in 1976

Intervention: prophylactic plasma transfusion before surgery/invasive procedures
Comparison: alternative haemostatic agents

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)
		Without prophylactic plasma transfusion before surgery/invasive procedures	With prophylactic plasma transfusion before surgery/invasive procedures	Difference	
All-cause mortality up to 30 days - not reported	-	-	-		-
Major bleeding within 24 hours № of participants: 21 (1 RCT)	Study authors reported, "in none of the patients was there any clinical or laboratory evidence of bleeding" (21 participants; Mannucci 1976)				⊕⊖⊖⊖ Very low[a,b]
Number of transfusions per participant within 7 days - not reported	-	-	-		-
Number of individuals requiring a transfusion within 7 days - not reported	-	-	-		-
Serious adverse events measured by plasma transfusion-related complications within 24 hours № of participants: 21 (1 RCT)	RR 9.82 (0.59 to 162.24)	Study population			⊕⊖⊖⊖ Very low[d,e]
		Low			
		10 per 1000[c]	98 per 1000 (6 to 1000)	88 more per 1000 (4 fewer to 1612 more)	
		High			
		100 per 1000[c]	982 per 1000 (59 to 1000)	882 more per 1000 (41 fewer to 16124 more)	
Serious adverse events measured by surgery or procedure-related complications within 30 days - not reported	-	-	-		-
Quality of life - not reported	-	-	-		-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two points due to indirectness (single study, 21 participants, single bedside procedure; Mannucci 1976).
[b]Downgraded one point due to imprecision (low or absent event incidence, small study).
[c]Assumed risks taken from available drug product information by Baxter AG, Austria, for the use of Prothromplex TOTAL (HPRA 2018). Prothromplex TOTAL is a 4 factor concentrate (II, VII, IX, and X) with added protein C. Prothromplex, Immuno Vienna as used in Mannucci 1976 was a three-factor concentrate (II, VII, IX) after which factor VII, Immuno, Vienna was administered. No published safety data found for Prothromplex, Immuno, Austria, as used in Mannucci 1976.
[d]Would have been downgraded two points due to indirectness (differences in plasma preparation in modern practice limit applicability of results from a study conducted in 1976, and use of prophylactic steroids before plasma transfusion in the study is not recommended by modern guidelines; Mannucci 1976). However downgraded only one point as already downgraded two points in another domain (maximum three downgrade points allowed by GRADE method).
[e]Downgraded two points due to imprecision (very wide confidence intervals, crossing the line of no difference, which could include both significant harm and benefit, and clinicians instituted a practice change in a single arm during the study, by giving participants prophylactic steroids before FFP transfusion, following four febrile or allergic reactions in the group).

Summary of findings 3. Thromboelastography threshold compared to standard of care (laboratory parameters) for patients undergoing non-cardiac surgery or invasive procedures

Thromboelastography threshold compared to standard of care (laboratory parameters) for patients undergoing non-cardiac surgery or invasive procedures

Patient or population: patients undergoing non-cardiac surgery/invasive procedures
Setting: individuals with cirrhosis undergoing invasive procedures. Study conducted in Italy
Intervention: thromboelastography threshold
Comparison: standard of care (laboratory parameters)

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)
		Without thromboelastography threshold	With thromboelastography threshold	Difference	
All-cause mortality up to 30 days - not reported	-	-	-		-

Major bleeding within 24 hours № of participants: 60 (1 RCT)	RR 0.33 (0.01 to 7.87)	Study population			⊕⊖⊖⊖ Very low[a,b,c]
		33 per 1000	11 per 1000 (0 to 262)	22 fewer per 1000 (33 fewer to 229 more)	
Number of transfusions per participant within 7 days - not reported	-	-	-		-
Number of individuals requiring a transfusion within 7 days № of participants: 60 (1 RCT)	RR 0.18 (0.08 to 0.39)	Study population			⊕⊕⊖⊖ Low[a,b]
		1000 per 1000	180 per 1000 (80 to 390)	820 fewer per 1000 (920 fewer to 610 fewer)	
Serious adverse events measured by plasma transfusion-related complications within 24 hours № of participants: 60 (1 RCT)	RR 0.33 (0.01 to 7.87)	Study population			⊕⊖⊖⊖ Very low[a,b,c]
		33 per 1000	11 per 1000 (0 to 262)	22 fewer per 1000 (33 fewer to 229 more)	
Serious adverse events measured by surgery or procedure-related complications within 30 days - not reported	-	-	-		-
Quality of life - not reported	-	-	-		-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one point due to high risk of bias across multiple domains (De Pietri 2016).
[b]Downgraded one point due to indirectness (single trial, 60 participants with cirrhosis; De Pietri 2016).

cWould be downgraded two points due to very serious imprecision (low event incidence, very wide confidence intervals including both serious harm and benefit). However downgraded only one point as already downgraded two points in other domains (maximum three downgrade points allowed by GRADE method).

BACKGROUND

Description of the condition

A coagulopathy has been defined as a condition leading to impairment of the blood's clotting ability (Hunt 2014). People undergoing surgical procedures may have a coagulopathy for a myriad of reasons including co-existing medical conditions; nutritional or absorptive abnormalities leading to vitamin K deficiency (which results in a reduction in vitamin K-dependent clotting factors); abnormal physiological states such as hypothermia or acidosis; coagulant factor dilution due to intravenous fluids or red cell transfusion; use of antiplatelet or anticoagulant medication; or clotting factor consumption due to bleeding (McGilvray 2001).

There are also people requiring surgery in whom both prothrombotic (procoagulant or hyper-coagulant) and coagulopathic (anticoagulant) states may coexist, such as those with liver disease, disseminated intravascular coagulation, renal failure, and systemic inflammatory response syndrome or sepsis (Martlew 2000). People with perioperative critical illness and sepsis are associated with a net procoagulant state, despite laboratory measurements of coagulopathy (McGilvray 2001).

Preoperative screening for people with coagulopathy historically involved measurements of activated partial thromboplastin time (aPTT) and prothrombin time (PT) (van Veen 2011), both of which measure the time for blood to clot, and are affected by the function of different clotting factors. The PT is often presented as the international normalised ratio (INR), which controls for variations in PT measurements due to sensitivity differences among the commercial reagents (Rand 2005).

Clinicians have used abnormal laboratory coagulation results as a marker of coagulopathy, and these abnormalities have formed the rationale for replacing coagulation factors through transfusion of human plasma prophylactically (in the absence of bleeding) before invasive procedures or surgery (Stanworth 2007).

Description of the intervention

Human plasma is the non-cellular component of blood, containing proteins that help the blood to clot (procoagulants) such as fibrinogen and factors II, V, VII, VIII, IX, X, and XI; anticoagulant proteins C and S and antithrombin; and immunoglobulins, water, albumin, and acute phase proteins (Desborough 2015). Plasma is collected either from a single whole blood donation following separation from red cell and platelet components, or from plasmapheresis.

One unit contains a variable volume of plasma (Desborough 2012), typically 200 mL to 300 mL (Benjamin 2012), and different preparations are available. Fresh frozen plasma (FFP) is frozen within eight hours of collection and contains greater concentrations of temperature-labile factors V and VIII than frozen plasma (FP), which is frozen within 24 hours (Benjamin 2012). FFP is stored typically at -30°C for up to 36 months (Norfolk 2013; Stanworth 2007). Once thawed to 1°C to 6°C, FFP retains overall coagulation factor content for up to five days, although factors V and VIII undergo the greatest degradation during this time (Stanworth 2007).

There is also variability of factor concentrations in pathogen-inactivated preparations, such as solvent-detergent treated FFP, which contains reduced fibrinogen, factor VIII, and protein S (Norfolk 2013), or methylene blue-treated FFP, which contains reduced fibrinogen and factor VIII (Pamphilon 2000).

Given the variability of clotting factor levels in healthy donors, together with processing, storage, and preparation differences (Stanworth 2007), the potency of coagulation factors in plasma can vary between pooled units from 50% to 150% of pooled standardised controls (Benjamin 2012), and even more between units of single donors. Indeed, mean factor VIII concentration has been the only quality-controlled measure for the specification of plasma in the European Union (Stanworth 2007).

Risks associated with the intervention

Plasma transfusion has the potential to cause life-threatening complications and carries higher risks compared with transfusion of other blood components (Khan 2007; MacLennan 2006). These include transfusion-related acute lung injury (TRALI) (Eder 2007; Holness 2004), transfusion-associated circulatory overload (TACO) (Narick 2012), anaphylaxis or acute allergic reactions - common in 1% to 3% of transfusions (Desborough 2015) - ABO incompatibility-induced haemolysis (Norfolk 2013), multi-organ failure (Watson 2009), and transfusion-transmitted infection. Plasma transfusion is also independently associated with nosocomial infection and sepsis (Karam 2013; Sarani 2008).

Globally, a significant difference exists in the risk of transfusion-transmitted infections between high-income and low-income countries (Dhingra 2013). World Health Organization (WHO) data from 2013 show the incomplete ability of 13 of 173 reporting countries to screen all collected blood for one or more of four transmissible infections - HIV, hepatitis B, hepatitis C, or syphilis - with limited access to test kits representing one such barrier to screening. Furthermore only 66% of donations in low-income countries were tested following basic quality-assured procedures (WHO 2017). Blood shortages and an unreliable donor base have historically encouraged the use of paid donors or transfusion without prior testing (WHO 2008). Evidence for increased prevalence and transmission of infections such as HIV in the commercial plasma-donor population has been demonstrated (Volkow 2005; Wu 2001), and this has remained a concern (Abolghasemi 2010). Although an increase of 10.7 million blood donations from voluntary non-renumerated donors between 2008 and 2013 was reported from 159 reporting countries, 71 of 178 countries in 2013 remained dependent on family/replacement and paid donations for more than 50% of their blood supplies (WHO 2017).

How the intervention might work

Plasma is a source of procoagulant factors, and a current practice exists to transfuse plasma prophylactically (in the absence of bleeding), based on the rationale that replacing clotting factors through plasma transfusion will correct a coagulopathy and reduce perioperative bleeding risk (Desborough 2012; Rutherford 2008; Stanworth 2007). Reducing this risk has clinical importance given that perioperative bleeding and blood transfusion have been associated with increased morbidity and mortality (Glance 2011; Shander 2007).

Although further research into exact mechanisms is needed, more recent research has demonstrated that plasma transfusion is associated with protective and restorative effects on the integrity of the lining of blood vessel walls (vascular endothelial glycocalyx layer) (Kozar 2011; Peng 2013; Potter 2015; Rahbar 2015). The lining of blood vessels plays a fundamental role in the initiation and regulation of coagulation, and it is easily damaged by haemorrhagic shock, hypovolaemia, or trauma (Schott 2016).

Prophylactic administration of plasma is often based on mildly deranged laboratory tests (Luk 2002; Palo 2006; Stanworth 2011a; Triulzi 2015), despite evidence that coagulation factors at an INR less than two remain at concentrations adequate to support haemostasis (Deitcher 2002). Furthermore, the degree to which plasma transfusion corrects mildly abnormal coagulation tests is poor (Abdel-Wahab 2006; Holland 2006a; Stanworth 2011a; Williamson 1999).

Second, the underlying premise that abnormal coagulation tests are associated with an increased bleeding risk should be treated with caution (Desborough 2012). Studies suggest no difference in bleeding risk between people with normal or abnormal PT or aPTT undergoing a range of interventions, including spinal surgery (Schramm 2001), angiography (Darcy 1996), liver biopsy (McGill 1990; McVay 1990), thoracocentesis (Puchalski 2013), and abdominocentesis (McVay 1991). These laboratory tests may be prolonged for a variety of reasons (Stanworth 2007), and they are not validated in non-bleeding individuals (Dzik 2004). Their poor predictive value for bleeding risk - as reported in Chee 2008 and Segal 2005 - and their role as a poor marker for haemostasis - as discussed in Desborough 2012 and Stanworth 2007 - are not surprising in light of the complexity of haemostatic mechanisms in vivo involving interplay of the endothelium, inflammatory mediators, procoagulant and anticoagulant factors, platelets, and fibrinolysis.

An alternative approach to transfusing plasma based on an INR or PT threshold (which detects only low coagulation factor levels) involves using a test such as rotational thromboelastometry (ROTEM) or thromboelastography (TEG) that assesses how well a blood clot forms in whole blood (haemostasis) (Kinard 2013). ROTEM and TEG not only assess coagulation factor function but also platelet function, strength of the clot, and whether the clot is rapidly broken down (Whiting 2014). TEG may reduce prophylactic transfusions without increasing bleeding complications in people with liver disease undergoing invasive procedures (De Pietri 2016).

These issues may place people with presumed or confirmed coagulopathy undergoing prophylactic FFP transfusion before surgery at risk of potentially life-threatening transfusion-related complications (Khan 2007; MacLennan 2006), without clear evidence that the intervention has benefit.

Furthermore, plasma transfusion is expensive and, together with other blood product use, incurs costs of collecting the product, along with substantial administration costs pertaining to laboratory and staff utilisation, product wastage, and management of transfusion-related complications. These processes generate significant expense for the healthcare provider (Shander 2016; Stokes 2018).

Alternatives to prophylactic plasma transfusion include the following.

- No treatment or placebo.
- Intravenous fluids, including:
  - crystalloids, such as saline, dextrose, or balanced electrolyte solutions; or
  - colloids, which contain a suspension of macromolecules such as starches, gelatins, or dextrans (Lira 2014).
- Other prohaemostatic agents such as:
  - prothrombin complex concentrate, which is produced from plasma and contains a rich source of the vitamin K-dependent factors II, VII, IX, and X in a more concentrated volume compared with plasma;
  - cryoprecipitate, which is produced from plasma and is a rich source of fibrinogen, factor VIII, and von Willebrand factor in a concentrated volume and can increase fibrinogen levels with lower transfusion volumes compared with plasma (Norfolk 2013);
  - cryosupernatant, which is cryoprecipitate-depleted plasma that is used as an alternative to plasma for individuals with thrombotic thrombocytopenia purpura (O'Shaughnessy 2004);
  - fibrinogen concentrate, which contains the substrate converted to fibrin during the final step in the coagulation cascade and formation of a fibrin clot, and may reduce surgical bleeding when administered preoperatively;
  - antifibrinolytics, which increase clot strength by inhibiting the body's mechanism for lysis of formed clots; or
  - recombinant factor VIIa (rFVIIa), which is licensed for congenital factor VII deficiency, haemophilia, and inhibitory allo-antibodies but is also used off-licence in the setting of uncontrolled haemorrhage refractory to other treatments (Desborough 2016a).

Why it is important to do this review

There is significant variation in plasma transfusion and prescribing practice (Toumi 2015; Whitaker 2016), together with evidence of inappropriate use (Ejaz 2015; Luk 2002; Moylan 2008; Pahuja 2012; Palo 2006; Prathiba 2001; Stanworth 2011a; Stanworth 2011b; Tinmouth 2013; Triulzi 2015). Furthermore, evidence shows variation in dosing (Stanworth 2011a; Tinmouth 2013; Triulzi 2015), as well as coagulopathy thresholds for transfusion (Stanworth 2011b), with evidence of significant transfusions occurring for mild INR/PT derangement (Ejaz 2015; Triulzi 2015). These variations highlight inconsistencies in management strategies between clinicians.

Although numerous guidelines for plasma usage exist, there is significant variation in the guidance or quality of the evidence base. Some guidelines specifically highlight the absence of high-quality evidence (O'Shaughnessy 2004; Roback 2010; Szczepiorkowski 2013; Yaddanapudi 2014). Another - NICE 2015 - recommends plasma transfusion for people undergoing surgery with coagulopathy and risk of significant bleeding based on very low-quality randomised controlled trial (RCT) evidence and the opinion of the Guideline Development Group (Padhi 2015). One guideline recommends that prophylactic transfusion should be avoided (Liumbruno 2009). Another recommends prophylactic transfusion dependent on severity of the coagulation test derangement (Wong 2007), and another recommends seeking specialist advice for consideration of transfusion for people with coagulopathy undergoing intracranial, intraocular, or neuraxial

procedures (National Blood Authority 2012). Other guidelines make no mention of prophylactic use in non-cardiac surgery (American Society of Anesthesiologists 2006; American Society of Anesthesiologists 2015).

These variations in FFP usage, dosing, and thresholds, together with variations in guidance, highlight the need to review high-quality RCT evidence for the role of plasma. A systematic review first published in 2004 and updated in 2012 demonstrated lack of consistent evidence for prophylactic use across a range of clinical settings (Stanworth 2004; Yang 2012). Although a Cochrane Review has been performed to examine the role of FFP in cardiovascular surgery (Desborough 2015), as yet no Cochrane Review has targeted non-cardiovascular surgery. In the cardiovascular review, 14 trials compared prophylactic use versus no FFP associated with cardiac surgery. Overall, these trials were small and were not powered to determine changes in mortality as a primary outcome. Review authors recommended that large studies are required to assess the therapeutic effects of FFP on clinical outcomes following bleeding.

This Cochrane Review is needed to update previous reviews with recent RCT evidence (Stanworth 2004; Yang 2012), specifically targeting prophylactic use of plasma in non-cardiac surgery or invasive procedures, given that its role is currently uncertain, whereas transfusions carry risk of harm. This review will examine the evidence for FFP compared with no plasma or alternative pro-haemostatic agents. It will also examine coagulopathy thresholds for transfusion and will include studies that utilise classical laboratory measurements (PT, INR, aPTT).

OBJECTIVES

To determine the clinical effectiveness and safety of prophylactic plasma transfusion for people with coagulation test abnormalities (in the absence of inherited bleeding illnesses or use of anticoagulant medication) requiring non-cardiac surgery or invasive procedures.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), with no restriction on language or publication status.

Types of participants

We included people of all ages with laboratory confirmed or presumed abnormal coagulation (as defined by the study) undergoing non-cardiac surgery or invasive procedures.

We excluded:

- people with clinical evidence of bleeding before enrolment (as they would likely have received blood products); and
- people with inherited bleeding disorders or using anticoagulants (e.g. warfarin, rivaroxaban, apixaban).

We used a broad definition of the term 'surgery' to capture as comprehensive an evidence base as possible. We used the definition created by the American College of Surgeons in 2007 (ACS 2007), given that it encompasses not only the definition of incision and destruction of tissues, but also diagnostic and therapeutic treatments using a variety of instruments including probes or needles (Appendix 1).

We also used the section "Classification of procedures" from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM 2011), which classifies operations for guidance. Examples such as oesophago-gastro-duodenoscopy and liver biopsy, or tracheostomy and chest drain insertion, are registered under the group of operative procedures of the digestive system or the respiratory system, respectively.

We excluded studies that assessed only central line insertion because these studies are already included in another Cochrane Review (Hall 2016).

Types of interventions

We included RCTs comparing three types of plasma transfusion regimens.

- Prophylactic plasma transfusion before surgery/invasive procedures versus no prophylactic plasma transfusion before surgery/invasive procedures (colloid, crystalloid, placebo, or no treatment).
- Plasma transfusion before surgery/invasive procedures compared to alternative pro-haemostatic agents (prothrombin complex concentrate, cryosupernatant, fibrinogen concentrate; antifibrinolytics, and rFVIIa).
- Different haemostatic thresholds for administering a prophylactic plasma transfusion before surgery/invasive procedures (INR, PT, thromboelastography variables).

