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Plasma transfusions prior to insertion of central lines for patients with abnormal coagulation

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effect of different prophylactic plasma transfusion regimens prior to central line insertion in patients with abnormal coagulation.

BACKGROUND

Description of the condition

Coagulopathy refers to the condition in which the blood's ability to clot is impaired (Hunt 2014). Patients requiring a central line (central venous catheter (CVC)) often become

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NOTES
This review will be a rapid review (definition of a rapid review as previously agreed with the Cochrane Haematological Malignancies Group), we will only include English language publications.

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coagulopathic as a consequence of their underlying illness, co-morbidities or the effects of treatment. Central venous catheters are catheters with tips that lie within the proximal third of the superior vena cava (large vein which returns blood to the heart), the right atrium or the inferior vena cava (Bishop 2007; Smith 2013). They can be inserted through a superficial vein (e.g. the basilic or cephalic veins in the arm) or a central vein (most commonly the jugular, subclavian or femoral veins) (Bishop 2007; Smith 2013). There are four main types: 1) a non-tunnelled line into a central vein (short-term use); 2) a line inserted into a superficial vein (medium-term use); 3) a tunnelled line (long-term use); 4) a totally implanted device (long-term use) (Bishop 2007; Smith 2013). They have a number of uses, these include: administration of chemotherapy and other irritant drugs with fewer complications; intensive monitoring and treatment of critically ill patients; administration of total parenteral nutrition; and long-term intermittent intravenous access for patients requiring repeated treatments (Smith 2013). Patients requiring CVCs can have a variety of conditions and include patients with liver failure, patients who are critically ill and patients requiring chemotherapy (Bishop 2007; Smith 2013).

A large national study of fresh frozen plasma (FFP) use in critical illness reported that 30% of patients admitted to the intensive care unit (ICU) developed an abnormality of coagulation (Walsh 2010). The aetiology of coagulopathy in critical illness is complex and multi-factorial; sepsis, haemodilution, haemorrhage, disseminated intra-vascular coagulation, hepatic and renal disease and anti-coagulant medication are all implicated (Hunt 2014). The causes of coagulopathy in non-critically ill patients undergoing CVC insertion are similarly broad. FFP is widely used in the management of coagulopathic patients with abnormal laboratory tests of blood coagulation (prolonged prothrombin time (PT) or elevated international normalised ratio (INR)), and may be administered as part of the resuscitation of actively bleeding patients, or as prophylaxis to prevent bleeding in coagulopathic patients undergoing invasive procedures such as CVC insertion.

Description of the intervention

Current practice in many centres is to correct disordered coagulation with FFP transfusion prior to internal jugular, femoral or subclavian venous catheterisation, in order to mitigate the risk of serious peri- or post-procedural bleeding. Plasma is the non-cellular component of blood and is prepared either from the centrifugation of whole blood or by plasmapheresis (Benjamin 2012). FFP refers to plasma that is frozen within eight hours to −30°C, whereas frozen plasma (F24) is that which is frozen within 24 hours. Both contain concentrations of clotting factors equivalent to those found in *in vivo* blood, although the levels of factor V and VIII fall rapidly on thawing (Stanworth 2007). Current recommendations regarding the correction of coagulopathy prior to CVC insertion reflect expert opinion rather than high-quality evidence from randomised controlled trials. An INR greater than or equal to 1.5 is frequently advocated as the threshold above which patients should undergo correction of coagulopathy prior to CVC insertion (Bishop 2007;Hunt 2014). Whilst the use of standard laboratory tests of coagulation to assess bleeding has been criticised, an INR over 1.5 demarcates the level above which the activity of some coagulation factors falls to less than 50% (Juffermans 2014). An alternative approach to transfusing based on an INR threshold (which only detects low coagulation factor levels) is to use a test such as rotational

thromboelastometry (ROTEM) or thromboelastography (TEG) that assesses how well a blood clot forms in whole blood (haemostasis). 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.

Recent studies report that 15% to 26% of non-bleeding critically ill patients receive prophylactic FFP transfusions prior to an invasive procedure such as CVC insertion (Dara 2005; Stanworth 2010; Stanworth 2011). However, there remains substantial heterogeneity in clinicians' views about the effectiveness of this intervention, with doubts over its effectiveness and the balance of the risk-benefit ratio (Watson 2011).