If sufficient data were available, we would have performed separate meta-analyses for these three comparisons, and we would have assessed age, type and dose of plasma components, and procedure type in subgroup analyses for each of these. We will do this in future updates should the opportunity arise.

Types of outcome measures

Primary outcomes

- All-cause mortality (up to 24 hours, and up to 30 days)
- Major bleeding within 24 hours and within seven days as defined by the study, or by the following (based on Schulman 2010).
  - Fatal bleeding.
  - Intracranial/intraspinal/pericardial/intraocular/ retroperitoneal, into a non-operated joint, or intramuscular causing compartment syndrome.
  - Surgical/invasive procedure site bleeding requiring a second intervention or reoperation.
  - Surgical/invasive procedure site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing.
  - Surgical/invasive procedure site bleeding that is unexpected and prolonged or causes haemodynamic instability (as defined by the study) and is associated with a 20-g/L drop in haemoglobin (Hb), or requiring two or more units of whole blood/red cells within 24 hours of bleeding.
  - Extrasurgical/invasive procedure site bleeding associated with a 20-g/L drop in Hb, or requiring two or more units of whole blood/red cells within 48 hours of bleeding.

Secondary outcomes

- Transfusion requirements (within seven days of surgery/invasive procedure).
  - Number of individuals requiring a transfusion.
  - Mean number of transfusions per participant.
- Use of haemostatic agents (within seven days of surgery/invasive procedure).
- Volume of blood loss (within seven days of surgery/invasive procedure).
- Serious adverse events (as defined in Appendix 2) due to:
  - plasma transfusion (e.g. TRALI, TACO, transfusion-related infection, transfusion-related dyspnoea, acute transfusion reaction) within 24 hours; or
  - surgery/invasive procedure (e.g. delayed wound healing, infection) within 30 days after the operation/invasive procedure.
- Resource use: hospital/intensive treatment unit (ITU) length of stay, operating time, return to theatre for management of bleeding.
- Venous and arterial thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction) (within 30 days of surgery/invasive procedure, and within 90 days of surgery/invasive procedure).
- Coagulation test abnormalities PT, INR, aPTT, or as defined by the study (within 24 hours of surgery/invasive procedure).
- Quality of life, as defined by individual studies.

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist working in collaboration with the Cochrane Haematological Malignancies Group devised the search strategy. These are listed in the appendices.

Electronic searches

We searched the following databases with no limitation on dates or language or publication status. Before review submission, we reran the search and, if additional studies were identified, we would have incorporated these into the review and would have updated findings as required. This strategy served to avoid missing new studies completed during the review process.

Databases searched included the following.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (www.cochranelibrary.com/) (Appendix 3).
- MEDLINE (OvidSP, 1946 to 28 January 2019) (Appendix 4).
- Embase (OvidSP, 1974 to 28 January 2019) (Appendix 5).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOHost) (1937 to 28 January 2019) (Appendix 6).
- PubMed (e-publications and in-process citations ahead of print only) (www.ncbi.nlm.nih.gov/pubmed) (Appendix 7).
- Transfusion Evidence Library (1950 to 28 January 2019) (www.transfusionevidencelibrary.com) (Appendix 8).
- Latin American Caribbean Health Sciences Literature (LILACS) (1982 to 28 January 2019) (lilacs.bvsalud.org/en/) (Appendix 9).
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 28 January 2019) (Appendix 10).

Ongoing trial databases included:

- ClinicalTrials.gov (clinicaltrials.gov) (Appendix 11); and
- WHO International Clinical Trials Registry Search Platform (ICTRP) (apps.who.int/trialsearch/) (Appendix 12).

Searching other resources

We conducted handsearches of the reference lists of included studies and any relevant systematic reviews to identify further relevant studies. We made contact with the lead authors of relevant studies to identify any unpublished material, missing data, or information regarding ongoing studies.

Data collection and analysis

Selection of studies

We managed study selection with reference to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two review authors (JH, KW) had planned to independently screen titles and abstracts identified by the search of databases for relevance against the eligibility criteria and immediately excluded clearly irrelevant studies. Given the large numbers of titles and abstracts identified, an additional review author (LE) assisted with the screening process. Two review authors (JH, KW) screened all titles and abstracts independently. We retrieved full-text papers for all references for which a decision on eligibility could not be made from title and abstract alone.

Three review authors (JH, KW, LE) then assessed the references for relevance from full text. Two (of the three review authors) assessed full text independently. They were not blinded to individual study meta-data such as author, institution, or publication journal. We requested additional information from study authors as necessary to assess the eligibility of individual studies for inclusion.

We used Covidence software to perform simultaneous independent screening and to assist with discrepancy resolution (Covidence 2016). We resolved disagreement between review authors regarding a study's eligibility through discussion and consensus, and through consultation with the third review author as necessary.

We reported the search results and the screening and selection process using a PRISMA flow diagram (Liberati 2009). We recorded the reasons for excluding studies based on full-text assessment and added those to the Characteristics of excluded studies table.

We collated multiple reports of one study so that the study, and not the report, was the unit of analysis.

Data extraction and management

As recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), two review authors (JH, LE) independently extracted data using Covidence onto standardised pre-piloted forms, and performed a cross-check for agreement of data. These review authors were not blinded to names of authors, institutions, journals, or study outcomes. We reported characteristics of the included studies in the Characteristics of included studies table.

We exported data from Covidence into Cochrane's systematic review software Review Manager 5 (RevMan 2014).

Data collected included:

- source: study ID, report ID, study author ID, citation and contact details, date of extraction;
- general study details and eligibility: eligibility for inclusion confirmed, reason for exclusion, funding source, conflict of interest declared, references to other relevant studies;
- study methods: location and country, clinical setting, number of centres, study design/type, recruitment dates and study duration, length of follow-up, power calculation, stopping rules, method of sequence generation, method of allocation sequence concealment, method of blinding, bias concerns;
- participant characteristics: age, gender, study population, primary diagnosis and/or operation, baseline laboratory measures of coagulopathy (PT, INR, aPTT, thromboelastography variables, platelet count, Hb) or evidence of presumed coagulopathy, total number screened, number included, number excluded, arm sample size, number analysed, number who received treatment, dropout rate, protocol violations, missing data;
- intervention characteristics: number of study arms, description of arms, type of plasma, control product (e.g. crystalloid, colloid, placebo, alternative pro-haemostatic agent), no treatment, haemostatic threshold for administering transfusion, dose of intervention/control; and
- outcomes and results: all-cause mortality within 24 hours and 30 days, major bleeding within 24 hours and seven days, transfusion requirements or number of patients requiring transfusion, use of haemostatic agents, blood loss volume, serious adverse events due to transfusion within 24 hours or surgery within 30 days, operating time, return to theatre for haemostatic control, hospital/critical care length of stay, venous and arterial thromboembolism, change in laboratory measures of coagulation (PT, INR, aPTT, thromboelastography variables) within 24 hours of plasma transfusion, estimate of effects with confidence intervals, key conclusions from study authors, miscellaneous comments from review authors, correspondence with study authors required.

Assessment of risk of bias in included studies

We assessed the risk of bias for all included RCTs using the Cochrane 'Risk of bias' tool according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (JH, LE) worked independently to assess each domain of potential bias listed below as 'high', 'unclear', or 'low' risk of bias. We reported a brief description of the judgement statements upon which we assessed potential bias in the Characteristics of included studies table. We ensured that a consensus on the degree of risk of bias was met through comparison of review authors' statements. If necessary, we had planned to consult with a third review author (KW). We used the Cochrane tool for assessing risk of bias, which included the following domains.

- Selection bias.
- Performance bias.
- Detection bias.
- Attrition bias.
- Reporting bias.
- Other bias.

Measures of treatment effect

For continuous outcomes, we recorded mean, standard deviation, and total number of participants in both treatment and control groups. We were unable to perform analyses given the small number of included studies.

In the future, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs) for continuous outcomes using the same scale, and standardised mean difference (SMD) when the scales are different. If available, we will extract and report hazard ratios (HRs) for mortality data. If HRs are not available, we will make every effort to estimate the HR as accurately as possible using available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we will use HRs in favour of risk ratios (RRs) in a meta-analysis, but for completeness, we will also perform a separate meta-analysis of data from studies providing only RRs for the same outcome.

For dichotomous data, we recorded the number of events and the total number of participants in both treatment and control groups. We were unable to pool data due to the small number of included studies.

In future updates, we will report the pooled RR with 95% CI, or when the number of observed events is small (< 5% of sample per group) and when trials include balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI (Deeks 2011). We will report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), and we will perform quantitative measurements, or will provide a narrative report, as appropriate. If data allow, we will undertake quantitative assessments using Review Manager 5.

Unit of analysis issues

We did not include any clustered or cross-over trials. In the future, if clustered or cross-over trials will be included, we anticipate that unit of analysis issues may arise with recurring events or multiple treatment events. We would follow guidance from Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We would report adverse event outcomes as groups of transfusion-related and surgery-related adverse events, as well as venous or arterial events. However often this is not possible due to duplicate counting of the same participant who may have experienced more than one adverse event of the same category (e.g. more than one transfusion-related adverse event). In this case, we would report subgroup categories of adverse events separately and would report the 99% CI of the pooled RR to allow for multiple statistical testing. If this is not possible, we would provide a narrative summary.

Dealing with missing data

We recorded participants lost to follow-up for each study. We contacted the authors of two trials by email for further information and are currently awaiting responses (Boyd 1996; De Pietri 2016). We utilised the assistance of Cochrane Russia for translation of one study to assess eligibility (Tseĭmakh 2008).

Assessment of heterogeneity

Given the small number of included studies, we were unable to combine studies to perform a meta-analysis. In the future, if

clinical and methodological characteristics of individual studies are sufficiently homogeneous, we would combine the data to perform a meta-analysis. We would evaluate the extent of heterogeneity by visually inspecting forest plots as well as by utilising statistical methods. We would assess statistical heterogeneity of treatment effects between studies using a Chi^2 test (with $P < 0.1$). We would quantify heterogeneity using the I^2 statistic and would classify it as low ($I^2 \leq 50\%$), moderate (50% to 80%), or considerable (> 80%) (Deeks 2011). We would use a random-effects model for low to moderate statistical heterogeneity given that we anticipate different but related effects across studies. If statistical heterogeneity is considerable, we would not report the overall summary statistic. We would explore potential causes of heterogeneity by performing sensitivity and subgroup analyses as appropriate (Deeks 2011).

Assessment of reporting biases

We were unable to complete a formal analysis of publication bias, given the small number of included studies. In the future, when at least 10 studies are incorporated into a meta-analysis, we will explore potential publication bias (small-trial bias) by generating a funnel plot and performing an appropriate test for asymmetry as recommended in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

We planned to perform meta-analyses based on recommendations from Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). However, we identified an insufficient number of studies to do this.

In the future, if further studies are included, and provided they are sufficiently homogenous in their study design, we will conduct separate meta-analyses (and subgroup analyses) for the three intervention comparisons. In the event of limited quantitative data for statistical analysis and synthesis, we will report findings through qualitative narrative summaries and tables. If sufficient data are available for meta-analysis, we will perform this using Review Manager 5. One review author will enter data into the software programme, which will be independently checked for errors by a second review author. Given the likely variation in intervention practice, we will use a random-effects model in the first instance. We will use the Mantel-Haenszel method for dichotomous data and the inverse variance method for continuous data. We will use the Peto method when event numbers are small.

If heterogeneity is found to be above 80%, and if we identify a cause for the heterogeneity, we will explore this by performing subgroup analyses. If we cannot find a cause for the heterogeneity, we will not perform a meta-analysis but will comment on the results as a narrative while presenting results from all studies in tables.

Subgroup analysis and investigation of heterogeneity

We planned to carry out separate subgroup analyses. However given the small number of included studies, it was not possible to do this. In the future, if sufficient data are available, we will carry out separate subgroup analyses for the three intervention comparisons to assess heterogeneity for the following.

- Age of individual (neonate, infant, child, adult).
- Type of procedure.
- Plasma type.
- Plasma dose.

We will categorise control interventions into three groups.

- No prophylactic plasma transfusion before surgery (colloid, crystalloid, placebo, or no treatment).
- Alternative pro-haemostatic agents (prothrombin complex concentrate, cryosupernatant, fibrinogen concentrate; antifibrinolytics, and rFVIIa).
- Different haemostatic thresholds for administering a prophylactic plasma transfusion before surgery (INR, PT, thromboelastography variables).

Sensitivity analysis

We were unable to perform sensitivity analyses due to the small number of included studies. If possible, in the future, we will perform sensitivity analyses to examine the robustness of our findings, by considering only:

- studies with low risk of bias; or
- studies with a low dropout rate (< 20%).

'Summary of findings' table

We used GRADEproGDT and the guidance provided in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* to produce a 'Summary of findings' table for each of the three intervention comparisons (GRADEpro 2015; Schünemann 2011a; Schünemann 2011b). We will utilise the GRADE approach, which defines the quality of the body of evidence as 'high', 'moderate', 'low', or 'very low', based on the following five considerations: design and implementation limitations causing risk of bias, indirectness of evidence, inconsistency or imprecision of results, and risk of publication bias. These tables will include the following outcomes.

- Mortality within 30 days.
- Major bleeding within 24 hours.
- Transfusion requirements measured by mean number of transfusions per participant.
- Transfusion requirements measured by number of individuals requiring a transfusion.
- Serious adverse events measured by plasma transfusion-related complications within 24 hours.
- Serious adverse events measured by surgery-related complications within 30 days.
- Quality of life, as defined by individual studies.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies.

Results of the search

A literature search, conducted by CD and current up to 28 January 2019, identified a total of 10,448 references plus 758 ongoing studies. After removing duplicates, we screened 6326 references

and 706 ongoing studies. Any two of three review authors (JH, LE, or KW) excluded 6974 records independently on the basis of the abstract. We retrieved 58 full-text references for independent assessment by the same review authors.

We identified 11 studies within 17 full-text references as potentially eligible for inclusion: five completed studies (De Pietri 2016; Mannucci 1976; Müller 2015; NCT00953901; Veelo 2012); three ongoing studies (NCT02561026; NCT02637427; Smart 2017); and three studies awaiting classification (Boyd 1996; NCT02777424; Tseĭmakh 2008). (See the PRISMA study flow diagram in Figure 1.)

Figure 1. PRISMA study flow diagram.

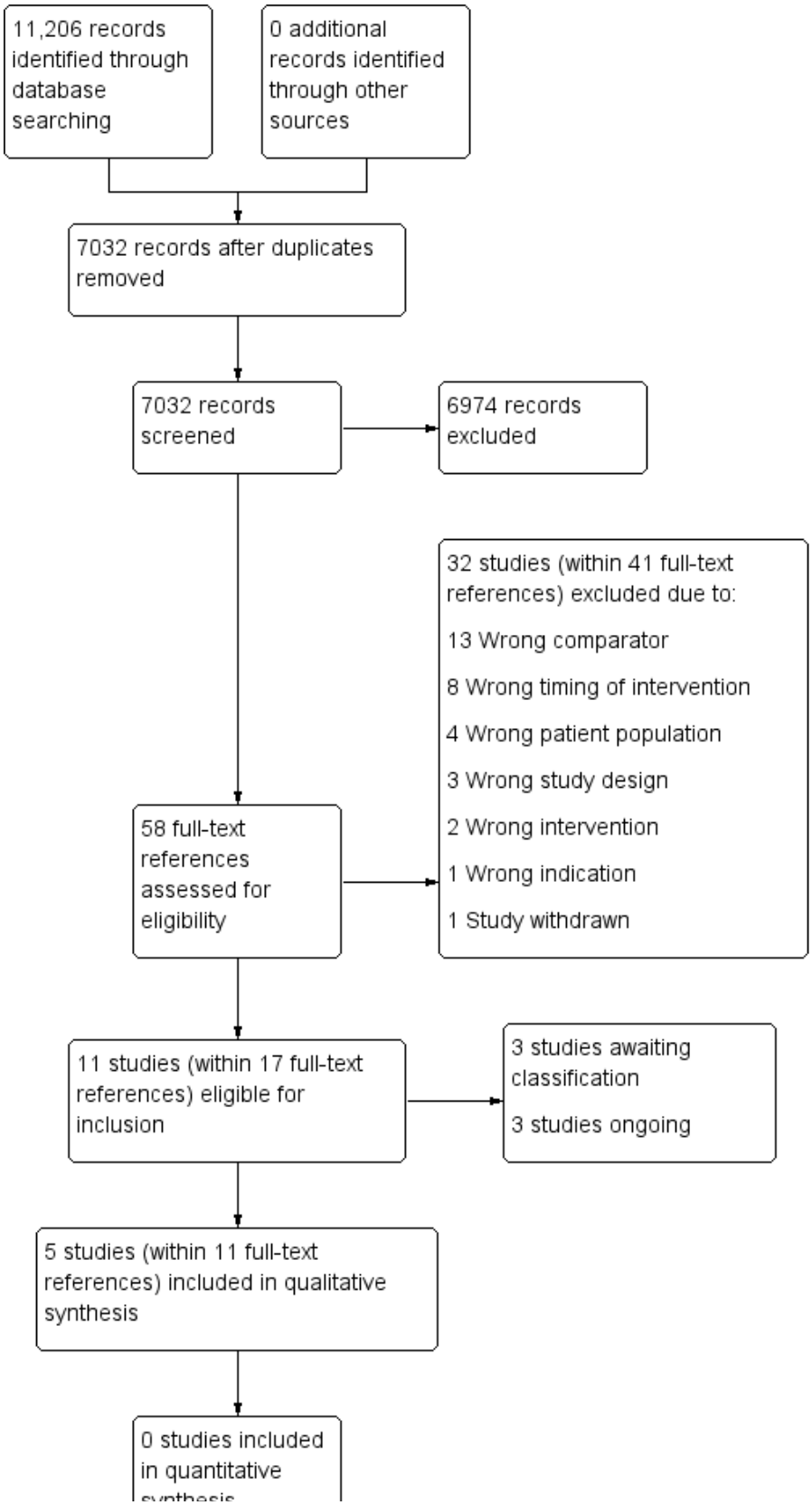
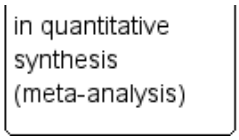


Figure 1. (Continued)



Included studies

We included five studies in the review (see Characteristics of included studies).

We grouped the included trials by type of intervention. One trial compared prophylactic plasma transfusion before invasive procedures versus no prophylactic plasma transfusion before invasive procedures (Müller 2015). Another trial compared prophylactic transfusion with FFP or platelets or both with neither FFP nor platelets before invasive procedures (Veelo 2012); one trial compared plasma transfusion before an invasive procedure versus alternative pro-haemostatic agents (prothrombin complex concentrate) (Mannucci 1976); and two trials compared different haemostatic thresholds for administering a prophylactic plasma transfusion before surgical/invasive procedures (INR, PT, thromboelastography variables) (De Pietri 2016; NCT00953901).