How the intervention might work

Plasma transfusion is administered to coagulopathic patients in order to correct multiple clotting factor deficiencies and therefore reduce the incidence of bleeding. However, although a dose of 10 to 15 ml/kg is required to significantly improve the INR (O'Shaughnessy 2004), patients are commonly under-dosed and therefore exposed to the risks associated with FFP transfusion but not the proposed benefits (Hall 2012). It remains unclear whether FFP transfusion in coagulopathic non-bleeding patients, despite improving standard laboratory tests of coagulation, reduces the incidence of clinically important bleeding or improves other meaningful patient-oriented outcomes such as mortality. Clinical studies also indicate that the INR is often minimally reduced following FFP administration, especially when only modestly increased pretransfusion (Stanworth 2011).

Risks associated with the intervention

The risks associated with FFP transfusion include transfusion-associated lung injury (Khan 2007; Rana 2006), transfusion-associated circulatory overload (Narick 2011), multi-organ failure (Watson 2009), and sepsis (Sarani 2008). The requirement to administer FFP to correct coagulopathy prior to central line insertion may additionally delay the start of treatments such as vasoactive medication, which may be time-critical in an emergency situation. Delays in initiating treatment may lead to poorer patient outcomes (increased morbidity and mortality).

Why it is important to do this review

The evidence to support the use of prophylactic FFP transfusion in coagulopathic patients requiring CVC insertion is weak (Hunt 2014; Stanworth 2007; Tinmouth 2011). There is no high-quality evidence, outside the setting of major trauma and haemorrhagic shock, that FFP administration improves mortality (Murad 2010). Standard laboratory tests of coagulation poorly reflect *in vivo* haemostasis (Holland 2006), and abnormalities in INR and PT may not increase the risk of bleeding during CVC insertion (Segal 2005). Several case series have demonstrated the safety of performing invasive procedures without clinically significant bleeding in patients with an elevated INR who did not receive FFP cover (Doerfler 1996; Fisher 1999; Foster 1992; Haas 2010; Mumtaz 2000; Weigand 2009). The use of an INR threshold above which FFP transfusion is required prior to CVC insertion has therefore been called into question. It is uncertain whether plasma transfusions are effective at preventing bleeding in patients with deranged coagulation undergoing an invasive procedure. If

effective, the INR threshold above which plasma transfusions are clinically effective is also uncertain. Wide variation in the use of FFP prior to central venous catheterisation exists, indicating significant clinician uncertainty and potentially exposing patients to varying risk (Watson 2011).

OBJECTIVES

To assess the effect of different prophylactic plasma transfusion regimens prior to central line insertion in patients with abnormal coagulation.

METHODS

Criteria for considering studies for this review

Types of studies—We will include only randomised controlled trials (RCTs), irrespective of publication status.

Types of participants—We will include patients of any age with abnormal coagulation (as defined by the studies) requiring insertion of a central venous catheter (tunnelled or untunnelled), or porta-cath. We will exclude patients who are experiencing clinically significant bleeding at the time of the catheter insertion because such patients are routinely resuscitated with blood products including plasma.

Types of interventions—We will include RCTs comparing two types of plasma transfusion regimes:

1. No plasma transfusion prior to central line insertion versus:
   - **i)** plasma transfusion prior to central line insertion when the INR is 1.5 to 3 times control; OR
   - **ii)** plasma transfusion when the INR is greater than 3 times control;
   - **iii)** plasma transfusion when rotational thromboelastography is above a certain threshold (as defined by the study).
2. Plasma transfusion prior to central line insertion when the INR is greater than 1.5 times control versus:
   - **i)** plasma transfusion prior to central line insertion when the INR is 2 to 3 times control; OR
   - **ii)** plasma transfusion when the INR is greater than 3 times control;
   - **iii)** plasma transfusion when rotational thromboelastography is above a certain threshold (as defined by the study).

We will report each analysis separately, as subgroups within the two main comparisons.

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Types of outcome measures

Primary outcomes

- Major procedure-related bleeding within 24 hours of the procedure.