Design

Four trials were published in English between 1976 and 2016. The remaining trial, whose full-text report has not been published, was started in 2006 and was stopped in 2008, after enrolling two participants (NCT00953901). Four studies were parallel-group two-arm studies (De Pietri 2016; Müller 2015; NCT00953901; Veelo 2012). In the fifth trial, after a two-arm study was completed, a third additional arm was added, in which both interventions from the two separate arms were combined (Mannucci 1976).

Sample size

The trials recruited 236 participants, ranging from 2 in NCT00953901 to 81 in Müller 2015. Three trials were stopped early due to poor recruitment (Müller 2015; NCT00953901; Veelo 2012). The initial plan was to recruit 400 participants in Müller 2015, 188 participants in NCT00953901, and 152 participants in Veelo 2012. Reasons reported for poor recruitment included short time frame for the opportunity to recruit (due to procedure urgency), refusal of consent (Müller 2015), and physician preference for management leading to resistance to recruit (Müller 2015; Veelo 2012).

Setting

All included studies were set in high-income countries according to the World Bank classification (WB 2017). They were conducted in three countries: two in Italy (De Pietri 2016; Mannucci 1976); two in the Netherlands (Müller 2015; Veelo 2012); and one in the United States (NCT00953901). One was a multi-centre trial incorporating four centres (Müller 2015).

Type of procedure

Four studies investigated solely bedside invasive procedures (such as chest drain insertion, needle liver biopsy, or abdominal paracentesis) (Mannucci 1976; Müller 2015; NCT00953901; Veelo 2012). One study investigated invasive procedures, which included bedside, radiologically interventional procedures (such as transjugular intrahepatic porto-systemic shunt), other invasive procedures (such as oesophago-gastro-duodenoscopy or colonoscopy), and major surgically operative procedures (17% of study participants, including hepatic resection, thoracotomy, or other abdominal surgery) (De Pietri 2016). No study solely investigated major operative surgical procedures.

Participants

Four trials included only adults (De Pietri 2016; Müller 2015; NCT00953901; Veelo 2012), and one study did not report the age of participants (Mannucci 1976). Two trials included only participants with chronic liver disease (De Pietri 2016; Mannucci 1976), and two trials included only participants in intensive care (Müller 2015; Veelo 2012).

One study excluded participants taking anticoagulants or antiplatelets at the time of, or within seven days of, enrolment (De Pietri 2016). One study excluded participants with a bleeding time greater than seven minutes (Mannucci 1976). Another study excluded participants with an INR greater than three, and those taking vitamin K antagonists, activated protein C, abciximab, tirofiban, ticlopidine, or prothrombin complex concentrates, although heparin and low molecular weight heparin were not exclusion criteria provided they were discontinued for an 'appropriate period' (Müller 2015). One study excluded participants with prothrombin time greater than 20 seconds and those receiving clopidogrel (Veelo 2012).

Interventions

One study compared solely the use of FFP versus no FFP (Müller 2015). Another study compared the use of FFP or platelets or both with neither FFP nor platelets (Veelo 2012). One study compared use of FFP versus use of factors II, IX, and X followed by VII (Mannucci 1976). Two studies compared use of FFP versus different coagulopathy test thresholds (De Pietri 2016; NCT00953901).

Studies comparing FFP vs no FFP

One study compared FFP transfusion versus no FFP transfusion (Müller 2015). The other study compared transfusion with FFP or platelets (if low count and/or acetylsalicylic acid used) or both with neither FFP nor platelet transfusion (Veelo 2012). In this study, of the 35 participants randomised to the correction arm, 18 (51%) underwent FFP transfusion, and 23 (66%) underwent platelet transfusion. Given that more than 50% of participants in the group received FFP, and given the paucity of trials available for inclusion, we currently included this study and its data in the review. However, we also contacted the first author to request data related only to participants who received FFP. We are grateful for her acknowledgement of this request, and we are awaiting further correspondence.

Studies comparing FFP vs alternative pro-haemostatic agents

One study compared FFP versus factors II, IX, and X, followed by VII (Mannucci 1976). In this study, after completing recruitment

of participants to the two arms, researchers recruited a further cohort of participants to each receive a combination of FFP and prothrombin complex concentrate (PCC), thereby subsequently generating a third (non-parallel) arm.

Studies comparing different transfusion thresholds

One study compared transfusing FFP using a thromboelastography R-time threshold > 40 minutes as a transfusion trigger versus using an INR > 1.8 as a transfusion trigger (De Pietri 2016). Another study compared liberal (to keep INR < 1.6) versus restrictive (INR 1.6 to 3) FFP transfusion regimens (NCT00953901).

Outcomes

No studies measured all primary outcomes defined by the review. Two studies measured all-cause mortality up to 24 hours - Müller 2015 - or at 30 days - Veelo 2012 - as defined in the review criteria above. One study measured 90-day mortality (De Pietri 2016). We contacted study authors for information regarding 24-hour and 30-day mortality, and we are currently awaiting a response.

Four studies measured major bleeding within 24 hours (De Pietri 2016; Mannucci 1976; Müller 2015; Veelo 2012), and one study within seven days (De Pietri 2016).

No studies measured all secondary outcomes defined by the review.

Ongoing studies

We identified three ongoing studies (NCT02561026; NCT02637427; Smart 2017). Both NCT02561026 and NCT02637427 are pilot studies determining feasibility for a large trial (Characteristics of ongoing studies). NCT02561026 is an open-label parallel-group two-arm trial conducted in Canada to compare prophylactic FFP transfusion versus no transfusion before an invasive procedure. This multi-centre trial aimed to recruit 80 participants across three hospitals in an intensive care unit setting. Recruitment was expected to be complete by August 2018.

NCT02637427 is a parallel-group two-arm, single-blinded (to outcome assessor) trial conducted in the United States to compare prophylactic FFP transfusion versus no transfusion before an invasive procedure outside of the operating room. This multi-centre trial aimed to recruit 110 participants over two locations. It is expected to complete recruitment by April 2020.

Smart 2017 is a parallel-group, two-arm, prospective, randomised controlled trial comparing blood product use, bleeding events, and costs during and after endoscopic procedures in participants with liver cirrhosis with transfusion as guided by thromboelastometry versus conventional coagulation tests. An abstract has been published, and a full study report has not been published.

Studies awaiting classification

Three studies are awaiting classification (Boyd 1996; NCT02777424; Tseĭmakh 2008). The timing of the intervention in Boyd 1996 requires further clarification. Following contact with the study author, we are awaiting further information. In NCT02777424, the need for 'surgery' is not an absolute requirement to meet the study's inclusion criteria for enrolment. Given that the review's inclusion criteria require that participants undergo either surgery or invasive procedures, further assessment of this study will be needed following its completion to determine whether a subgroup of participants undergoing surgery (or invasive procedures) can be included in the review. Tseĭmakh 2008 was written in Russian, and we are awaiting a translation of the full text by Cochrane Russia. See Characteristics of studies awaiting classification for further information.

Excluded studies

We excluded 32 studies within 41 full-text references after assessing their eligibility through a full-text review (see Characteristics of excluded studies).

We excluded:

- 13 studies as the comparator did not meet our eligibility criteria (ChiCTR-INR-17013901; Freeman 1998; Galganski 2017; Laine 2003; Lerner 1997; Mintz 2006; NCT00235183; NCT03700723; Palmieri 2013; Ramies 2002; Tinmouth 2008; Wieding 1999; Williamson 1999);
- eight studies as timing of the intervention did not meet our eligibility criteria (Hedstrand 1987; Liu 1994; NCT02352181; NCT00994045; Pieters 2015; Sommoggy 1990; Urwyler 2009; Wang 2010);
- four studies as the participant population did not meet our eligibility criteria (Cao 2016; Jilma-Stohlawetz 2011; Lance 2012; NCT00302965);
- three studies as the study design did not meet our eligibility criteria (Gazzard 1975; Hildebrandt 2007; Kerner 2008);
- two studies as the intervention did not meet our eligibility criteria (Bauer 1986; NCT00656396);
- one study as the indication for the intervention did not meet our eligibility criteria (Rocha 2017); and
- one study as the study was withdrawn before participant enrolment was complete (NCT00233246).

Risk of bias in included studies

See Figure 2 and Figure 3 for visual representations of 'Risk of bias' assessments across all included trials and for each individual item in the included trials. See the Characteristics of included studies section 'Risk of bias' table for further information about bias identified within individual trials.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

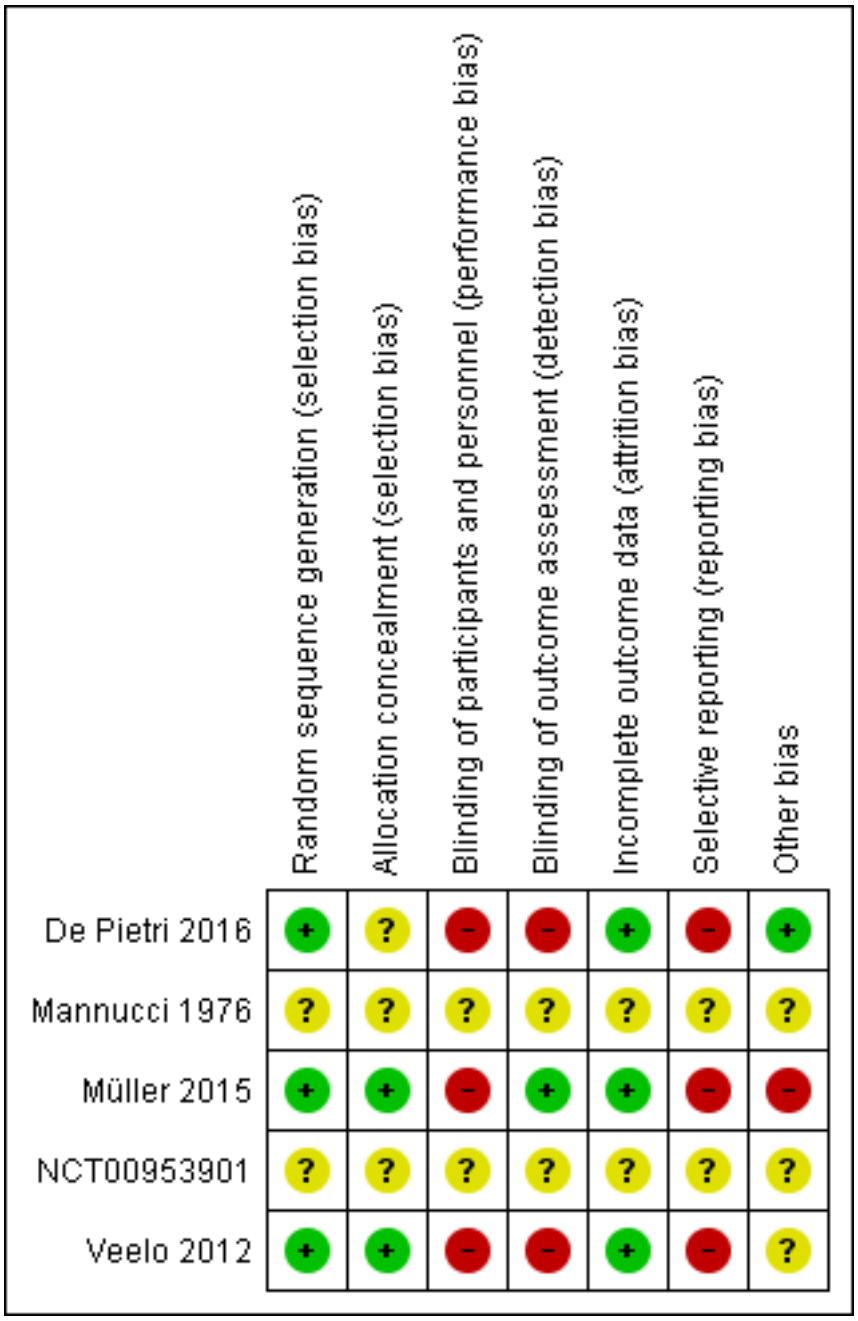
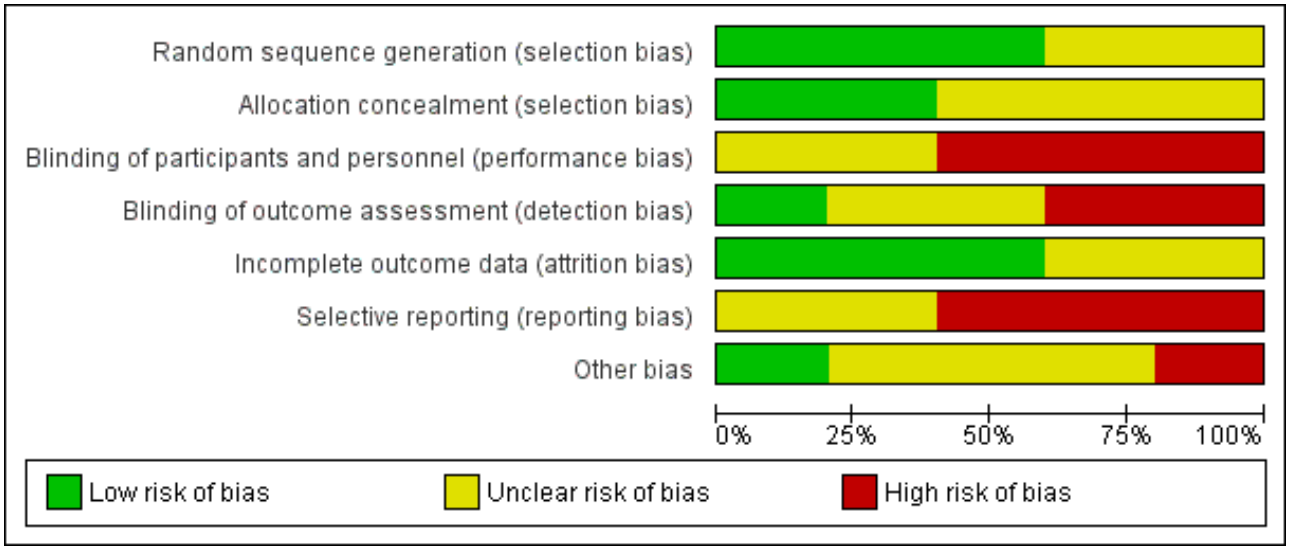


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



One study was completed in 2008 after recruiting two patients (NCT00953901). No report has been published, thereby precluding an analysis.

Allocation

Two trials were at low risk of selection bias due to adequate methods of sequence generation and allocation concealment (Müller 2015; Veelo 2012).

Random sequence generation

Three trials were at low risk of bias due to random sequence generation because they used computer-generated - Müller 2015 and Veelo 2012 - or electronically generated randomisation (De Pietri 2016).

One trial was at unclear risk of bias because it did not provide any details about the method of sequence generation (Mannucci 1976).

Allocation concealment

Two trials were at low risk of bias due to allocation concealment because they used either a web-based permuted block system - Müller 2015 - or consecutively numbered, opaque, sealed envelopes (Veelo 2012).

Two trials were at unclear risk of bias due to allocation concealment. Mannucci 1976 used a system of sealed envelopes, but it is unclear from the report whether opaque, sequentially numbered, sealed envelopes were used. De Pietri 2016 provided no information about the method of allocation concealment.

Blinding

Blinding of participants and personnel

One study was at unclear risk of performance bias because information in the study report was insufficient to make an assessment (Mannucci 1976).

Three studies were at high risk of performance bias (except for all-cause mortality) because of their open-label design (De Pietri 2016; Müller 2015; Veelo 2012).

Blinding of outcome assessors

One study was at low risk of detection bias, given its blinded endpoint evaluation design, which blinded the outcome assessor from the intervention during assessment of bleeding (Müller 2015).

One study was at unclear risk of detection bias given absence of information in the study report to permit assessment (Mannucci 1976).

Two studies were at high risk of bias (except for all-cause mortality) because of their open-label design (De Pietri 2016; Veelo 2012).

Incomplete outcome data

Three studies were at a low risk of attrition bias. In one study, all randomised participants were included in an intention-to-treat (ITT) analysis (De Pietri 2016). In another study, all participants who were randomised and underwent a procedure were included (Müller 2015). In the third study, a clear CONSORT diagram was reported, demonstrating an equal number of participants in each study arm who did not undergo the procedure after randomisation (Veelo 2012).

One study was at an unclear risk of attrition bias because information was insufficient to permit assessment (Mannucci 1976).

Selective reporting

One study was at unclear risk of bias as no protocol or trial registration was found, thereby precluding assessment (Mannucci 1976).

Three studies were at high risk of bias (De Pietri 2016; Müller 2015; Veelo 2012). One study recognised limitations in an outcome assessment method, leading to risk of under-reporting (Müller 2015). In another study, the time span for the primary outcome was

not clearly reported (De Pietri 2016), whereas in yet another study, the primary outcomes were not defined in the report (Veelo 2012). Two studies reported an outcome that was not predefined in their protocol - De Pietri 2016 - or public registry (Veelo 2012). All three studies did not report an outcome that had been predefined in their protocol - De Pietri 2016 and Müller 2015 - or in the public registry (Veelo 2012).

Other potential sources of bias

Balance of baseline characteristics

One study was at low risk of bias because it reported and demonstrated similar baseline characteristics between arms (De Pietri 2016).

Two studies were at unclear risk of bias. The first study did not report participant baseline characteristics (Mannucci 1976). The second reported baseline characteristics but did not highlight nor discuss a statistically significant difference (among patients with expected prolonged duration of mechanical ventilation) between arms (Veelo 2012). The material risk of this difference is unclear.

One study was at high risk of bias because it reported a statistically significant imbalance in participants with liver disease between groups (Müller 2015).

Early termination of study

One study was at unclear risk of bias because it was terminated early after randomising only 47% of its recruitment target due to increasing clinician resistance to transfusing FFP following recognition of a low incidence of bleeding in the no FFP group (Veelo 2012).

One study was at high risk of bias because it was terminated early after randomising only 20% of its recruitment target owing to a slow rate of inclusion (Müller 2015). As a result, study authors could not demonstrate non-inferiority between the two arms.

Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic plasma transfusion before surgery/invasive procedures compared to no prophylactic plasma transfusion before surgery/invasive procedures (colloid, crystalloid, placebo, or no treatment) for patients undergoing non-cardiac surgery or invasive procedures; **Summary of findings 2** Prophylactic plasma transfusion before surgery/invasive procedures compared to alternative haemostatic agents for patients undergoing non-cardiac surgery/invasive procedures; **Summary of findings 3** Thromboelastography threshold compared to standard of care (laboratory parameters) for patients undergoing non-cardiac surgery or invasive procedures

See Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3 for the main comparisons.

Studies comparing fresh frozen plasma (FFP) vs no FFP

One study compared FFP transfusion versus no FFP transfusion (Müller 2015). Another study compared FFP or platelet transfusion or both versus neither FFP nor platelet transfusion (Veelo 2012).

Primary outcomes

Mortality up to 24 hours and up to 30 days

One study reported all-cause mortality up to 24 hours (Müller 2015). We are uncertain whether there is any difference between the two groups (1 trial, 76 participants; risk ratio (RR) 0.70, 95% confidence interval (CI) 0.48 to 1.03; low-quality evidence) (Analysis 1.1).

Another study reported intensive care unit (ICU) mortality up to 30 days (Veelo 2012). We are very uncertain whether there is any difference between the two groups (1 trial, 72 participants; RR 0.38, 95% CI 0.13 to 1.10; very low-quality evidence) (Analysis 1.1).

Major bleeding within 24 hours and within seven days

Two studies reported major bleeding at 24 hours (Müller 2015; Veelo 2012).

In the study comparing FFP transfusion versus no transfusion (Müller 2015), we are very uncertain whether there is any difference in major bleeding between the two arms (1 trial, 76 participants; RR 0.33, 95% CI 0.01 to 7.93; very low-quality evidence) (Analysis 1.2). A single bleeding event (haemothorax) was reported following the invasive procedure (chest drain insertion) in a participant assigned to the non-transfusion group, which fulfilled the above criteria of major bleeding (requiring 3 units of red blood cells (RBCs), 3 units of FFP, and 1 unit of platelets). Haemostasis was achieved following this treatment.

In the study comparing FFP or platelet transfusion or both versus neither FFP nor platelet transfusion, we are very uncertain whether there is any difference in major bleeding between the two groups (1 trial, 72 participants; RR 1.59, 95% CI 0.28 to 8.93; very low-quality evidence) (Analysis 1.2) (Veelo 2012).

No study reported bleeding within seven days.

Secondary outcomes

Transfusion requirements within seven days

One study reported the number of participants requiring transfusion (Veelo 2012), although the time scale for this outcome was not reported. No RBC transfusion occurred in either group (1 trial, 72 participants; very low-quality evidence).

One study reported transfusion requirements as median number (and interquartile range (IQR)) of transfusions per participant in the first 24 hours only (Müller 2015; Table 1). Study authors reported no difference in RBCs, FFP, or platelet transfusion between groups (1 trial, 76 participants; RBC P = 0.91, FFP P = 0.06, platelets (PLTs) P = 0.43; very low-quality evidence).

Use of haemostatic agents within seven days

No study reported this outcome.

Volume of blood loss within seven days

One study reported this outcome as median (grams) blood loss (with IQR) per participant, although the duration of assessment for this outcome is unclear from the report (Veelo 2012). Study authors reported no difference between the two study arms (1 trial, 72 participants; median 3.0 grams, IQR 1.0 to 6.0 in the intervention group vs median 3.0 grams, IQR 2.0 to 6.0 in the no intervention group (P = 0.96; Table 1).

Serious adverse events from plasma transfusion (within 24 hours) or from surgery/intervention (within 30 days)

One study reported a lung injury score at 24 hours after randomisation as median and IQR (Müller 2015). Study authors reported that a difference between the two groups "did not reach statistical significance" (1 trial, 76 participants; median 2, IQR 0.8 to 2.5 in the intervention arm vs median 1.25, IQR 0.4 to 2.4 in the no intervention arm (P = 0.28; Table 1). Study authors did not provide quantitative data regarding baseline lung injury scores for the two arms nor changes in score between baseline and 24 hours post procedure. They qualitatively describe in the report's narrative that baseline scores were increased in both groups.

No study reported surgical or procedure-related adverse events (excluding bleeding).

Resource use

Hospital length of stay

No study reported this outcome.

ICU length of stay

Two studies reported ICU length of stay as median and IQR (Table 1) (Müller 2015; Veelo 2012). Study authors from both studies showed no evidence of a difference between the two groups (Müller 2015: 76 participants, P = 0.13; Veelo 2012: 72 participants, P = 0.21).

Duration of operation/intervention

No study reported this outcome.

Return to theatre/intervention room

One study reported a single major bleeding event within 24 hours (Müller 2015). However study authors did not report the need to transfer/return to the theatre/intervention room for intervention to achieve haemostasis, although the follow-up period was not described in the study report. Therefore no events were reported for this outcome (1 trial, 76 participants).

Venous and arterial thromboembolism within 30 days and 90 days

No study reported this outcome.

Coagulation test abnormalities

One study reported this outcome as median international normalised ratio (INR) and IQR before and after transfusion (Table 1) (Müller 2015). Study authors reported a reduction in INR following FFP transfusion (1 trial, 38 participants; median 1.8, IQR 1.5 to 2.5 before FFP transfusion vs median 1.4, IQR 1.3 to 1.63 after FFP transfusion; P < 0.001). However only 21 of 38 participants (54%) demonstrated a reduction in INR < 1.5 after transfusion.

Quality of life

No study reported this outcome.

Studies comparing FFP vs other pro-haemostatic alternatives

Only one study compared FFP versus factors II, IX, X, and VII (Mannucci 1976).

Primary outcomes

Mortality up to 24 hours and up to 30 days

Mannucci 1976 did not report this outcome.

Major bleeding within 24 hours and within seven days

Mannucci 1976 reported this outcome, although the time span for its measurement is unclear from the report. The study followed up with participants for 12 months. No major bleeding events were reported in either group (1 trial, 21 participants; very low-quality evidence). We are very uncertain of the significance of this result, given the very low quality of evidence for this outcome.

Secondary outcomes

Transfusion requirements within seven days

Mannucci 1976 did not report this outcome.

Use of haemostatic agents within seven days

Mannucci 1976 did not report this outcome.

Volume of blood loss within seven days

Mannucci 1976 did not report this outcome.

Serious adverse events from plasma transfusion (within 24 hours) or from surgery/intervention (within 30 days)

Mannucci 1976 reported serious adverse events from plasma transfusion (defined by the criteria in Appendix 2). We are very uncertain whether there was any difference in these events between the two groups (1 trial, 21 participants; RR 9.82, 95% CI 0.59 to 162.24; very low-quality evidence) (Analysis 2.1). During the study period, following four events in the FFP group, there was a practice change whereby all subsequent participants in the FFP group received prophylactic steroids, which may have reduced the rate of, or clinical detection of, future events, and may have masked their true incidence. The study was also likely underpowered to detect a difference between groups.

Mannucci 1976 did not report serious adverse events related to the procedure within 30 days.

Resource use

Mannucci 1976 did not report hospital length of stay, ICU length of stay, procedure duration, or need to return to the theatre/procedure room.

Venous and arterial thromboembolism within 30 days and 90 days

We are very uncertain whether there is a difference in thromboembolism with the use of FFP. Mannucci 1976 reported no cases of thromboembolism in the groups, although the timing of assessment of this outcome was not reported (1 trial, 21 participants; very low-quality evidence). Participants were followed up for 12 months.

Coagulation test abnormalities

Mannucci 1976 reported the number of participants with corrected indices of coagulation. We are very uncertain whether there is a difference between the groups of participants with persistently deranged indices (1 trial, 21 participants; aPTT: RR 2.75, 95% CI 0.68 to 11.13; PT: RR 0.44, 95% CI 0.2 to 0.96; Normotest: RR 0.43, 95% CI 0.21 to 0.88; very low-quality evidence) (Analysis 2.2).

Quality of life

Mannucci 1976 did not report this outcome.

Studies comparing different transfusion thresholds

Two studies compared different transfusion thresholds. One study compared a liberal (to keep INR < 1.6) versus restrictive (INR 1.6 to 3) FFP transfusion regimen (NCT00953901). However this study ceased recruitment after enrolling two participants and reported no outcomes.

Another study compared FFP transfusion using a thromboelastography R-time threshold > 40 minutes as a transfusion trigger vs a transfusion trigger with INR > 1.8 (De Pietri 2016).

Primary outcomes

Mortality up to 24 hours and up to 30 days

No study reported 24-hour or 30-day mortality. One study reported all-cause mortality up to 90 days (De Pietri 2016). We are very uncertain whether there is a difference between groups (1 trial, 60 participants; RR 1.14, 95% CI 0.47 to 2.75; very low-quality evidence) (Analysis 3.1).

Major bleeding within 24 hours and within seven days

One study reported data for this outcome (De Pietri 2016). One participant (1/30) developed major bleeding according to the above criteria on the day following the invasive procedure (paracentesis), requiring packed red cells and FFP transfusions. This participant had been randomised to the standard of care group and had received FFP before undergoing the procedure. There were no events in the thromboelastography (TEG) group (0/30). We are very uncertain whether there is a difference between the groups (1 trial, 60 participants; RR 0.33, 95% CI 0.01 to 7.87; very low-quality evidence) (Analysis 3.2).

Secondary outcomes

Transfusion requirements within seven days

One study reported data for this outcome (De Pietri 2016). The number of individuals requiring overall blood products in the TEG group may be reduced versus the number in the standard of care (SOC) group (1 trial, 60 participants; RR 0.18, 95% CI 0.08 to 0.39; low-quality evidence). However we are very uncertain whether there was a reduction in participants within the TEG group requiring either FFP alone (1 trial, 60 participants; RR 0.03, 95% CI 0.00 to 0.48; very low-quality evidence), PLTs alone (1 trial, 60 participants; RR 0.20, 95% CI 0.05 to 0.84; very low-quality evidence), or both FFP and PLTs (1 trial, 60 participants; RR 0.75, 95% CI 0.18 to 3.07; very low-quality evidence) (Analysis 3.3).

No study reported the mean number of transfusions per patient.

Use of haemostatic agents within seven days

No study reported this outcome.

Volume of blood loss within seven days

No study reported this outcome.

Serious adverse events from plasma transfusion (within 24 hours) or from surgery/intervention (within 30 days)

One study reported an allergic reaction during FFP transfusion in the SOC group (1/30) compared to none in the TEG group (0/30) (De Pietri 2016). We are very uncertain whether there was a difference between groups (1 trial, 60 participants; RR 0.33, 95% CI 0.01 to 7.87; very low-quality evidence) (Analysis 3.4).

No study reported surgical or procedure-related serious adverse events (excluding bleeding, as already described above and in Analysis 3.2).

Resource use

No study reported hospital length of stay, ICU length of stay, or procedure duration. Studies did not describe the necessity to return to the theatre or the intervention room to control bleeding in the participant with a post-procedural bleeding event.

Venous and arterial thromboembolism within 30 days and within 90 days

No study reported this outcome.

Coagulation test abnormalities

No study reported this outcome.

Quality of life

No study reported this outcome.

DISCUSSION

The objective of this review was to determine the clinical effectiveness and safety of prophylactic plasma transfusion for people with confirmed or presumed coagulopathy requiring non-cardiac surgery or invasive procedures.

Five trials were eligible for inclusion in this systematic review (De Pietri 2016; Mannucci 1976; Müller 2015; NCT00953901; Veelo 2012). One study was terminated after recruiting only two patients; this study report has not been published (NCT00953901). No results can be ascertained from this study.

Of the four completed studies, all were carried out in high-income countries between the years 1976 and 2016; they involved a total of 234 participants, all of whom were > 18 years of age.

Two trials studied participants in an intensive care unit (ICU) setting (153 participants) (Müller 2015; Veelo 2012). Two trials studied only procedures carried out by participants' bedside (153 participants; in Müller 2015 and Veelo 2012, although seven participants in Veelo 2012 subsequently underwent surgical tracheotomy as opposed to percutaneous dilatational tracheotomy due to landmark recognition difficulties). Only one trial studied participants who underwent surgical procedures in an operating theatre such as hepatic resection, other abdominal surgery, or thoracotomy (10 participants out of a total of 60) (De Pietri 2016).

Only one trial studied fresh frozen plasma (FFP) as a single intervention compared with no intervention (Müller 2015). Another study compared FFP or platelet transfusion or both versus neither FFP nor platelet transfusion (Veelo 2012). A single trial studied the use of FFP versus the use of a combination of alternative pro-haemostatic agents - Prothromplex (containing factors II, IX, and X), followed by factor VII concentrate (Mannucci 1976). A single study compared different haemostatic thresholds for FFP transfusion, reporting a thromboelastography (TEG)-measured R-time > 40 minutes compared with an international normalised ratio (INR) >1.8 (De Pietri 2016).

Summary of main results

Given the very low-quality evidence, we are very uncertain whether there is a difference in:

- mortality with the use of prophylactic FFP versus no FFP. No trials studying other eligible comparators reported mortality up to 30 days;
- major bleeding within 24 hours, whether compared with no FFP or alternative pro-haemostatic agents, or using different transfusion thresholds. Few or no events in the studies and small study sample sizes have contributed to this uncertainty;
- transfusion requirements, in the form of number of transfusions per participant (one study comparing FFP transfusion vs no transfusion) or number of participants requiring a transfusion (one study comparing FFP or platelet transfusion or both vs neither FFP nor platelet transfusion);
- serious adverse events from FFP transfusion versus no transfusion or other pro-haemostatic agents, or using different thresholds for transfusion;
- surgical/interventional adverse events in participants transfused with FFP using a TEG-guided transfusion trigger versus standard tests for coagulation. No trials comparing FFP use versus no FFP use or use of an alternative pro-haemostatic product reported this outcome; or
- arterial or thromboembolism rate. Only one study, which compared participants receiving FFP versus factors II, IX, X, and VII, reported this outcome (Mannucci 1976).

For participants receiving FFP transfusion via a TEG-guided transfusion trigger versus standard tests of coagulation (INR), the number of participants subsequently requiring transfusion (for overall blood products) via a TEG-guided trigger may have been reduced. Our confidence is limited due to the low quality of evidence for this outcome. However we are very uncertain whether there is a difference in individual product use (FFP, platelets, or both), given that the evidence is of very low quality.

No studies reported the outcome looking at quality of life.

Overall completeness and applicability of evidence

This review aimed to provide the most up-to-date and comprehensive assessment of the clinical effectiveness and safety of prophylactic plasma transfusion for people with confirmed or presumed coagulopathy requiring non-cardiac surgical or invasive procedures.

To facilitate development of wide and comprehensive criteria for inclusion, we used a broad definition of surgical or surgically interventional procedures. We used the definition of the American College of Surgeons, which includes consideration of the use of probes or needles. We also used the classification system from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM 2011), which codifies various surgically oriented or interventional procedures within its operative classification.

Our search in any language has resulted in consideration of a foreign language trial, resulting in collaboration with Cochrane Russia for its translation (Tseĭmakh 2008).

We sought contact with the author of one study for further information required to determine its eligibility for inclusion based on our criteria (Boyd 1996). A second study awaiting classification is still ongoing (NCT02777424). Both studies compare use of FFP versus an alternative pro-haemostatic agent. Two ongoing studies are comparing FFP use versus no transfusion (NCT02561026; NCT02637427), and one ongoing study is comparing transfusion of blood products guided by thromboelastometry versus conventional coagulation tests (Smart 2017).

Several limitations may affect the strength and applicability of our review.

- Two studies (153 participants) of the four included in this review (234 participants) were set in the intensive care unit (Müller 2015; Veelo 2012). Given that these studies represent 65% of participants included in this review on which review findings are based, and given that individuals in the ICU represent more severe acute illness or physiological derangement compared with other individuals with a coagulopathy requiring surgery or interventional procedures, caution is required in extrapolating or generalising these findings to other person cohorts.
- Of the four included studies, two trials studied bedside interventional procedures (Müller 2015; Veelo 2012), and one trial studied percutaneous needle liver biopsy (likely carried out in an interventional area or theatre, although the locality is not clear from the report) (Mannucci 1976). Only a single trial included major operative surgery such as solid organ (liver) resection, other abdominal surgery, or thoracotomy (together with other invasive procedures) (De Pietri 2016). Major general surgery was therefore under-represented by the included studies, and no included studies represented major head and neck, neurological, or orthopaedic surgery.
- No trials eligible for inclusion in the review studied children.
- Significant variability is evident in methods used by the four studies for assessing, grading, and reporting bleeding. One study did not report its approach to assessment of bleeding (Mannucci 1976), another study - Müller 2015 - used the HEmorrhage MEasurement (HEME) tool (Arnold 2007), another study - De Pietri 2016 - used the World Health Organization (WHO) bleeding score (Miller 1981), and the authors of still another study generated a scale of clinically irrelevant bleeding, minor bleeding, and major bleeding (Veelo 2012).
- The dose of FFP given to individuals in the four studies was variable. In two studies, 12 mL/kg was used (Mannucci 1976; Müller 2015); in one study, 10 mL/kg ideal body weight was used (De Pietri 2016); and in another study, 300 to 600 mL was used (dependent on prothrombin time (PT) result), equating to 4.3 to 8.6 mL/kg for a 70-kg individual (Veelo 2012).
- It is questionable whether the sample size for important primary outcomes including mortality and bleeding, as well as other important outcomes such as adverse events or thromboembolism, was sufficiently large to detect a difference. Lack of any events for some outcomes precluded meaningful analysis. Two of the four studies terminated recruitment early due to a slow rate of recruitment (81 participants; Müller 2015), or due to increasing resistance to FFP transfusion by physicians owing to observations of a low bleeding rate in an open-label trial (72 participants; Veelo 2012). One trial recruited 21 patients (Mannucci 1976).

- Although three of the four studies were conducted over the last decade, one study was conducted in 1976 (Mannucci 1976). Given the development of strategies to reduce adverse events from plasma transfusion, including pathogen reduction techniques or use of male donors (Rogers 2015), how applicable these historical data remain to modern clinical practice remains questionable.
- Although one of the included studies utilised thromboelastography (De Pietri 2016), accessibility of such a modality for use in global clinical practice will depend on availability at individual institutions, which requires significant cost, equipment maintenance, quality control procedures, and user training (Subramanian 2018). Furthermore, there may be intra-operator and inter-operator variability in generated results (Quarterman 2014), although newer systems that utilise an automated process for sample and reagent mixing and activation may reduce the scope for operator-dependent variability and the requirement for training (Hartmann 2018).

Quality of the evidence

All five included studies were parallel-group randomised controlled trials (RCTs). Two were open-label trials, with high risk of both performance bias and detection bias (De Pietri 2016; Veelo 2012). One study used an open-label blinded-endpoint design with high risk of performance bias (Müller 2015). In one study, details of study design were unclear (Mannucci 1976). Another study, which ceased recruitment after enrolling two participants, was a double-blinded trial (NCT00953901). No published report is available for review of its methods or analysis of its methodological quality.

Our judgements for risk of bias of included studies can be found in the risk of bias tables in the Characteristics of included studies section of the review, and they are summarised in Figure 2 and Figure 3

- We judged three studies to be at high risk of bias in three out of seven domains (De Pietri 2016; Müller 2015; Veelo 2012).
- We judged one study to be at low risk of bias in three out of seven domains (De Pietri 2016).
- We judged two studies to be at low risk of bias in four out of seven domains (Müller 2015; Veelo 2012).

We assessed the quality of evidence using the GRADE approach, finding that quality ranged from low to very low.

With regard to the main outcomes of this review, we assessed the quality of evidence as low for the following.

- Number of individuals requiring transfusion, overall use of products within seven days, and comparison of FFP use versus different transfusion thresholds: we downgraded the evidence due to serious risk of bias and indirectness in these studies.

We assessed the quality of evidence as very low for the following.