Defining procedure-related bleeds can be challenging as coagulopathic patients may bleed spontaneously in the absence of an intervention. We have sought to capture this group as accurately as possible by excluding patients who are already actively bleeding at the time of CVC insertion, and by defining 'procedure-related bleeding' as that causing a significant fall in haemoglobin (Hb), e.g. 20 g/l or greater in the absence of another cause; a fall in systolic blood pressure (SBP) of at least 20 mmHg or an increase in heart rate (HR) of at least 20 beats per minute (BPM) or greater; haemothorax (blood in the space between the outside of the lungs and the inside of the chest wall); requiring an intervention such as a transfusion to treat bleeding; or major bleeding (not further defined) as reported by individual studies.

- All-cause mortality up to 30 days after the procedure.

Secondary outcomes

- Minor procedure-related bleeding within 24 hours of the procedure (defined as prolonged bleeding at the insertion site, which only requires treatment with a pressure bandage, or haematoma at the insertion site), or minor bleeding (not further defined) as reported by individual studies.
- Serious adverse events:
- - Transfusion-related complications within 24 hours of the procedure (including transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions).
  - Line-related complications within seven days of the procedure (infection, thrombosis, other).
- Total number of days in hospital.
- Proportion of patients receiving plasma transfusions and red cell transfusions within 24 hours of the procedure.
- Change in INR up to 24 hours following the procedure.
- Quality of life, as defined by the individual studies.

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) will formulate the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches—We will limit our searches to five main electronic databases and two ongoing trial databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, current issue) (Appendix 1);
- PubMed (e-publications only) (Appendix 2);
- MEDLINE (1946 to present) (Appendix 3);
- EMBASE (1974 to present) (Appendix 4);
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to present) (Appendix 5);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Appendix 6);
- ClinicalTrials.gov (Appendix 7).

We will combine searches in MEDLINE with the Cochrane RCT highly sensitive search filter, as detailed in Chapter six of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We will combine searches in EMBASE with the relevant SIGN RCT studies filter (www.sign.ac.uk/methodology/filters.html). We will exclude studies published in languages other than English. We will not limit searches by year of publication or publication type.

Searching other resources—We will handsearch the reference lists of included studies in order to identify further relevant studies, and we will make contact with lead authors of the included studies to identify any unpublished material, missing data or information regarding ongoing studies.

Data collection and analysis

Selection of studies—We will select studies for inclusion with reference to Chapter seven of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two authors (DH, LE) will independently screen all the remaining references for relevance against the full eligibility criteria using DistillerSR. We will retrieve full-text articles for all references for which a decision on eligibility cannot be made from the title and abstract alone. We will request additional information from study authors as necessary to assess the eligibility for inclusion of individual studies. The two authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, we will refer the decision on eligibility to a third author (TW). We will report the results of study selection using a PRISMA flow diagram (Moher 2009).

Data extraction and management—As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (DH, LE) will independently extract data onto standardised forms and perform a cross-check using DistillerSR software (Higgins 2011a). We will pilot the data extraction form on two included RCTs. The review authors will come to a consensus; if an agreement cannot be reached, a third author (TW)

will be consulted. The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. We will extract the following information for each study:

1. Source: study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details.
2. General study information: publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed.
3. Study details and methods: location; country; setting; number of centres; total study duration; recruitment dates; length of follow-up; power calculation; primary analysis (and definition); stopping rules; method of sequence generation; allocation concealment; blinding (of clinicians, participants and outcome assessors); and any concerns regarding bias.
4. Characteristics of interventions: number of study arms; description of experimental arm; description of control arm; type of plasma product (e.g. fresh frozen plasma, frozen plasma (including solvent detergent and methylene blue treated plasma); type of thromboplastin used to measure INR.
5. Characteristics of participants: age; gender; primary diagnosis; type of catheter inserted; platelet count.
6. Participant flow: total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for review outcomes); number of allocated patients who received planned treatment; number of drop-outs with reasons (percentage in each arm); protocol violations; missing data.
7. Outcomes: major procedure-related bleeding within 24 hours of the procedure; minor procedure-related bleeding within 24 hours of the procedure; transfusion-related complications within 24 hours of the procedure; line-related complications within seven days of the procedure; total number of days in hospital; proportion of patients receiving plasma transfusions within 24 hours; change in INR up to 24 hours post-procedure; all-cause mortality up to 30 days from the procedure; quality of life.