- ICU mortality at 30 days: we downgraded the evidence for very serious risk of indirectness due to inclusion of a single trial of 76 participants, conducted in an intensive treatment unit (ITU) setting in patients undergoing a single procedure (percutaneous tracheostomy), which reported this outcome, thereby limiting applicability of study findings to the review's wider surgical setting. We also downgraded the evidence for serious risk of imprecision, given the wide confidence interval that crossed the line of no difference.
- Major bleeding within 24 hours: we downgraded the evidence due to serious risk of bias in some trials, serious or very serious risk of indirectness in some trials, and serious risk of imprecision in all trials.
- Number of transfusions per participant within seven days: we downgraded the evidence due to serious risk of bias, indirectness, and imprecision in some trials.
- Number of individuals requiring a transfusion within seven days in the setting of FFP transfusion versus no transfusion: we downgraded the evidence due to the trial's serious risk of bias, indirectness, and imprecision.
- Serious adverse events measured by plasma transfusion-related complications within 24 hours: we downgraded the evidence due to serious risk of bias in some trials, serious risk of indirectness in all trials, and serious or very serious risk of imprecision in all trials.
- Serious adverse events measured by surgery-related complications within 30 days in the setting of FFP use based on different transfusion thresholds: we downgraded the evidence due to serious risk of bias, indirectness, and imprecision in these trials.

Potential biases in the review process

This review reflects no obvious bias. A wide and comprehensive search was performed with no restriction on language, country, or publication status. We are grateful to Cochrane Russia for translation of a Russian text (Tseĭmakh 2008). We contacted authors of two trials for further information and are currently awaiting response (Boyd 1996; De Pietri 2016).

We used Covidence software to permit two of three review authors (JH, LE, KW) to independently and carefully screen each reference, abstract, or full text for relevance. Given the large number of references initially found through the wide search (7032 results), three review authors carried out this task. Two review authors (JH and LE) independently extracted and agreed on data from included studies. Two review authors (PF and JH) independently extracted and checked for agreement of data from ongoing studies or studies awaiting classification. Given the small number of included trials, construction of a funnel plot for identification of publication bias was not possible. In one included trial (NCT00953901), which was terminated after two participants were enrolled, no result data were published, thereby precluding assessment. Given early termination and the small patient sample size (two participants), publication bias is unlikely.

We pre-specified all reported outcomes and subgroups for analysis in advance; these were published in the review protocol before the search was conducted.

Agreements and disagreements with other studies or reviews

This review has shown lack of clear evidence demonstrating benefit for the use of prophylactic FFP before non-cardiac surgical or invasive procedures across a range of outcomes. This is consistent with two previous systematic reviews, which indicated lack of effectiveness within a range of different clinical settings (Stanworth 2004; Yang 2012).

However this review has highlighted the uncertainty of our confidence in the evidence and in the results due to low- or predominantly very low-quality evidence for important patient-centred outcomes. This is also consistent with findings of the aforementioned systematic reviews, which found limited evidence for most clinical situations - Stanworth 2004 - and noted little improvement in methodological quality over the years - Yang 2012.

Moreover, the small number of trials pertaining to non-cardiac surgery, the large number of trials in which only a small number of participants were enrolled, and the low incidence of certain outcome events (such as bleeding or adverse events), as highlighted by previous reviews, represent a consistent theme over the past 15 years and within this review.

The limited quality of evidence in this review is also consistent with that of a recent Cochrane Review on plasma use in the alternative setting of cardiovascular surgery (Desborough 2015), which judged the quality of evidence as moderate or low for most outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Given available RCT evidence, we can neither support nor oppose the prophylactic use of FFP in non-cardiac surgery or invasive procedures over a range of clinically important outcomes. This is due to lack of confidence in the certainty of evidence and in general applicability of review findings due to an absence of high-quality evidence, together with a paucity of evidence in settings such as major body cavity surgery, extensive soft tissue surgery, orthopaedic surgery, or neurosurgery.

Recent data show that inappropriate prophylactic transfusion of plasma is still commonplace (Desborough 2016b; Görlinger 2015; Lu 2017), despite more than a decade of reviews and narratives highlighting lack of evidence for this approach (Desborough 2012; Desborough 2016b; Holland 2006b; Stanworth 2004; Stanworth 2007; Verghese 2008; Weeder 2014; Yang 2012; Zakeri 2017).

Furthermore, given the global challenges of providing safe transfusion, particularly in areas of the world where testing for one or more markers of transfusion-transmissible diseases in donors is not available, and given the seven-fold difference in blood donation rates between low-income (4.6 per 1000 population per year) and high-income (32.1 per 1000 population per year) countries (WHO 2017), it is necessary to ensure that this limited resource is used effectively and appropriately.

By highlighting both the lack of high-quality evidence and the paucity of available data for the utility of prophylactic FFP transfusion, this review demonstrates uncertainty regarding its prophylactic role in clinical practice in the setting of non-cardiac surgery or invasive procedures in the absence of inherited bleeding disorders or use of anticoagulants.

Implications for research

High-quality multi-centre trials examining the safety and effectiveness of prophylactic FFP are required. These should involve participants in common major surgical operative settings, given that major body surgery was under-represented (10 participants in a single study; De Pietri 2016), and that extensive soft tissue, orthopaedic, and neurological surgeries were not represented by the available evidence. Furthermore, studies investigating paediatric participants are needed; lack of available trials for this cohort for inclusion within this review highlights the deficiency of data for this group.

Such studies would require sample sizes large enough to be adequately powered to determine differences in important patient-centred outcomes including 30-day survival, risk of major bleeding, requirement for transfusion, and risk of adverse events. Given the low incidence of bleeding and adverse events reported in this review, larger estimated sample sizes are likely required than were previously envisaged by study authors (Veelo 2012).

Furthermore, issues that may impact clinical utility, including type of plasma used (such as pathogen inactivated), post-thaw duration before infusion, and plasma dosage, would need to be considered in a study protocol. This challenge would likely be compounded by difficulties associated with recruiting large numbers of individuals owing to challenges of consent, randomisation, and enrolment of participants within a limited clinical window of opportunity, participant refusal for enrolment, or resistance of clinicians to include participants for fear of randomisation to study arms contrary to their strongly upheld beliefs (Müller 2015; Veelo 2012). Variability in FFP doses reported, together with variability in bleeding definitions and in tools used for assessment and reporting of bleeding, reflects issues that have potential implications for the ability to detect a difference between study arms and to limit the degree to which meaningful comparison of studies and meta-analysis can occur. Consistency of these issues would be valuable in future research. Future studies may also consider examining measures of quality of life. Furthermore, although research comparing FFP versus other pro-haemostatic agents has utility, these comparisons were positioned on a backdrop of poor-quality evidence when FFP was compared with no FFP.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

De Pietri 2016

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Number of study centres:** 1 **Power calculation:** reduction in blood product transfusion was used as a primary outcome to calculate sample size. Assuming a 20% difference in the average transfusion requirement (1000 mL in the SOC group and 800 mL in the TEG group) with a 5% alpha error and a 20% beta error, 30 patients in each group were required **Length of follow-up:** 90 days from procedure **Study duration for participants:** 90 days **Stopping rules:** not reported
Participants	**Baseline characteristics** Thromboelastography threshold • *Age*: 57.8 ± 9.4 • *Sex*: male 16 (53.3%) • *Type of surgery*: paracentesis (n = 12); central vein cannulation (n = 1); variceal band ligation (n = 6); hepatic resection (n = 3); abdominal surgery (n = 2); endoscopic polypectomy (n = 3); radiofrequency ablation (n = 2); thoracotomy (n = 1)

De Pietri 2016 *(Continued)*

- *PT*: 44.3 ± 16.6 (%)
- *INR*: 1.87 ± 0.55
- *aPTT*: 1.35 ± 0.26
- *TEG/ROTEM*: R (minutes) 19.4 ± 11 K, (minutes) 11.8 ± 60 MA, (mm) 21.5 ± 12.6, α-angle 35.5 ± 9.30 CL30, (%) 96.9 ± 12.2 LY30, (%) 0.15 ± 0.37
- *Hb*: 109 ± 19
- *Platelet count*: 56.5 ± 32.5
- *Number with a coagulopathy*: 12
- *Underlying diagnosis*: liver cirrhosis
- *Ethnic group*: not reported

Standard of care (laboratory parameters)

- *Age*: 58.6 ± 12.1
- *Sex*: male 22 (73.3%)
- *Type of surgery*: paracentesis (n = 7); thoracocentesis (n = 5); central vein cannulation (n = 2); transjugular intrahepatic portosystemic shunt procedure (n = 1); variceal band ligation (n = 4); hepatic resection (n = 2); abdominal surgery (n = 2); radiofrequency ablation (n = 1); liver biopsy (n = 3); biopsy of sites other than liver (n = 1); abdominal drainage (n = 1); endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (n = 1)
- *PT*: 40.4 ± 14.3 (5)
- *INR*: 2.01 ± 0.69
- *aPTT*: 1.34 ± 0.20
- *TEG/ROTEM*: R (minutes) 18.7 ± 12.8 K, (minutes) 10.9 ± 7.90 MA, (mm) 25.0 ± 16.8, α-angle 36.7 ± 10.8 CL30, (%) 99.3 ± 1.20 LY30, (%) 0.12 ± 0.37
- *Hb*: 103 ± 13
- *Platelet count*: 61.3 ± 41.9
- *Number with a coagulopathy*: 16
- *Underlying diagnosis*: liver cirrhosis
- *Ethnic group*: not reported

Included criteria: cirrhosis (histologically or imaging proven); age 18 to 80 years; undergoing an invasive procedure; INR > 1.8, and/or platelet count 50 × 10^9/L

Excluded criteria: ongoing bleeding; previous or current thrombotic events defined as any documented blood clot in a venous or arterial vessel; anti-platelet or anticoagulant therapy at the time of enrolment or that had been discontinued less than 7 days before evaluation for the study; presence of documented infection or sepsis according to ACCP-SCCM criteria; haemodialysis in the previous 7 days

Pretreatment: no statistical imbalance between arms in baseline characteristics. More men than women in standard of care group

Number screened: 153

Number recruited: 60

Type of surgery: 28 participants underwent procedures with risk of bleeding lower than 3% according to the literature: paracentesis (n = 19); thoracocentesis (n = 5); central vein cannulation (n = 3); transjugular intrahepatic portosystemic shunt procedure (n = 1). 32 participants underwent procedures with bleeding risk exceeding 3%: variceal band ligation (n = 10); hepatic resection (n = 5); abdominal surgery (n = 4); endoscopic polypectomy (n = 3); radiofrequency ablation (n = 3); liver biopsy (n = 3); biopsy of sites other than liver (n = 1); abdominal drainage (n = 1); endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (n = 1); thoracotomy (n = 1)

Number excluded: 93

Interventions	**Intervention characteristics** Thromboelastography threshold

De Pietri 2016 *(Continued)*

	• *Type of plasma*: FFP • *Dose of plasma*: 10 mL/kg ideal body weight • *Timing of transfusion*: before procedure, if R-time > 40 minutes Standard of care (laboratory parameters) • *Type of plasma*: FFP • *Dose of plasma*: 10 mL/kg ideal body weight • *Timing of transfusion*: before procedure, if INR > 1.8
Outcomes	All-cause mortality Major bleeding Number of individuals requiring a transfusion Serious adverse events due to plasma transfusion Serious adverse events due to surgery Return to theatre to treat bleeding
Identification	**Sponsorship source:** University of Modena and Reggio Emilia **Country:** Italy **Setting:** liver patients **Comments:** **Author's name:** Lesley De Pietri **Institution:** Azienda Ospedaliero Universitaria Policlinico di Modena **Email:** **Address:** Division of Anesthesiology and Intensive Care Unit, Department of Surgery, Azienda Ospedaliero Universitaria Policlinico di Modena, Modena, Italy **Trial Registration:** NCT02362178 **Date trial registered:** 23 January 2015 **Date trial started recruiting participants:** February 2011 **Date trial completed recruitment:** August 2014 **Conflicts of interest of study authors:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed electronically by block of 4 in a 1:1 rate"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported

De Pietri 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "study design: in this randomised, controlled, open-label, intention-to-treat (ITT) trial..." Comment: apart from all-cause mortality, the study is at risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "in this randomised, controlled, open-label...trial" Quote: "no transfusion side effects were reported in the TEG group, whereas an allergic reaction during FFP infusion occurred in the SOC group" Comment: blinding of assessors is not described. Potential risk of detection bias in all outcomes apart from all-cause mortality is due to knowledge of allocated interventions by outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants included in ITT analysis
Selective reporting (reporting bias)	High risk	Comment: study protocol described. Time frame for reporting of bleeding episodes "48 hours from admission". Time span for reporting the primary outcome is not clear from the report's description Comment: protocol described transfusion-related side effect time scale 48 hours. The report reduced this time scale to 6 hours Comment: reporting of blood test abnormalities post procedure was not a described outcome in the protocol nor in the report on methods/efficacy assessment. Aside from Hb, INR, and PLT count, other variables were not shown (quote: "none of the other variables showed statistical difference..."), precluding potential for meta-analysis Comment: comparison of blood product cost between groups was a secondary outcome described in the protocol. This was not described in the report on efficacy assessment nor in the results
Other bias	Low risk	Baseline characteristics Quote: "no significant differences in terms of age, sex, clinical features, cirrhosis prognostic scores, and clotting parameters were present between the two study groups at baseline" Comment: a table describing demographic, clinical, and biochemical characteristics of patients enrolled, together with P values, is concordant with the above quote

Mannucci 1976

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Power calculation:** not reported **Stopping rules:** not reported **Length of follow-up:** 12 months **Study duration for participants:** not reported

Mannucci 1976 *(Continued)*

Number of study centres: 1

Participants	**Baseline characteristics** Prophylactic plasma transfusion before surgery • *Age*: not reported • *Sex*: not reported • *Type of surgery*: needle biopsy • *PT*: not reported • *INR*: not reported • *aPTT*: not reported • *TEG/ROTEM*: not reported • *Hb*: not reported • *Platelet count*: not reported • *Number with a coagulopathy*: 10 • *Underlying diagnosis*: chronic liver disease • *Ethnic group*: not reported Alternative haemostatic agents • *Age*: not reported • *Sex*: not reported • *Type of surgery*: needle biopsy • *PT*: not reported • *INR*: not reported • *aPTT*: not reported • *TEG/ROTEM*: not reported • *Hb*: not reported • *Platelet count*: not reported • *Number with a coagulopathy*: 11 • *Underlying diagnosis*: chronic liver disease • *Ethnic group*: not reported **Included criteria:** chronic liver disease; undergoing needle biopsy; prothrombin time, kaolin-activated partial thromboplastin time, and 'Normotest' results all above the upper normal limit **Excluded criteria:** bleeding time 7 minutes or longer **Pretreatment:** not reported **Number screened:** 30 **Number recruited:** 21 **Number excluded:** 9 **Type of surgery:** needle biopsy (n = 30)
Interventions	**Intervention characteristics** Prophylactic plasma transfusion before surgery • *Type of plasma/alternative agent*: FFP • *Dose of plasma/alternative agent*: 12 mL/kg • *Timing of transfusion*: before biopsy, over 45 to 60 minutes Alternative haemostatic agents

Mannucci 1976 *(Continued)*

- *Type of plasma/alternative agent*: Prothromplex (Immuno, Vienna) containing factors II, IX, and X, followed by factor VII concentrate (Immuno, Vienna)
- *Dose of plasma/alternative agent*: Prothromplex 25 units/kg; factor VII concentrate 25 units/kg
- *Timing of transfusion*: before biopsy, over 15 minutes

Outcomes	Major bleeding Serious adverse events due to plasma transfusion Venous and arterial thromboembolism Coagulation test abnormalities
Identification	**Sponsorship source:** not reported **Country:** Italy **Setting:** liver patients **Comments:** **Author's name:** P.M. Mannucci **Institution:** University of Milan and Haemophilia and Thrombosis Centre **Email:** not reported **Address:** 3rd Department of Clinical Medicine, University of Milan and Haemophilia and Thrombosis Centre, Angelo Bianchi Bonomi, Via Pace 15, 20122 Milan, Italy **Trial registration:** not reported **Date trial registered:** not reported **Date trial completed recruitment:** not reported **Date trial started recruiting participants:** not reported **Conflicts of interest of study authors:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "21 consecutive patients were randomly allocated by a system of sealed envelopes to treatment with either FFP or concentrates" Comment: system of random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "21 consecutive patients were randomly allocated by a system of sealed envelopes to treatment with either FFP...or concentrates" Comment: it is unclear from the report whether the envelopes were opaque and sequentially numbered to reduce risk of allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported whether participants and personnel were blinded

Mannucci 1976 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: attrition rate/number analysed/number lost to follow-up is not reported. Therefore information is insufficient to permit a judgement
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration to assess whether all planned outcomes were reported
Other bias	Unclear risk	Comment: baseline characteristics were not reported

Müller 2015

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Power calculation:** based on the assumption that the occurrence of major bleeding in patients with a coagulopathy undergoing invasive procedures was less than 1%. Group size calculation was focused on demonstrating non-inferiority. With a sample size in each group of 198, a 1-sided Z test with continuity correction (pooled) achieved 80% power to reject the null hypothesis that the proportion of bleeding patients in the experimental group (no FFP transfusion) was higher than, that is, inferior to, the proportion in the control group (FFP transfusion) with a margin of 0.03. It was assumed that the expected difference in proportions is zero and the proportion in the control group is 0.01. The 1-sided significance level of the test was targeted at 0.05. Therefore, study authors intended to enrol 200 patients per treatment arm, 400 in total. Owing to slow inclusion, the trial was stopped before the pre-defined target enrolment was reached **Stopping rules:** not reported **Length of follow-up:** 28 days (according to clinicaltrials.gov database and protocol. Not described in report) **Study duration for participants:** 28 days **Number of study centres:** 4
Participants	**Baseline characteristics** Prophylactic plasma transfusion before surgery • *Age*: median 64 years (IQR 54 to 70) • *Sex*: male 26; female 12 • *Type of surgery*: central venous catheter (n = 29); chest tube (n = 4); tracheotomy (n = 2); abdominal drain (n = 3) • *PT*: not reported • *INR*: median 1.8 (IQR 1.5 to 2.2) • *aPTT*: median 43 (IQR 38 to 52) • *TEG/ROTEM*: not reported • *Hb*: median 93 (IQR 84 to 102) • *Platelet count*: median 92 × 10^9/L (IQR 52 to 180) • *Number with a coagulopathy*: DIC 17 • *Underlying characteristic*: pulmonary disease (n = 5); liver disease (n = 6); cardiac failure (n = 6); mechanical ventilation within 24 hours (n = 32); sepsis within 24 hours (n = 18); pneumonia within 24 hours (n = 10)

Müller 2015 *(Continued)*

- *Ethnic group*: not reported

No prophylactic plasma transfusion before surgery (colloid, crystalloid, placebo, or no treatment)

- *Age*: median 66 years (IQR 62 to 72)
- *Sex*: male 18; female 20
- *Type of surgery*: central venous catheter (n = 29); chest tube (n = 3); tracheotomy (n = 2); abdominal drain (n = 4)
- *PT*: not reported
- *INR*: median 1.9 (IQR 1.6 to 2.2)
- *aPTT*: median 41 (IQR 36 to 49)
- *TEG/ROTEM*: not reported
- *Hb*: median 93 (IQR 86 to 104)
- *Platelet count*: median 110 × 10^9/L (IQR 52 to 183)
- *Number with a coagulopathy*: DIC 14
- *Underlying characteristic*: pulmonary disease (n = 4); liver disease (n = 17); cardiac failure (n = 6); mechanical ventilation within 24 hours (n = 29); sepsis within 24 hours (n = 18); pneumonia within 24 hours (n = 9)
- *Ethnic group*: not reported

Included criteria: adults in intensive care (aged 18 years and older) with INR ≥ 1.5 undergoing insertion of a central venous catheter, thoracocentesis, percutaneous tracheotomy, or drainage of abscess or fluid collection (n = 81)

Excluded criteria: people with clinically overt bleeding (defined as decrease in haemoglobin (Hb) > 160 g/L or need for transfusion or haemodynamic instability due to bleeding at the time of the procedure); thrombocytopenia < 30 × 10^9/L; patients treated with vitamin K antagonists, activated protein C, abciximab, tirofiban, ticlopidine, or prothrombin complex concentrates; patients with a history of congenital or acquired coagulation factor deficiency or bleeding diathesis; use of heparin < 1 hour before the procedure; use of therapeutic doses of low molecular weight heparin < 12 hours before the procedure

Pretreatment: more men than women in the FFP transfusion group (P = 0.09). Greater number of patients with liver disease in the 'no FFP transfusion' group, reaching statistical significance (P = 0.006)

Number screened: a total of 1478 patients had an INR ≥ 1.5 and ≤ 3.0

Number recruited: 81 participants. Five did not undergo an intervention and were therefore excluded from further analysis (2 FFP; 3 no FFP)

Number excluded: 615 patients did not fulfil inclusion criteria, leaving 263 patients with an INR ≥ 1.5 and ≤ 3.0 scheduled to undergo a pre-defined intervention. Of these, 65 patients declined informed consent. An additional 83 patients were missed and 34 patients did not participate for other reasons, including refusal of treating physicians to include a specific patient (3.8%)

Type of surgery: central venous catheter insertion (n = 58); chest tube insertion (n = 7); tracheotomy (n = 4); abdominal drain insertion (n = 7)

Interventions	**Intervention characteristics** Prophylactic plasma transfusion before surgery • *Type of plasma*: FFP (manufactured by Sanquin, the Dutch National Bloodbank) • *Dose of plasma*: 12 mL/kg • *Timing of transfusion*: before invasive procedure No prophylactic plasma transfusion before surgery (no treatment)
Outcomes	All-cause mortality Major bleeding

Müller 2015 *(Continued)*

	Number of transfusions per participant
	Serious adverse events due to plasma transfusion
	ITU length of stay
	Return to theatre to treat bleeding
	Coagulation test abnormalities
Identification	**Sponsorship source:** Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)
	Country: Netherlands
	Setting: patients in intensive care units undergoing invasive procedures
	Comments:
	Author's name: Marcella C.A. Müller
	Institution: Department of Intensive Care Medicine, Academic Medical Center, University of Amsterdam
	Email: m.c.muller@amc.uva.nl.
	Address: Department of Intensive Care Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
	Trial registration: Dutch trial registry NTR2262NCT01143909
	Date trial registered: 26 March 2010
	Date trial completed recruitment: June 2013
	Date trial started recruiting participants: May 2010
	Conflicts of interest of study authors: NPJ reports grants from Netherlands Organisation for Scientific Research (NWO) during the conduct of the study. The other study authors disclose no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation procedure is password protected, web-based, using permuted blocks and stratified by study centre and invasive procedure"
Allocation concealment (selection bias)	Low risk	Quote: "the randomisation procedure is password protected, web-based, using permuted blocks and stratified by study centre and invasive procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "since manufacturing a completely matched placebo in full compliance with the current good manufacturing practice standards was considered not possible, a prospective, randomised, open-label, blinded endpoint evaluation (PROBE) design was chosen" Comment: investigators and clinicians were unblinded to the intervention. It is unclear how many participants were sedated and were not aware of the intervention
Blinding of outcome assessment (detection bias)	Low risk	Quote: "the potential bleeding site was assessed by a physician blinded to the intervention who filled out a predefined bleeding score form consisting

Müller 2015 *(Continued)*

All outcomes		of blood pressure, heart rate, Hb level, and occurrence of procedure-related bleeding with or without the need for intervention or transfusion. Subsequently this blinded physician assigned a score of major bleeding, minor bleeding, or no bleeding at 1 and 24 hours after the intervention"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants who were randomised and underwent an invasive procedure were included in the analysis
Selective reporting (reporting bias)	High risk	Quote (from protocol): regarding primary outcomes: "relevant bleeding is defined using a validated tool (HEME) in the critically ill" Quote (from report): "the HEME tool used to assess procedure-related relevant bleeding in our trial has been validated for ICU patients, with a high interrater agreement" Comment: primary outcome was reported using prescribed measurement method Quote (from report): "... the World Health Organization bleeding scale...is validated for patients with cancer but not in the critically ill. A possible disadvantage of the HEME tool is that some items, such as decrease in systolic blood pressure or increase in heart rate, may also occur in the absence of bleeding. However, assessors were asked to consider such physiologic changes only if they occurred in the absence of other causes" Comment: limitations and method of primary outcome assessment described. Risk of under-reporting in the presence of concomitant pathologies (e.g. sepsis, cardiogenic shock, hepato-renal syndrome), causing physiological dysfunction Quote (from protocol): "the occurrence of relevant bleedings (using a binary variable), expressed in a relative risk estimate and absolute risk increase" Quote (from report): "the primary endpoint of procedure-related major bleeding only occurred once, rendering planned non-inferiority analysis impossible. Therefore, a post hoc non-inferiority analysis for all types of bleeding complications (major and minor) was performed according to the method of Dunnett and Gent" Quote (from report): "post hoc analysis showed a trend toward non-inferiority with a 5% higher bleeding rate in the transfused group compared to non-transfused patients" Comment: post hoc analysis (due to low incidence of primary outcome measure on a background of patient under-recruitment) was used, which was not pre-defined in the protocol. Adverse event outcome measure (predefined in protocol) was not reported. Therefore potential risk of reporting bias was due to selective outcome reporting
Other bias	High risk	Comment: the major limitation of this trial is that it was stopped early due to slow inclusion. Despite the addition of extra recruitment sites, the study was able to randomise only 20% of the targeted participant number. There was an imbalance in the number of participants with a history of liver disease between treatment arms. 45% (17/38) of participants had liver disease in the no FFP arm, whereas only 16% (6/38) had liver disease in the FFP arm

NCT00953901

Methods	**Study design:** randomised trial

NCT00953901 *(Continued)*

	Study grouping: parallel group **Masking:** double-blinded
Participants	**Included criteria:** • Consenting hospitalised adult • > 18 years old • Female or male • Patients with abnormal INR (INR 1.6 to 3) due to vitamin K depletion or antagonism (Coumadin and/or broad-spectrum antibiotics) or liver insufficiency • Patients who are about to undergo 1 of the 3 common minimally invasive procedures (thoracocentesis, abdominal paracentesis, and central vein cannulation) **Excluded criteria:** not stated
Interventions	Drug: fresh frozen plasma transfusion
Outcomes	**Primary outcome measures:** New-onset pulmonary edema **Secondary outcome measures:** Postprocedural bleeding complications Number of blood product transfusions Hospital mortality Length of intensive care unit and hospital stay
Identification	**Sponsorship source:** Mayo Clinic **Country:** United States of America **Setting:** patients undergoing commonly performed invasive procedures **Institution:** Mayo Clinic, Rochester. **Address:** Mayo Clinic, Rochester, Minnesota, United States, 55905 **Trial registration:** NCT00953901 **Date trial registered:** 6 August 2009 **Date trial started recruiting participants:** July 2006 **Date trial completed recruitment:** December 2007
Notes	**Study completion:** December 2008 **Recruitment:** N = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgement

NCT00953901 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgement
Selective reporting (reporting bias)	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. Given no trial report was published, and based on available information in the trial registry, available information is insufficient to permit a judgement
Other bias	Unclear risk	Comment: trial recruitment completed in 2008 with 2 participants. No trial report was published on assessment of other bias such as differences in baseline characteristics

Veelo 2012

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Power calculation:** reduction in bleeding was used as a primary outcome to calculate sample size. Assuming a 15% absolute decrease in bleeding following correction of subclinical bleeding disorders with a 5% alpha error and a 20% beta error, 76 patients in each group were required **Stopping rules:** not reported **Length of follow-up:** unclear; outcomes up to 12 hours post procedure **Study duration for participants:** unclear; outcomes at up to 12 hours post procedure **Number of study centres:** 1
Participants	**Baseline characteristics** Prophylactic plasma or platelet transfusion or both before percutaneous dilatational tracheotomy • *Age*: median (IQR) 64 (56 to 72) • *Sex* (male/female): 22/13 • *Type of surgery*: percutaneous dilatational tracheotomy • *PT*: mean (SD) 16.0 (1.2) • *INR*: not reported • *aPTT*: not reported • *TEG/ROTEM*: not reported • *Hb*: not reported • *Platelet count*: median (IQR) 81 (63 to 85) • *Number with a coagulopathy*: 19/35

Veelo 2012 *(Continued)*

- *Underlying diagnosis*: post surgery (n = 5); coma (n = 3); cardiac arrest (n = 4); acute respiratory failure (n = 19); trauma (n = 2); other reason for mechanical ventilation (n = 2); complicated weaning (n = 10); expected prolonged duration of mechanical ventilation (n = 12); need for frequent airway suctioning (n = 3); low GCS (n = 5); critical illness polyneuromyopathy (n = 4); other reason for tracheotomy (n = 1); acute renal failure (n = 9); chronic renal failure (n = 2); sepsis (n = 7); massive transfusion (n = 5); haematological malignancy (n = 2)
- *Ethnic group*: not reported

No prophylactic plasma or platelet transfusion or both before percutaneous dilatational tracheotomy

- *Age*: median (IQR) 68 (60 to 76)
- *Sex* (male/female): 16/21
- *Type of surgery*: percutaneous dilatational tracheotomy
- *PT*: mean (SD) 16.6 (1.1)
- *INR*: not reported
- *aPTT*: not reported
- *TEG/ROTEM*: not reported
- *Hb*: not reported
- *Platelet count*: median (IQR) 56 (47 to 70)
- *Number with a coagulopathy*: 22/37
- *Underlying diagnosis*: post surgery (n = 9); coma (n = 4); cardiac arrest (n = 4); acute respiratory failure (n = 18); trauma (n = 1); other reason for mechanical ventilation (n = 1); complicated weaning (n = 17); expected prolonged duration of mechanical ventilation (n = 4); need for frequent airway suctioning (n = 2); low GCS (n = 6); critical illness polyneuromyopathy (n = 5); other reason for tracheotomy (n = 3); acute renal failure (n = 3); chronic renal failure (n = 2); sepsis (n = 9); massive transfusion (n = 5); haematological malignancy (n = 3)
- *Ethnic group*: NR

Included criteria: patients planned for bedside PDT with mild coagulation disorders (prothrombin time (PT) 14.7 to 20.0 seconds and/or platelet count 40 to 100 × 10^9/L) and/or active treatment with acetylsalicylic acid at any dose were eligible

Excluded criteria: age < 18 years; need for surgical tracheotomy; contraindications to transfusion of blood products; use of clopidogrel. A patient would also be excluded from participation in this trial if the attending physician insisted on the need for transfusion of FFP and/or platelets

Pretreatment: no difference with regard to gender, age (years), APACHE II score. Time from admission to tracheotomy (days), reason for mechanical ventilation, post-surgical, coma, cardiac arrest, acute respiratory failure, trauma, reason for tracheotomy, complicated weaning, need for frequent airway suctioning, low GCS score; possible reasons for coagulation disorders, acute renal failure, chronic renal failure, sepsis, massive transfusion, liver cirrhosis, haematological, duration of mechanical ventilation, length of stay in ICU, ICU mortality, hospital mortality. Two significant differences were expected prolonged duration of mechanical ventilation AND platelet count more in men than in women (not statistically significant)

Number screened: 355

Number recruited: randomised 72; 4 in each arm did not undergo PDT*

Number excluded: 283 (refused consent 27, surgical procedure 53, clopidogrel 13, PT > 20 seconds 11, normal coagulation 179)

Type of surgery: percutaneous dilatational tracheotomy

Interventions	**Intervention characteristics** Prophylactic plasma or platelet transfusion or both before percutaneous dilatational tracheotomy • *Type of plasma*: FFP • *Dose of plasma*: participants with 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

Veelo 2012 *(Continued)*

	PT was between 14.7 and 18.0 seconds, the patient received 1 unit of FFP; if the PT was between 18.0 and 20.0 seconds, the patient received 2 units of FFP) • *Type of platelets*: platelet concentrates prepared from 5 pooled buffy coats • *Dose of platelets*: participants with a low platelet count and/or active use of acetylsalicylic acid received 5 units of platelet concentrates • *Timing of transfusion*: before procedure No prophylactic plasma or platelet transfusion or both before percutaneous dilatational tracheotomy • *Type of plasma/platelets*: NA • *Dose of plasma/platelets*: participants 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 • *Timing of transfusion*: NA
Outcomes	All-cause mortality Major bleeding Number of individuals requiring a transfusion Use of haemostatic agents Volume of blood loss per participant ITU length of stay
Identification	**Sponsorship source:** Academic Medical Centre (AMC) (The Netherlands) - Department of Intensive Care **Country:** The Netherlands **Setting:** University hospital in The Netherlands/1 centre ICU **Comments:** **Author's name:** Denise P. Veelo **Institution:** Department of Intensive Care Medicine and Department of Anaesthesiology, Academic Medical Centre, University of Amsterdam **Email:** d.p.veelo@amc.uva.nl **Address:** Department of Intensive Care Medicine, Academic Medical Centre, University of Amsterdam, Meibergdreef 91105 AZ Amsterdam, The Netherlands **Trial registration:** NTR694 ISRCTN31808827 **Date trial registered:** NTR: 29 May 2006; ISRCTN: 19 July 2006 **Date trial completed recruitment:** NTR/ISRCTN: 01 July 2009; Study report: October 2009 **Date trial started recruiting participants:** 1 July 2006 **Conflicts of interest of study authors:** study authors declare no conflicts of interest
Notes	*Of 72 participants, 7 did not undergo percutaneous dilatational tracheotomy due to unexpected anatomical landmark recognition difficulties. They subsequently underwent surgical tracheotomy. One patient did not undergo tracheotomy due to logistical difficulties. As participants not receiving percutaneous dilatational tracheotomy had received plasma or platelets in the intervention group, with most subsequently receiving a surgical tracheotomy, study authors analysed all cases (personal communication from study author D Veelo)

Veelo 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated randomisation scheme was used. Each assignment ("correction" or "no correction") was recorded on a piece of paper folded three times and enclosed in a consecutively numbered, opaque, sealed envelope"
Allocation concealment (selection bias)	Low risk	Quote: "each assignment ("correction" or "no correction") was recorded on a piece of paper folded three times and enclosed in a consecutively numbered, opaque, sealed envelope" Comment: appropriate concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open-label design study. At high risk of bias apart from all-cause mortality
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: open-label design study. Outcomes at high risk of bias apart from all-cause mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: clear CONSORT flow diagram. Equal numbers of patients not undergoing PDT (N = 4) after randomisation present in each study arm. Attrition bias likely to be low
Selective reporting (reporting bias)	High risk	Comment: no protocol available, but registered ISRCTN31808827 Primary outcome measures: Volume of blood loss during PDT Intensity of intra-tracheal bleeding Time until no blood is visible in tracheal aspirates These were all reported Secondary outcome measures: Number of blood products used during and after tracheotomy - not clearly reported
Other bias	Unclear risk	Baseline characteristics: Quote: "expected prolonged duration of mechanical ventilation, N = 12 [Correction group] N = 4 [No correction group]; P = 0.02" Comment: differences in baseline characteristics have not been commented on by the study authors. The risk of material bias of this difference is unclear Quote: "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" Comment: trial was stopped early due to increased resistance to recruitment and low rate of bleeding in either arm of the study

ACCP: American College of Chest Physicians.
aPTT: activated partial thromboplastin time.
DIC: disseminated intravascular coagulation.
ERCP: endoscopic retrograde cholangiography.
FFP: fresh frozen plasma.
GCS: Glasgow Coma Scale.
Hb: haemoglobin.
INR: international normalised ratio.
ISRCTN: International Standard Randomized Controlled Trials Number.
ITU: intensive treatment unit.
NR: not reported.
NTR: Netherlands Trial Register
PDT: percutaneous dilatational tracheotomy
PLT: platelet.
PT: prothrombin time.
ROTEM: rotational thromboelastometry.
SCCM: Society of Critical Care Medicine.
SD: standard deviation.
SOC: standard of care.
TEG: thromboelastography.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bauer 1986	The intervention did not meet our eligibility criteria (plasma transfusion to prevent bleeding)
Cao 2016	The participant population did not meet our eligibility criteria
ChiCTR-INR-17013901	The comparator did not meet our eligibility criteria
Freeman 1998	The comparator did not meet our eligibility criteria
Galganski 2017	The comparator did not meet our eligibility criteria
Gazzard 1975	The study design did not meet our eligibility criteria
Hedstrand 1987	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Hildebrandt 2007	The study design did not meet our eligibility criteria
Jilma-Stohlawetz 2011	The participant population did not meet our eligibility criteria
Kerner 2008	The study design did not meet our eligibility criteria
Laine 2003	The comparator did not meet our eligibility criteria
Lance 2012	The participant population did not meet our eligibility criteria
Lerner 1997	The comparator did not meet our eligibility criteria
Liu 1994	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Mintz 2006	The comparator did not meet our eligibility criteria
NCT00233246	The study was withdrawn before enrolment

Study	Reason for exclusion
NCT00235183	The comparator did not meet our eligibility criteria
NCT00302965	The participant population did not meet our eligibility criteria
NCT00656396	The intervention did not meet our eligibility criteria (plasma transfusion to prevent bleeding)
NCT00994045	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
NCT02352181	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
NCT03700723	The comparator did not meet our eligibility criteria
Palmieri 2013	The comparator did not meet our eligibility criteria
Pieters 2015	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Ramies 2002	The comparator did not meet our eligibility criteria
Rocha 2017	The indication for the intervention did not meet our eligibility criteria
Sommoggy 1990	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Tinmouth 2008	The comparator did not meet our eligibility criteria
Urwyler 2009	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Wang 2010	Timing of the intervention did not meet our eligibility criteria (before surgery or invasive procedure)
Wieding 1999	The comparator did not meet our eligibility criteria
Williamson 1999	The comparator did not meet our eligibility criteria

Characteristics of studies awaiting assessment *[ordered by study ID]*

Boyd 1996

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Masking:** not reported
Participants	**Enrolment:** number not reported **Included criteria:** • Over 18 years of age • Bleeding time > 10 minutes (both FFP and conjugated oestrogen groups) • Bleeding time between 8 minutes and 9 minutes and 30 seconds (control group)