Assessment of risk of bias in included studies—We will assess all RCTs using the Cochrane ‘Risk of bias’ tool as described in Chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (DH, LE) will work independently to assess each element of potential bias listed below as ‘high’, ‘low’ or ‘unclear’ risk of bias. We will report a brief description of the judgement statements upon which the authors have assessed potential bias in the ‘Characteristics of included studies’ table. We will reach a consensus on the degree of risk of bias through comparison of the review authors statements and, where necessary, through consultation with a third author

(TW). We will use The Cochrane Collaboration's tool for assessing risk of bias, including the following domains:

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel.
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting.
- Other bias.

Measures of treatment effect—For continuous outcomes we will record the mean, standard deviation and total number of participants in both the treatment and control groups. For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CI). For continuous outcomes measured with different scales, we will present the standardised mean difference (SMD). We will extract and report hazard ratios (HR), if available for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose built method based on the Parmar and Tierney tool (Parmar 1998; Tierney 2007).

For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups. We will report the pooled risk ratios (RR) with a 95% CI. Where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI (Deeks 2011).

If the data allow, we will undertake quantitative assessments using Review Manager 5.

Where appropriate, we will report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with CIs.

If the data available cannot be reported in any of the formats described above we will produce a narrative report and, if appropriate, we will present the data in tables.

Unit of analysis issues—We do not expect to encounter unit of analysis issues as cluster-randomised trials, cross-over studies and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If patients are randomised more than once we will contact the authors of the study to provide us with data on the CVCs associated with the initial randomisation.

Dealing with missing data—Where data are identified as missing or unclear in the published literature, we will contact study authors directly. We will record the number of patients lost to follow-up for each study. Where possible, we will analyse data using an

intention-to-treat (ITT) analysis but if insufficient data are available, we will use per protocol (PP) analyses (Higgins 2011c).

Assessment of heterogeneity—If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at P value < 0.1. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if the I^2 value is over 50% or considerable if the I^2 is over 80%. We will explore potential sources of statistical heterogeneity in each included study and perform sensitivity analyses as appropriate. We anticipate that at least moderate clinical and methodological heterogeneity will be identified within the studies selected for inclusion. We will thus use the random-effects model. If statistical heterogeneity is considerable, we will not pool the studies in a meta-analysis and we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases—Where at least 10 studies are identified for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Lau 2006; Sterne 2011).

Data synthesis—We will perform analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into the Cochrane statistical package Review Manager 5. One review author (DH) will enter the data into the software. A second author (LE) will then check the data for accuracy.

Where meta-analysis is feasible, we will use the random-effects model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and we will use the inverse variance method (and standardised mean differences as necessary) for continuous outcomes. We will use the generic inverse variance method for time-to-event outcomes.

If heterogeneity is found to be above 80%, we will not perform a meta-analysis. We will comment narratively on results and we will comment on any trends in the data within the results section of the review.

Summary of findings—We will use GRADE to build separate ‘Summary of findings’ tables for both types of FFP transfusion regimen specified in the Types of interventions, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). The outcomes we will include, comparing plasma transfusion strategies prior to central line, are listed below:

1. Major procedure-related bleeding within 24 hours of the procedure.
2. All-cause mortality up to 30 days after the procedure.

3. Respiratory deterioration attributable to transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI) or transfusion-associated dyspnoea (TAD) within 24 hours of the procedure.
4. Minor procedure-related bleeding within 24 hours of the procedure.
5. Proportion of patients receiving plasma transfusions within 24 hours of the procedure.
6. Line-related complications within seven days of the procedure (infection, thrombosis, other).
7. Quality of life.

Subgroup analysis and investigation of heterogeneity—If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity:

- Type of central line inserted (venous tunnelled, venous untunnelled, porta-cath, whether an emergency or elective procedure).
- Type of patient (intensive care, liver disease, other).
- Age of patient (neonate, child (1 to 15 years), adult (16 years or older)).
- Whether patients had associated platelet count abnormalities.

Investigation of heterogeneity between studies will also include, if appropriate:

- Type of plasma component (fresh frozen plasma, frozen plasma (including solvent detergent and methylene blue treated plasma).
- Type of thromboplastin used to measure INR.

Sensitivity analysis—If sufficient data are available we will assess the robustness of our findings by performing the following sensitivity analyses where appropriate:

- Including only those studies with a ‘low’ risk of bias for detection and selection bias.
- Including only those studies with less than a 20% drop-out rate.

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Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Catheterization, Central Venous] this term only

#2 MeSH descriptor: [Catheters, Indwelling] this term only

#3 MeSH descriptor: [Central Venous Catheters] this term only

#4 MeSH descriptor: [Vascular Access Devices] this term only

#5 hickman* or “port catheter*” or port-a-cath* or “invasive line*” or portacath* or TIVAD*

#6 ((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or “in-dwelling” or implant* or placement* or subclavian or femoral or jugular) near/5 (catheter* or line* or cannul* or port*))

#7 ((vascular or venous) near/2 (access* or reservoir*))

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 MeSH descriptor: [Plasma] explode all trees

#10 MeSH descriptor: [Blood Component Transfusion] this term only

#11 plasma

#12 #10 and #11

#13 (plasma near/5 (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 autologous or allogen* or allo-gen* or homolog*))

#14 (FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or “clinical plasma”)

#15 (plasma near/3 (“pathogen inactivated” or “pathogen reduced” or universal or donor*))

#16 ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) near/5 plasma)

#17 #9 or #12 or #13 or #14 or #15 or #16

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#18 MeSH descriptor: [Blood Coagulation Disorders] explode all trees

#19 ((coagulation* or clotting or bleeding) near/5 (disorder* or abnormal* or anomaly or disturb* or defect* or disseminated intravascular))

#20 ((abnormal* or elevated or prolonged) near/3 (international normalised ratio or international normalized ratio or INR))

#21 coagulopath*

#22 #18 or #19 or #20 or #21

#23 #8 and #22

#24 (#8 or #22) and #17

#25 #23 or #24

Appendix 2. PubMed (for epublications) search strategy

#1 hickman* OR port catheter* OR port-a-cath* OR invasive line“ OR portacath* OR TIVAD*

#2 ((central* OR venous* OR vascular* OR intravenous* OR tunnel* OR indwelling OR ”in-dwelling“ OR implant* OR placement* OR subclavian OR femoral OR jugular) AND (catheter* OR line* OR cannul* OR port*))

#3 ((vascular OR venous) AND (access* OR reservoir*))

#4 #1 OR #2 OR #3

#5 (plasma AND (transfus* OR prophyla* OR fresh* OR frozen OR freez* OR prefrozen OR prefreez* OR thaw* OR prethaw* OR infus* OR treatment* OR therapy OR administ* OR donor* OR donat* OR autologous OR allogen* OR allo-gen* OR homolog*))

#6 (FFP OR SDFFP OR MBFFP OR uniplas* OR octaplas* OR FP24 OR frischplasma OR clinical plasma)

#7 (plasma AND (pathogen inactivated OR pathogen reduced OR universal OR donor*))

#8 ((pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR thawed) AND plasma)

#9 #5 OR #6 OR #7 OR #8

#10 ((coagulation* OR clotting OR bleeding) AND (disorder* OR abnormal* OR anomaly OR disturb* OR defect* OR disseminated intravascular))

#11 ((abnormal* OR elevated OR prolonged) AND (international normalised ratio OR international normalized ratio OR INR))

#12 coagulopath*

#13 #10 OR #11 OR #12

#14 #4 AND #13

#15 (#4 OR #13) AND #9

#16 #14 OR #15

#17 (random* OR blind* OR control group OR placebo OR controlled trial OR controlled study OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#18 #16 AND #17

Appendix 3. MEDLINE (OvidSP) search strategy

1.	Catheterization, Central Venous/
2.	Catheters, Indwelling/
3.	Central Venous Catheters/
4.	Vascular Access Devices/
5.	(hickman* or port-a-cath* or port catheter* or port-a-cath* or invasive line* or portacath* or TIVAD*).tw.
6.	((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or ”in-dwelling“ or implant* or placement* or subclavian or femoral or jugular) adj5 (catheter* or line* or cannul* or port*)).tw.
7.	((vascular or venous) adj2 (access* or reservoir*)).tw.
8.	or/1-7
9.	Plasma/
10.	Blood Component Transfusion/ and plasma.tw.
11.	(plasma adj5 (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 allogen* or allo-gen*)).tw.
12.	(FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or clinical plasma).tw.
13.	(plasma adj3 (pathogen inactivated or pathogen reduced or universal or donor*)).tw.

14. ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) adj5 plasma).tw.
15. or/9-14
16. exp Blood Coagulation Disorders/
17. ((coagulation* or clotting or bleeding) adj5 (disorder* or abnormal* or anomaly or disturb* or defect* or disseminated intravascular)).tw.
18. ((abnormal* or elevated or prolonged) adj3 (international normali?ed ratio or INR)).tw.
19. coagulopath*.tw.
20. or/16-19
21. 8 and 20
22. (8 or 20) and 15
23. 21 or 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi*.tw.
27. placebo.ab.
28. clinical trials as topic.sh.
29. randomly.ab.
30. groups.ab.
31. trial.ti.
32. or/24-31
33. 23 and 32

Appendix 4. EMBASE (OvidSP) search strategy

1. exp Central Venous Catheterization/
2. exp Indwelling Catheter/
3. exp Central Venous Catheter/
4. (hickman* or port catheter* or port-a-cath* or invasive line* or portacath* or TIVAD*).tw.
5. ((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or ”in-dwelling“ or implant* or placement* or subclavian or femoral or jugular) adj5 (catheter* or line* or cannul* or port*)).tw.

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6.	((vascular or venous) adj2 (access* or reservoir*)).tw.
7.	or/1-6
8.	Fresh Frozen Plasma/
9.	Plasma Transfusion/
10.	(plasma adj5 (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 autologous or allogen or allogen* or homolog*)).tw.
11.	(FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or clinical plasma).tw.
12.	(plasma adj3 (pathogen inactivated or pathogen reduced or universal)).tw.
13.	((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) adj5 plasma).tw.
14.	or/8-13
15.	Blood Clotting Disorder/ or Bleeding Disorder/ or Bleeding Tendency/ or Disseminated Intravascular Clotting/ or Hypocoagulability/
16.	((coagulation* or clotting or bleeding) adj5 (disorder* or abnormal* or anomaly or disturb* or defect* or disseminated intravascular)).tw.
17.	((abnormal* or elevated or prolonged) adj3 (international normali?ed ratio or INR)).tw.
18.	coagulopath*.tw.
19.	or/15-18
20.	7 and 19
21.	(7 or 19) and 14
22.	20 or 21
23.	Randomized Controlled Trial/
24.	Randomization
25.	Single Blind Procedure/
26.	Double Blind Procedure/
27.	Crossover Procedure/
28.	Placebo/
29.	exp Clinical Trial/
30.	Prospective Study/

31.	(randomi* or double-blind* or single-blind* or RCT*).tw.
32.	(random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
33.	(crossover* or cross over* or cross-over* or placebo*).tw.
34.	((treble or triple) adj blind*).tw.
35.	or/23-34
36.	Case Study/
37.	case report*.tw.
38.	(note or editorial).pt.
39.	or/36-38
40.	35 not 39
41.	22 and 40
42.	limit 41 to embase

Appendix 5. Transfusion Evidence Library search strategy

Subject area: FFP

OR (Title: hickman OR catheter OR line OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Keywords: FFP OR plasma)

Appendix 6. WHO International Clinical Trials Registry Platform (ICTRP) search strategy

(Title: hickman OR catheter OR line OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Intervention: FFP OR plasma)

OR

(Condition: coagulation OR clotting OR coagulopathy OR coagulopathies OR coagulopathic OR bleeding OR hemorrhagic) AND (Intervention: FFP OR plasma)

Appendix 7. ClinicalTrials.gov search strategy

(Search Terms: hickman OR catheter OR line OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Intervention: FFP OR plasma transfusion OR fresh plasma OR frozen plasma OR uniplas OR octaplas OR universal plasma)

OR

(Search Terms: coagulation OR clotting OR coagulopathy OR coagulopathies OR coagulopathic OR bleeding OR hemorrhagic) AND (Intervention: FFP OR plasma

transfusion OR fresh plasma OR frozen plasma OR uniplas OR octaplas OR universal plasma)