Boyd 1996 *(Continued)*

	Excluded criteria: • Patients receiving oestrogen treatment • Patients receiving non-steroidal anti-inflammatory drugs
Interventions	**Intervention characteristics** Conjugated oestrogen group • Type of biological agent: conjugated oestrogen (Premarin, Wyeth Ayerst Laboratories, Philadelphia, PA) • Dose of intervention: 50 mg • Timing of intervention: following induction of anaesthesia* FFP group • Type of biological agent: FFP • Dose of intervention: 2 units • Timing of intervention: following induction of anaesthesia* Control group • Type of biological agent: none
Outcomes	**Main outcome measures:** • Bleeding time measurements [time frame: end of surgery, at 24 hours, and at 48 hours] • Other laboratory tests (creatinine, blood urea nitrogen, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, and TEG values) [time frame: end of surgery, at 24 hours, and at 48 hours]
Notes	**Sponsorship source:** not reported **Country:** United States of America **Setting:** university regional referral centre for renal transplantation **Author's name:** Gwendolyn L. Boyd **Institution:** University of Alabama at Birmingham **Address:** Department of Anesthesiology, University of Alabama at Birmingham, 619 19th St S, JT 845, Birmingham, AL 35233-6810 **Trial registration:** not reported **Date trial registered:** not reported **Date trial started recruiting participants:** not reported **Date trial completed recruitment:** not reported *It is unclear from the report whether the intervention was completed prior to the start of surgery. Inclusion or exclusion of this study is dependent on this information, which has been sought from the primary author (personal communication)"

NCT02777424

Methods	**Study design:** randomised trial **Study grouping:** parallel group

NCT02777424 *(Continued)*

	Masking: open-label; blinded assessment of primary endpoint **Number of study centres:** 2
Participants	**Estimated N = 46** **Included criteria:** • Patient with spontaneous intracranial haemorrhage or traumatic intracranial haemorrhage or patient requiring neurological surgery • Coagulation disorder defined by PT < 60% • 18 years and older (adult, senior) • Female or male **Excluded criteria:** • Concomitant use with oral anticoagulant drugs • Acquired deficiency of coagulation factors whose treatment is established • Hypersensitivity to a PCC • History of thrombocytopenia induced by heparin • Disseminated intravascular coagulation • Extracranial active bleeding • Hypersensitivity to vitamin K
Interventions	**Intervention characteristics** Experimental group • *Type of intervention:* prothrombin complex concentrate • *Dose of intervention:* administration of a single dose of prothrombin complex concentrate (25 U/kg equivalent factor IX) Active comparator • *Type of comparator:* FFP • *Dose of comparator:* administration of a single dose of fresh frozen plasma of 15 mL/kg intervention
Outcomes	**Primary outcomes:** proportion of patients with correction of prothrombin time (PT > 60%) [time frame: end of treatment administration (an average of 1 hour)] **Secondary outcomes:** not described
Notes	**Sponsorship source:** Fondation Ophtalmologique Adolphe de Rothschild **Country:** France **Setting:** adult neurological patients with coagulopathy **Author's name:** Laurence Salomon **Institution:** Fondation Ophtalmologique Adolphe de Rothschild **Email:** lsalomon@for.paris **Address:** Fondation Ophtalmologique Adolphe de Rothschild, Paris, France 75019 **Trial registration:** NCT02777424 **Date trial registered:** 19 May 2016 **Date trial started recruiting participants:** January 2016

NCT02777424 *(Continued)*	
	Estimated date trial completed recruitment: July 2019

Tseĭmakh 2008	
Methods	Comparative study
Participants	Participants with pancreonecrosis, N = 60
Interventions	Cryosupernatant plasma vs fresh frozen plasma
Outcomes	Laboratory indices, lethality, other outcomes
Notes	English translation of study abstract by study authors is available from study report, from which the above information is taken. Full-text report in Russian. Currently awaiting translation of report by Cochrane Russia

FFP: fresh frozen plasma.
PCC: Prothrombin complex concentrate
PT: prothrombin time.
TEG: thromboelastography.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02561026	
Trial name or title	Transfusion of plasma prior to invasive procedures pilot trial (TOPPIT)
Methods	**Study design:** randomised controlled trial in 3 Canadian hospitals **Study grouping:** parallel group **Masking:** open-label
Participants	**Estimated enrolment:** N = 80 **Included criteria:** • Age 18 years to 65 years (adult) • Admission or planned admission (e.g. patients in emergency department who are being seen by the ICU team) to an intensive care unit • Elevated INR between 1.5 and 2.5 • Requiring an invasive procedure in the next 24 hours including central venous line, arterial line, paracentesis, thoracocentesis, bronchoscopy, endoscopy, and ultrasound-guided biopsy (mass or organ) or fluid drainage • Female or male **Excluded criteria:** • Active bleeding, defined as visible or suspected blood loss in last 48 hours, resulting in a fall in haemoglobin ≥ 20 g/L, requiring a red cell transfusion or an intervention to control bleeding • Full-dose therapeutic anticoagulation with warfarin, heparin, low molecular weight heparin, or other novel oral anticoagulants • Congenital bleeding disorders including haemophilia, von Willebrand disease, or platelet function disorders • Acquired coagulation factor deficiencies • Frozen plasma transfusion during this ICU admission

NCT02561026 *(Continued)*

	• Use of other haemostatic blood products (recombinant factor VIIa, prothrombin complex concentrate, cryoprecipitate, fibrinogen concentrate) during the ICU admission • Previous enrolment in the study Patients will not be excluded for thrombocytopenia nor for anti-platelet drugs. As a pilot trial for a pragmatic large randomised controlled trial, both thrombocytopenic patients and patients on anti-platelet agents will be enrolled as they are routinely encountered in clinical practice. Specific therapy (i.e. platelet transfusions) will not be mandated but will be left to local routine practice. Information regarding platelet counts, anti-platelet medications, platelet transfusions, and other haemostatic therapies will be collected
Interventions	**Intervention characteristics** Experimental group: • *Type of intervention:* frozen plasma transfusion • *Dose of intervention:* not described • *Timing of intervention:* before an invasive procedure Comparator group • *Type of intervention:* no FP transfusion
Outcomes	**Primary outcomes**: • Recruitment feasibility, as measured by the number of participants screened per month at each centre [time frame: monthly, up to 21 months] **Secondary outcomes:** • Bleeding assessment (changes in haemoglobin and red cell transfusions as measured by a standardised bleeding assessment tool) [time frame: 24 to 48 hours post procedure] • Ventilator requirement [time frame: 24 to 48 hours post frozen plasma transfusion] Requirement for mechanical ventilation as it pertains to the feasibility of study procedures • Overall length of stay [time frame: length of stay will be measured as the number of days elapsed between hospital admission and hospital discharge dates up to 21 months] • ICU length of stay [time frame: ICU length of stay will be measured as the number of days elapsed between intensive care unit admission and discharge dates up to 21 months]
Starting date	January 2016
Contact information	**Sponsorship source:** Ottawa Hospital Research Institute **Country:** Canada **Setting:** ICU non-bleeding patients with a coagulopathy requiring an invasive procedure **Authors name:** Alan Tinmouth **Institution:** Ottawa Hospital **Email:** echatelain@ohri.ca **Address:** The Ottawa Hospital, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, K1H8L6 **Trial registration:** NCT02561026 ID20150215-01H **Date trial registered:** 25 September 2015 **Date trial started recruiting participants:** January 2016

NCT02561026 *(Continued)*

	Estimated date trial completed recruitment: August 2018
Notes	

NCT02637427

Trial name or title	Does plasma reduce bleeding in patients undergoing invasive procedures?
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Masking:** single-blinded (outcomes assessor)
Participants	**Estimated enrolment:** N = 110 **Included criteria:** • INR level between 1.50 and 2.50 inclusive • Undergoing an invasive procedure at the bedside, at an endoscopy laboratory, or in radiology • 21 years and older (adult, senior) • Female or male **Excluded criteria:** • Undergoing a surgical procedure in the operating room • Active bleeding • Undergoing a procedure involving or proximal to the central nervous system or spinal cord • Cardiac catheterisation • Using 4 factor plasma concentrates • Using systemic heparin/heparinoid therapy, direct factor X inhibitors, and other anticoagulants for which plasma will not correct prolonged INR • Platelet count < 50,000/µL • Congenital coagulation disorders • Acquired disorders (i.e. lupus anticoagulant) for which plasma will not correct the disorder • Women who are pregnant • Unwillingness to consider blood transfusion
Interventions	**Intervention characteristics** Experimental group • *Type of intervention:* FFP transfusion • *Dose of intervention:* 15 cc/kg, range 10 to 20 cc/kg, to a maximum of 5 units • *Timing of intervention:* pre-procedure Comparator group • *Type of intervention:* no transfusions before the procedure
Outcomes	**Primary outcomes:** • Change in haemoglobin level [time frame: within 2 days post procedure] (change from pre-procedure haemoglobin) • Trial feasibility (rates of eligible and enrolled study participants) [time frame: 16 months study enrolment]

NCT02637427 *(Continued)*

	Secondary outcomes: • Red blood cell transfusion [time frame: within 2 days post procedure] (differences in number of units of red blood cell transfusions between the 2 study arms) • Transfusion-associated cardiac overload (TACO) [time frame: within 2 days post procedure] (difference in rates between the 2 study arms) • Transfusion-related acute lung injury (TRALI) [time frame: within 2 days post procedure] (difference in rates between the 2 study arms) • Major bleed [time frame: within 2 days post procedure] (2 g/dL or greater fall in haemoglobin level) • Change in INR level post procedure [time frame: day of procedure] (change from pre-procedure INR level) • Change in INR level day 1 [time frame: day 1 post procedure] (change from pre-procedure INR level) • Change in INR level day 2 [time frame: day 2 post procedure] (change from pre-procedure INR level) • Mortality [time frame: in-hospital up to 30 days] (death) • Infection [time frame: within 2 days post procedure] (pneumonia or bloodstream infection) • ICU admission [time frame: within 2 days post procedure] (new admission to the intensive care unit)
Starting date	January 2016
Contact information	**Sponsorship source:** Rutgers, The State University of New Jersey **Country:** **Setting:** **Author's name:** Jeffrey L Carson, Helaine Noveck **Institution:** Johns Hopkins University, The Johns Hopkins Hospital. Robert Wood Johnson University Hospital **Email:** jeffrey.carson@rutgers.edu. helaine.noveck@rutgers.edu **Address:** Johns Hopkins University, The Johns Hopkins Hospital, Baltimore, Maryland, United States, 21287 **Trial registration:** NCT02637427 Pro20150001801 U.S. NIH Grant/Contract: 1R34HL125804-01A1 **Date trial registered:** 22 December 2015 **Date trial started recruiting participants:** January 2016 **Estimated date trial completes recruitment:** April 2020
Notes	

Smart 2017

Trial name or title	A prospective, randomised clinical trial comparing blood product use, bleeding events, and cost during and after endoscopic procedures in patients with cirrhosis and coagulopathy: rotational thromboelastometry (ROTEM) versus conventional therapy
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Smart 2017 *(Continued)*

Participants	Enrolment: N = 41 **Included criteria**: • Cirrhosis • INR > 1.5 and/or platelet count < 50,000/μL • Undergoing endoscopic procedure
Interventions	**Intervention characteristics** Experimental group • *Type of intervention:* ROTEM guided transfusion • *Dose of intervention:* platelet, cryoprecipitate, and FFP transfusion determined by ROTEM tests • *Timing of intervention:* before and after endoscopy Comparator group • *Type of intervention:* conventional coagulation-guided transfusion • *Dose of intervention:* platelet, cryoprecipitate, and FFP transfusion determined by aPTT, PT, INR, platelet count, and fibrinogen tests • *Timing of intervention:* before and after endoscopy
Outcomes	Outcomes included: • Intra-procedural and post-procedural blood loss • Types and numbers of blood products transfused • Complications • Cost **Results** • ROTEM group participants were transfused significantly lower volumes of blood products compared to conventional group participants (309 mL vs 461 mL; P = 0.049) • No statistically significant difference in blood loss and bleeding events between 2 groups • More participants in the ROTEM group received cryoprecipitate compared with the conventional group (65% vs 19%; P = 0.003) • More participants in the conventional group received FFP than in the ROTEM group (62% vs 10%; P = 0.001) • Platelet use was equivalent between groups • Total transfusion costs were higher in the ROTEM group than in the conventional group (576.41 vs 317.68; P = 0.045)
Starting date	Completed
Contact information	**Setting:** participants with cirrhosis undergoing endoscopic procedures **Authors' names:** Smart L, Wellner M, Gray N, Michaels A, Kirkpatrick R, Conteh L, Mumtaz K, Hanje A **Institution:** University of Louisville, Louisville (Smart, Wellner); The Ohio State University Wexner Medical Center, Columbus, America (Gray, Michaels, Kirkpatrick, Conteh, Mumtaz, Hanje)
Notes	Written abstract from 68th Annual Meeting of the American Association for the Study of Liver Diseases, 2017 Citation: Smart L, Wellner M, Gray N, Michaels A, Kirkpatrick R, Conteh L, et al. A prospective, randomised clinical trial comparing blood product use, bleeding events, and cost during and after endoscopic

Smart 2017 *(Continued)*

procedures in patients with cirrhosis and coagulopathy: rotational thromboelastometry (ROTEM) versus conventional therapy. Hepatology 2017;66(Suppl 1):243A-244A

aPTT: activated partial thromboplastin time.
FFP: fresh frozen plasma.
FP: frozen plasma.
ICU: intensive care unit.
INR: international normalised ratio.
PT: prothrombin time.
ROTEM: rotational thromboelastometry.
TACO: transfusion-associated circulatory overload.
TRALI: transfusion-related acute lung injury.

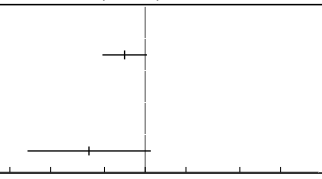
DATA AND ANALYSES

Comparison 1. Prophylactic plasma transfusion before surgery versus no prophylactic plasma transfusion before surgery (colloid, crystalloid, placebo, or no treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Up to 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Up to 30 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Major bleeding	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Within 24 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

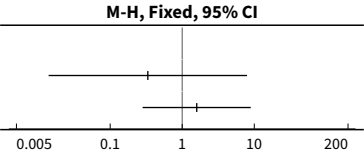
Analysis 1.1. Comparison 1 Prophylactic plasma transfusion before surgery versus no prophylactic plasma transfusion before surgery (colloid, crystalloid, placebo, or no treatment), Outcome 1 All-cause mortality.

Study or subgroup	prophylactic plasma transfusion prior to surgery	no prophylactic plasma transfusion prior to surgery (colloid, crystalloid, placebo or no treatment)	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 Up to 24 hours				
Müller 2015	19/38	27/38		0.7[0.48,1.03]
1.1.2 Up to 30 days				
Veelo 2012	4/35	11/37		0.38[0.13,1.1]



Analysis 1.2. Comparison 1 Prophylactic plasma transfusion before surgery versus no prophylactic plasma transfusion before surgery (colloid, crystalloid, placebo, or no treatment), Outcome 2 Major bleeding.

Study or subgroup	prophylactic plasma transfusion prior to surgery n/N	no prophylactic plasma transfusion prior to surgery (colloid, crystalloid, placebo or no treatment) n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Within 24 hours				
Müller 2015	0/38	1/38		0.33[0.01,7.93]
Veelo 2012	3/35	2/37		1.59[0.28,8.93]

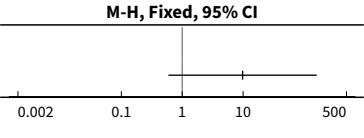


Comparison 2. Prophylactic plasma transfusion before surgery versus alternative haemostatic agents

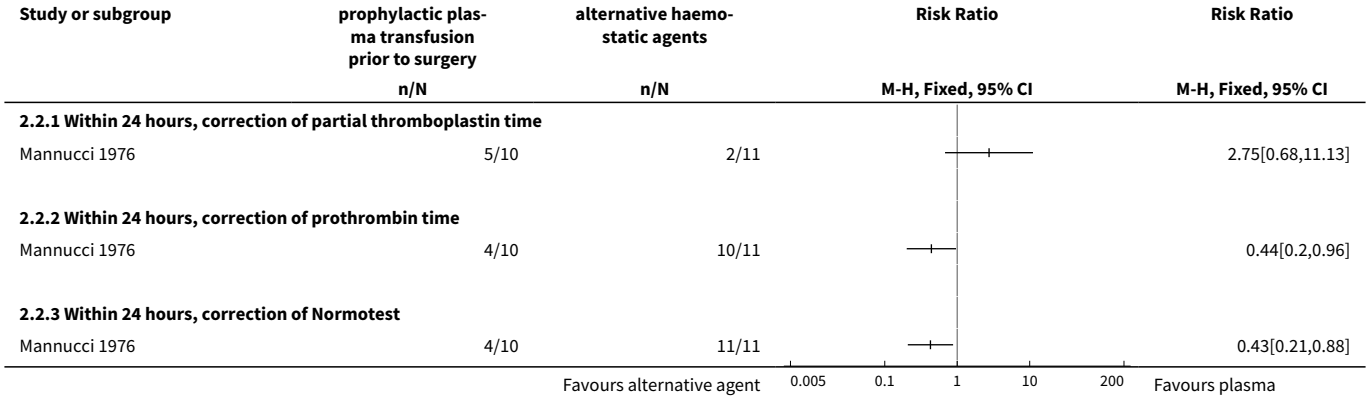
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse event due to plasma transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Within 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Coagulation test abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Within 24 hours, correction of partial thromboplastin time	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Within 24 hours, correction of prothrombin time	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Within 24 hours, correction of Normotest	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Prophylactic plasma transfusion before surgery versus alternative haemostatic agents, Outcome 1 Serious adverse event due to plasma transfusion.

Study or subgroup	prophylactic plasma transfusion prior to surgery n/N	alternative haemostatic agents n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Within 24 hours				
Mannucci 1976	4/10	0/11		9.82[0.59,162.24]



Analysis 2.2. Comparison 2 Prophylactic plasma transfusion before surgery versus alternative haemostatic agents, Outcome 2 Coagulation test abnormalities.

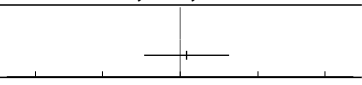


Comparison 3. Thromboelastography threshold versus standard of care (laboratory parameters)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Up to 90 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Within 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Within 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of individuals requiring a transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Within 7 days, overall blood product use	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Within 7 days, FFP use only	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Within 7 days, PLT use only	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Within 7 days, FFP and PLT use	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse event due to plasma transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Within 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Thromboelastography threshold versus standard of care (laboratory parameters), Outcome 1 All-cause mortality.

Study or subgroup	thromboelastography threshold n/N	standard of care (laboratory parameters) n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Up to 90 days				
De Pietri 2016	8/30	7/30		1.14[0.47,2.75]



Analysis 3.2. Comparison 3 Thromboelastography threshold versus standard of care (laboratory parameters), Outcome 2 Major bleeding.

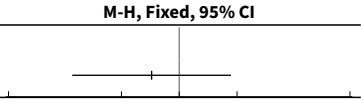
Study or subgroup	thromboelastography threshold n/N	standard of care (laboratory parameters) n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Within 24 hours				
De Pietri 2016	0/30	1/30		0.33[0.01,7.87]
3.2.2 Within 7 days				
De Pietri 2016	0/30	1/30		0.33[0.01,7.87]

Analysis 3.3. Comparison 3 Thromboelastography threshold versus standard of care (laboratory parameters), Outcome 3 Number of individuals requiring a transfusion.