Additional references

* *Indicates the major publication for the study*

Benjamin 2012 . Benjamin R, McLaughlin L. Plasma components: properties, differences, and uses. Transfusion. 2012; 52(Suppl 1):9S–19S. [PubMed: 22578375]

Bishop 2007 . Bishop L, Dougherty L, Bodenham A, Mansi J, Crowe P, Kibbler C, et al. Guidelines on the insertion and management of central venous access devices in adults. International Journal of Laboratory Hematology. 2007; 29:261–78. [PubMed: 17617077]

Dara 2005 . Dara S, Rana R, Afessa B, Moore S, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Critical Care Medicine. 2005; 33(11):2667–71. [PubMed: 16276195]

Deeks 2011 . Deeks, JJ.; Higgins, JPT.; Altman, DG.; Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Chapter 9: Analysing data and undertaking meta-analyses. Available from www.cochrane-handbook.org [updated March 2011]

DistillerSR . Distiller, SR. DistillerSR: Data Management Software. Evidence Partners; Ottawa, ON: 2015.

Doerfler 1996 . Doerfler M, Kaufman B, Goldenberg A. Central venous catheter placement in patients with disorders of hemostasis. Chest. 1996; 110(1):185–8. [PubMed: 8681626]

Fisher 1999 . Fisher N, Mutimer D. Central venous cannulation in patients with liver disease and coagulopathy - a prospective audit. Intensive Care Medicine. 1999; 25(5):481–5. [PubMed: 10401942]

Foster 1992 . Foster P, Moore L, Sankary H, Hart M, Ashmann M, Williams J. Central venous catheterization in patients with coagulopathy. Archives of Surgery. 1992; 127(3):273–5. [PubMed: 1550472]

Haas 2010 . Haas B, Chittams J, Trerotola S. Large-bore tunneled central venous catheter insertion in patients with coagulopathy. Journal of Vascular and Interventional Radiology. 2010; 21(2):212–7. [PubMed: 20123206]

Hall 2012 . Hall D, Lone N, Watson D, Stanworth S, Walsh T, Intensive Care Study of Coagulopathy (ISOC) Investigators. Factors associated with prophylactic plasma transfusion before vascular catheterization in non-bleeding critically ill adults with prolonged prothrombin time: a case-control study. British Journal of Anaesthesia. 2012; 109(6):919–27. [PubMed: 23025970]

Higgins 2011a . Higgins, JPT.; Deeks, JJ.; Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Chapter 7: Selecting studies and collecting data. Available from www.cochrane-handbook.org [updated March 2011]

Higgins 2011b . Higgins, JPT.; Altman, DG.; Sterne, JAC.; Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Chapter 8: Assessing risk of bias in included studies. Available from www.cochrane-handbook.org [updated March 2011]

Higgins 2011c . Higgins, JPT.; Deeks, JJ.; Altman, DG.; Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Chapter 16: Special topics in statistics. Available from www.cochrane-handbook.org [updated March 2011]

Holland 2006 . Holland L, Sarode R. Should plasma be transfused prophylactically before invasive procedures? Current Opinion in Hematology. 2006; 13(6):447–51. [PubMed: 17053457]

Hunt 2014 . Hunt B. Bleeding and coagulopathies in critical care. New England Journal of Medicine. 2014; 370(9):847–59. [PubMed: 24571757]

Juffermans 2014 . Hall, D.; Walsh, T. FFP transfusion in the intensive care unit. In: Juffermans, N.; Walsh, T., editors. Transfusion in the Intensive Care Unit. 1st Edition. Springer; 2014. p. 151-9.

Europe PMC Funders Author Manuscripts

Khan 2007 . Khan H, Belsher J, Yilmaz M, Afessa B, Winters J, Moore S, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest. 2007; 131(5):1308–14. [PubMed: 17400669]

Lau 2006 . Lau J, Ioannidis J, Terrin N, Schmid C, Olkin I. The case of the misleading funnel plot. BMJ. 2006; 333(7568):597–600. [PubMed: 16974018]

Lefebvre 2011 . Lefebvre, C.; Manheimer, E.; Glanville, J. Chapter 6: Searching for studies. In: Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org [updated March 2011]

Moher 2009 . Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Annals of Internal Medicine. 2009; 151(4):264–9. [PubMed: 19622511]

Mumtaz 2000 . Mumtaz H, Williams V, Hauer-Jensen M, Rowe M, Henry-Tillman RS, Heaton K, et al. Central venous catheter placement in patients with disorders of hemostasis. American Journal of Surgery. 2000; 180(6):503–5. [PubMed: 11182407]

Murad 2010 . Murad M, Stubbs J, Gandhi M, Wang A, Paul A, Erwin P, et al. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion. 2010; 50(6):1370–83. [PubMed: 20345563]

Narick 2011 . Narick C, Triulzi D, Yazer M. Transfusion-associated circulatory overload after plasma transfusion. Transfusion. 2011; 52(1):160–5. [PubMed: 21762464]

O'Shaughnessy 2004 . O'Shaughnessy D, Atterbury C, Bolton M, Murphy M, Thomas D, Yates S, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. British Journal of Haematology. 2004; 126(1):11–28. [PubMed: 15198728]

Parmar 1998 . Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine. 1998; 17(24):2815–34. [PubMed: 9921604]

Rana 2006 . Rana R, Fernández-Pérez E, Khan S, Rana S, Winters J, Lesnick T, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion. 2006; 46(9):1478–83. [PubMed: 16965572]

Review Manager 5 . The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen: 2014.

Sarani 2008 . Sarani B, Dunkman W, Dean L, Sonnad S, Rohrbach J, Gracias V. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Critical Care Medicine. 2008; 36(4):1114–8. [PubMed: 18379235]

Schünemann 2011a . Schünemann, HJ.; Oxman, AD.; Higgins, JPT.; Vist, GE.; Glasziou, P.; Guyatt, GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org [updated March 2011]

Schünemann 2011b . Schünemann, HJ.; Oxman, AD.; Vist, GE.; Higgins, JPT.; Deeks, JJ.; Glasziou, P.; et al. on behalf of the Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org [updated March 2011]

Segal 2005 . Segal J, Dzik W, Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion. 2005; 45(9):1413–25. [PubMed: 16131373]

Smith 2013 . Smith RN, Nolan JP. Central venous catheters. BMJ. 2013; 347:f6570. [DOI: 10.1136/bmj.f6570]. [PubMed: 24217269]

Stanworth 2007 . Stanworth S. The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. Hematology. 2007; 2007:179–86. [PubMed: 18024627]

Stanworth 2010 . Stanworth S, Grant-Casey J, Lowe D, Laffan M, New H, Murphy M, et al. The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children. Transfusion. 2010; 51(1):62–70. [PubMed: 20804532]

Stanworth 2011 . Stanworth S, Walsh T, Prescott R, Lee R, Watson D, Wyncoll D, et al. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. Critical Care. 2011; 15(2):R108. [PubMed: 21466676]

Sterne 2011 . Sterne, JAC.; Egger, M.; Moher, D.; Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Chapter 10: Addressing reporting biases. Available from www.cochrane-handbook.org [updated March 2011]

Tierney 2007 . Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16. [DOI: 10.1186/1745-6215-8-16]. [PubMed: 17555582]

Tinmouth 2011 . Tinmouth A, McIntyre L. The conundrum of persistent inappropriate use of frozen plasma. Critical Care. 2011; 15(3):160. [PubMed: 21635704]

Walsh 2010 . Walsh T, Stanworth S, Prescott R, Lee R, Watson D, Wyncoll D. Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units. Critical Care Medicine. 2010; 38(10):1939–46. [PubMed: 20639745]

Watson 2009 . Watson G, Sperry J, Rosengart M, Minei J, Harbrecht B, Moore E, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. Journal of Trauma. 2009; 67(2):221–8. [PubMed: 19667872]

Watson 2011 . Watson D, Stanworth S, Wyncoll D, McAuley D, Perkins G, Young D, et al. A national clinical scenario-based survey of clinicians' attitudes towards fresh frozen plasma transfusion for critically ill patients. Transfusion Medicine. 2011; 21(2):124–9. [PubMed: 21062383]

Weigand 2009 . Weigand K, Encke J, Meyer F, Hinkel U, Munder M, Stremmel W, et al. Low levels of prothrombin time (INR) and platelets do not increase the risk of significant bleeding when placing central venous catheters. Medizinische Klinik. 2009; 104(5):331–5. [PubMed: 19444412]

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