Study or subgroup	thromboelastography threshold n/N	standard of care (laboratory parameters) n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Within 7 days, overall blood product use				
De Pietri 2016	5/30	30/30		0.18[0.08,0.39]
3.3.2 Within 7 days, FFP use only				
De Pietri 2016	0/30	16/30		0.03[0,0.48]
3.3.3 Within 7 days, PLT use only				
De Pietri 2016	2/30	10/30		0.2[0.05,0.84]
3.3.4 Within 7 days, FFP and PLT use				
De Pietri 2016	3/30	4/30		0.75[0.18,3.07]

Analysis 3.4. Comparison 3 Thromboelastography threshold versus standard of care (laboratory parameters), Outcome 4 Serious adverse event due to plasma transfusion.

Study or subgroup	thromboelastography threshold n/N	standard of care (laboratory parameters) n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Within 24 hours				
De Pietri 2016	0/30	1/30		0.33[0.01,7.87]



ADDITIONAL TABLES

Table 1. Additional data: outcomes reported for FFP versus no FFP with median and IQR

Outcome	Prophylactic transfusion			No prophylactic transfusion			P value
	Median	IQR	Total number of participants in group	Median	IQR	Total number of participants in group	
Number of transfusions after intervention, per participant (within 24 hours)							
Müller 2015							
RBC	1	0 to 2	38	1	0 to 3	38	0.91
FFP	0	0 to 1	38	2	0 to 2	38	0.06
PLT	1	0 to 2	38	0	0 to 1	38	0.43
Volume of blood loss per participant (within 7 days)							
Veelo 2012	3.0	1.0 to 6.0	35	3.0	2.0 to 6.0	37	0.96
Lung injury score (within 24 hours after randomisation)							
Müller 2015	2	0.8 to 2.5	38	1.25	0.4 to 2.4	38	0.28
ICU length of stay (within 30 days)							
Müller 2015	12	6 to 19	38	7	3 to 17	38	0.13
Veelo 2012	15	8 to 29	35	21	14 to 26	37	0.21

Table 1. Additional data: outcomes reported for FFP versus no FFP with median and IQR *(Continued)*

Coagulation test abnormalities (within 24 hours)

Müller 2015							
INR before FFP intervention	1.8	1.5 to 2.5	38	-	-	-	
INR after FFP intervention	1.4	1.3 to 1.63	38	-	-	-	< 0.001

FFP: fresh frozen plasma; ICU: intensive care unit; INR: international normalised ratio; IQR: interquartile range; PLT: platelets; RBC: red blood cells.

APPENDICES

Appendix 1. Definition of 'surgery', American College of Surgeons

In conjunction with the section "Classification of procedures" in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM 2011), we have used the following definition of 'surgery' from the American College of Surgeons (ACS 2007), to assist with determination of studies for inclusion.

"Surgery is performed for the purpose of structurally altering the human body by incision or destruction of tissues and is part of the practice of medicine. Surgery also is the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transportation of live human tissue, which include lasers, ultrasound, ionizing radiation, scalpels, probes, and needles. The tissue can be cut, burned, vaporized, frozen, sutured, probed, or manipulated by closed reduction for major dislocations and fractures, or otherwise altered by any mechanical, thermal, light-based, electromagnetic, or chemical means. Injection of diagnostic or therapeutic substances into body cavities, internal organs, joints, sensory organs, and the central nervous system is also considered to be surgery (this does not include administration by nursing personnel of some injections, such as subcutaneous, intramuscular, and intravenous when ordered by a physician). All of these surgical procedures are invasive, including those that are performed with lasers, and the risks of any surgical intervention are not eliminated by using a light knife or laser in place of a metal knife or scalpel. Patient safety and quality of care are paramount, and the College therefore believes that patients should be assured that individuals who perform these types of surgery are licensed physicians (defined as doctors of medicine or osteopathy) who meet appropriate professional standards."

Appendix 2. Definition of serious adverse event

We used a definition of 'Serious Adverse Event' based on guidance from Chou (Chou 2010), the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1994), the International Society of Blood Transfusion (ISBT) (ISBT 2011), and the United States of America Government (U.S. Government 2016).

Any undesirable medical occurrence in an individual administered a pharmaceutical, medical, or biological product, or undergoing an intervention, that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event that may not fulfil the criteria above, but may jeopardise the individual and may require medical or surgical intervention to prevent the criteria above.

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor: [Plasma] this term only
#2 MeSH descriptor: [Blood Component Transfusion] this term only
#3 plasma
#4 #2 and #3
#5 plasma:ti,ab near/5 (transfus*:ti,ab or prophyla*:ti,ab or fresh*:ti,ab or frozen:ti,ab or freez*:ti,ab or prefrozen:ti,ab or prefreez*:ti,ab or thaw*:ti,ab or prethaw*:ti,ab or liquid:ti,ab or infus*:ti,ab or treatment*:ti,ab or therap*:ti,ab or administ*:ti,ab or donor*:ti,ab or donat*:ti,ab or pasteurized:ti,ab or pasteurised:ti,ab or methylene:ti,ab or solvent:ti,ab or detergent:ti,ab or cryoprecipitate:ti,ab or supernatant:ti,ab or cryosupernatant:ti,ab)
#6 (homolog* or allogen* or allo-gen*or universal or clinical or human or pooled or versus) next plasma
#7 (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas* or octaplas* or lyoplas* or frischplasma or "plasma versus")
#8 (plasma near/3 (pathogen* or unit* or ratio*))
9 #1 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Specialties, Surgical] explode all trees
#11 MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#12 surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant*
#13 #10 or #11 or #12
#14 #9 and #13

Appendix 4. MEDLINE search strategy

1. *Plasma/
2. Plasma/ and transfus*.mp.
3. Blood Component Transfusion/ and plasma.mp.

4. (plasma adj5 (transfus* or prophyla* or fresh* or frozen or freez* or prefrozen or prefreez* or thaw* or prethaw* or liquid or infus* or treatment* or therap* or administ* or donor* or donat* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant)).tw,kf.
5. ((homolog* or allogen* or allo-gen*or universal or clinical or human or pooled or versus) adj plasma).tw,kf.
6. (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas* or octaplas* or lyoplas* or frischplasma or plasma versus).tw,kf.
7. (plasma adj3 (pathogen* or unit* or ratio*)).tw,kf.
8. or/1-7
9. exp Specialties, Surgical/
10. exp Surgical Procedures, Operative/
11. (surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant*).mp.
12. 9 or 10 or 11
13. Meta-Analysis.pt.
14. ((meta analy* or metaanaly*) and (trials or studies)).ab.
15. (meta analy* or metaanaly* or evidence-based).ti.
16. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.
17. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg*).ab.
18. Cochrane Database of systematic reviews.jn.
19. (additional adj (papers or articles or sources)).ab.
20. ((electronic* or online) adj (sources or resources or databases)).ab.
21. (relevant adj (journals or articles)).ab.
22. (reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
23. or/13-22
24. Review.pt.
25. RANDOMIZED CONTROLLED TRIALS AS TOPIC/
26. selection criteria.ab. or critical appraisal.ti.
27. (data adj (extraction or analys*)).ab.
28. RANDOMIZED CONTROLLED TRIALS/
29. or/25-28
30. 24 and 29
31. 23 or 30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomi*.tw.
35. (placebo or randomly or groups).ab.
37. trial.tw.
38. or/32-37
39. 31 or 38
40. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
41. Editorial.pt.
42. 40 or 41
43. 39 not 42
44. 8 and 12 and 43

Appendix 5. Embase search strategy

1. Plasma Transfusion/
2. Fresh Frozen Plasma/
3. Octaplas/
4. (plasma adj5 (transfus* or prophyla* or fresh* or frozen or freez* or prefrozen or prefreez* or thaw* or prethaw* or liquid or infus* or treatment* or therap* or administ* or donor* or donat* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant)).tw.
5. ((homolog* or allogen* or allo-gen*or universal or human or pooled or clinical or versus) adj plasma).tw.
6. (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas* or octaplas* or lyoplas* or frischplasma or plasma versus).tw.
7. (plasma adj3 (pathogen* or unit* or ratio*)).tw.
8. or/1-7
9. exp Surgery/
10. (surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant*).mp.
11. or/9-10
12. 8 and 11

13. Meta Analysis/
14. (meta analy* or metaanaly* or evidence-based).ti.
15. ((meta analy* or metaanaly*) and (trials or studies)).ab.
16. Systematic Review/
17. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.
18. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
19. ((electronic* or online) adj (sources or resources or databases)).ab.
20. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
21. Review.pt. and (data extraction or selection criteria).ab.
22. or/13-21
23. Editorial.pt.
24. 22 not 23
25. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
26. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.
27. or/24-26
28. 12 and 27
29. limit 28 to embase

Appendix 6. CINAHL search strategy

S1 (MM "Plasma")
S2 (MH "Plasma")
S3 TX transfus*
S4 S2 AND S3
S5 (MH "Blood Component Transfusion")
S6 TX plasma
S7 S5 AND S6
S8 TI (plasma N5 (transfus* or prophyla* or fresh* or frozen or freez* or prefrozen or prefreez* or thaw* or prethaw* or liquid or infus* or treatment* or therap* or administ* or donor* or donat* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant)) OR AB (plasma N5 (transfus* or prophyla* or fresh* or frozen or freez* or prefrozen or prefreez* or thaw* or prethaw* or infus* or treatment* or therap* or administ* or donor* or donat* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant))
S9 TI ((homolog* or allogen* or allo-gen*or universal or clinical or human or pooled or versus or unit*) N1 plasma) OR AB ((homolog* or allogen* or allo-gen*or universal or clinical or human or pooled or versus) N1 plasma)
S10 TX (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas* or octaplas* or lyoplas* or frischplasma or "plasma versus")
S11 TI (plasma N3 (pathogen or unit* or ratio*)) OR AB (plasma N3 (pathogen inactivated or pathogen reduced or unit* or ratio*))
S12 S1 OR S4 OR S7 OR S8 OR S9 OR S10 OR S11
S13 (MH "Specialties, Surgical+")
S14 (MH "Surgery, Operative+")
S15 TX (surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant*)
S16 S13 OR S14 OR S15
S17 S12 AND S16
S18 (MH Clinical Trials+)
S19 PT Clinical Trial
S20 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
S21 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))
S22 TI randomi* OR AB randomi*
S23 MH RANDOM ASSIGNMENT
S24 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
S25 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*)))
S26 MH PLACEBOS
S27 MH META ANALYSIS
S28 MH SYSTEMATIC REVIEW
S29 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")
S30 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")

S31 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)
S32 TI placebo* OR AB placebo*
S33 MH QUANTITATIVE STUDIES
S34 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33
S35 S17 AND S34

Appendix 7. PubMed search strategy

#1 (plasma[TIAB] AND (transfus*[TIAB] OR prophyla*[TIAB]))
#2 "plasma therapy"[TIAB] OR "plasma treatment"[TIAB] OR "plasma administration"[TIAB] OR "fresh plasma"[TIAB] OR "frozen plasma"[TIAB] OR "prefrozen plasma"[TIAB] OR "thawed plasma"[TIAB] OR "prethawed plasma"[TIAB] OR "liquid plasma"[TIAB] OR "infused plasma"[TIAB] OR "plasma infused"[TIAB] OR "donated plasma"[TIAB] OR "donor plasma"[TIAB] OR "pasteurised plasma"[TIAB] OR "pasteurized plasma"[TIAB] OR "freeze-dried plasma"[TIAB] OR "methylene blue plasma"[TIAB] OR "solvent-detergent plasma"[TIAB] OR "supernatant plasma"[TIAB] OR "cryosupernatant plasma"[TIAB] OR "homologous plasma"[TIAB] OR "allogeneic plasma"[TIAB] OR "allogenic plasma"[TIAB] OR "allo-genic plasma"[TIAB] OR "universal plasma"[TIAB] OR "clinical plasma"[TIAB] OR "human plasma"[TIAB] OR "pooled plasma"[TIAB] OR "versus plasma"[TIAB] OR FFP[TIAB] OR SDFFP[TIAB] OR F24[TIAB] OR FP24[TIAB] OR PF24[TIAB] OR MBFFP[TIAB] OR MB-FFP[TIAB] OR SD-FFP[TIAB] OR uniplas*[TIAB] OR octaplas*[TIAB] OR lyoplas*[TIAB] OR frischplasma[TIAB] OR "plasma versus"[TIAB] OR "pathogen-inactivated plasma"[TIAB] OR "pathogen-reduced plasma"[TIAB] OR "plasma units"[TIAB] OR "units of plasma"[TIAB] OR "plasma ratio"[TIAB]
#3 #1 OR #2
#4 surgery[TIAB] OR surgical*[TIAB] OR presurg*[TIAB] OR postsurg*[TIAB] OR operate*[TIAB] OR operation[TIAB] OR operations[TIAB] OR operating[TIAB] OR preoperat*[TIAB] OR perioperat*[TIAB] OR postoperat*[TIAB] OR transplant[TIAB] OR transplants[TIAB] OR transplanted[TIAB] OR transplanting[TIAB] OR transplantation*[TIAB]
#5 #3 AND #4
#6 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial OR systematic[sb]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#7 #5 AND #6

Appendix 8. Transfusion Evidence Library search strategy

Subject Area: Plasma/FFP

Appendix 9. LILACS search strategy

tw:((plasma OR FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR octaplas OR uniplas OR lyoplas) AND (surgery OR surgical OR surgically OR presurgery OR presurgical OR postsurgery OR operated OR operation OR operations OR operating OR preoperation OR preoperating OR perioperation OR perioperated OR postoperated OR postoperating OR transplant OR transplants OR transplanted OR transplanting OR transplantation OR transplantations)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials" OR "systematic_reviews"))

Appendix 10. Web of Science: CPCI-S search strategy

#1 TS=(plasma NEAR/5 (transfus* OR prophyla* OR fresh* OR frozen OR freez* OR prefrozen OR prefreez* OR thaw* OR prethaw* OR liquid OR infus* OR treatment* OR therap* OR administ* OR donor* OR donat* OR pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR pathogen*))
#2 TS=((homolog* OR allogen* OR allo-gen* OR universal OR clinical OR human OR pooled OR versus OR unit* OR ratio*) NEAR/1 plasma)
#3 TS=(FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR uniplas* OR octaplas* OR lyoplas* OR frischplasma OR plasma versus)
#4 #1 OR #2 OR #3
#5 TS=(surg* OR presurg* OR postsurg* OR operat* OR preoperat* OR perioperat* OR postoperat* OR transplant*)
#6 #4 AND #5
#7 TS=(systematic* OR random* OR blind* OR trial* OR controlled OR control group* OR groups)
#8 #6 AND #7

Appendix 11. ClinicalTrials.gov search strategy

Search Terms: randomized OR randomised OR randomly
Interventions: Biological: Plasma OR FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR uniplas OR octaplas OR lyoplas OR plasma transfusion OR prophylactic plasma OR fresh plasma OR frozen plasma OR liquid plasma
OR
Search Terms: randomized OR randomised OR randomly
Interventions: universal plasma OR human plasma OR units plasma OR plasma units OR pathogen-reduced plasma

Appendix 12. WHO ICTRP search strategy

Recruitment: ALL
Intervention: FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR plasma transfusion OR prophylactic plasma OR fresh plasma OR frozen plasma OR uniplas OR octaplas OR lyoplas OR universal plasma OR human plasma OR plasma units OR thawed plasma OR liquid plasma OR pathogen-reduced plasma OR pathogen-inactivated plasma
OR
randomized AND plasma transfusion OR randomized AND FFP OR randomized AND fresh plasma OR randomized AND frozen plasma OR randomized AND freeze dried plasma OR randomized AND prophylactic AND plasma OR randomized AND prophylaxis AND plasma OR randomized AND octaplas OR randomized AND uniplas OR randomized AND lyoplas OR randomized AND clinical plasma OR randomized AND universal plasma OR randomized AND human plasma OR randomized AND plasma units OR randomized AND units plasma OR randomized AND biological plasma OR randomized AND thawed plasma OR randomized AND liquid plasma OR randomized AND pathogen-reduced plasma OR randomized AND pathogen-inactivated plasma
OR
randomised AND plasma transfusion OR randomised AND FFP OR randomised AND fresh plasma OR randomised AND frozen plasma OR randomised AND freeze dried plasma OR randomised AND prophylactic AND plasma OR randomised AND prophylaxis AND plasma OR randomised AND octaplas OR randomised AND uniplas OR randomised AND lyoplas OR randomised AND clinical plasma OR randomised AND universal plasma OR randomised AND human plasma OR randomised AND plasma units OR randomised AND units plasma OR randomised AND biological plasma OR randomised AND thawed plasma OR randomised AND liquid plasma OR randomised AND pathogen-reduced plasma OR randomised AND pathogen-inactivated plasma
OR
randomly AND plasma transfusion OR randomly AND FFP OR randomly AND fresh plasma OR randomly AND frozen plasma OR randomly AND freeze dried plasma OR randomly AND prophylactic AND plasma OR randomly AND prophylaxis AND plasma OR randomly AND octaplas OR randomly AND uniplas OR randomly AND lyoplas OR randomly AND clinical plasma OR randomly AND universal plasma OR randomly AND human plasma OR randomly AND plasma units OR randomly AND units plasma OR randomly AND biological plasma OR randomly AND thawed plasma OR randomly AND liquid plasma OR randomly AND pathogen-reduced plasma OR randomised AND pathogen-inactivated plasma

CONTRIBUTIONS OF AUTHORS

- Jonathan Huber: content expert. Undertook screening and selection of trials, data extraction, assessment of risk of bias, analysis of results, and development, drafting, and preparation of the protocol and the final report.
- Simon Stanworth: content expert. Supported development and preparation of the protocol and the final report.
- Carolyn Doree: contributed to protocol development and served as search specialist.
- Patricia Fortin: extracted data.
- Marialena Trivella: contributed to protocol development, served as statistical expert, and supported preparation of the final report.
- Susan Brunskill: contributed to protocol development and served as methodologist.
- Sally Hopewell: contributed to protocol development and served as methodological expert.
- Kirstin Wilkinson: content expert. Supported development of the protocol and the final report. Undertook screening and selection of trials and data extraction.
- Lise Estcourt: content expert. Undertook screening and selection of trials, data extraction, assessment of risk of bias, and analysis of results, and developed and prepared the protocol and the final report.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given that we have used a broad definition of the term 'surgery' (based on the definition created by the American College of Surgeons in 2007 (ACS 2007), together with the classification of procedures from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM 2011)), we amended the review title to include non-cardiac surgery or invasive procedures, to reflect more accurately the scope of this review (Huber 2017).

We excluded studies that reported only on central line insertion because these studies are included in Hall 2016.

We amended the typographical time scale error for measurements of surgical adverse event outcomes as described in the protocol section 'Summary of findings table'. We measured this outcome within 30 days, consistent with our protocol description of this outcome in the methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

*Surgical Procedures, Operative; Anticoagulants [adverse effects] [*therapeutic use]; Blood Component Transfusion [*methods]; Hemorrhage [*prevention & control]; Hemostatics [therapeutic use]; Plasma; Preoperative Care; Randomized Controlled Trials as Topic; Thrombelastography

MeSH check words

Humans