Pathogen-reduced platelets for the prevention of bleeding (Protocol)

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This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 4

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[Intervention Protocol]

Pathogen-reduced platelets for the prevention of bleeding

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Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 4, 2011.

Citation: Butler C, Doree C, Estcourt L, Stanworth S, Brunskill SJ, Hopewell S, Murphy MF. Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: CD009072. DOI: 10.1002/14651858.CD009072.

ABSTRACT

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

To determine the effectiveness and safety of pathogen-reduced platelets for the prevention of bleeding in all patients requiring platelet transfusion(s).

BACKGROUND

Description of the condition

Significant progress has been made in recent years to improve the safety of blood transfusion with regard to transfusion-transmitted infections (TTI). Consequently the risk of viral TTIs (e.g. human immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C (HCV) and human T-cell lymphotropic virus (HTLV) type I and II) is now considered to be low in the developed world (Bihl 2007). Nevertheless, there remains the threat both of newly-emerging blood-transmitted infections (e.g. from viruses, prions and protozoans) and of TTIs caused by bacterial contamination of blood products. Platelet concentrates in particular are more vulnerable to bacterial contamination owing to their higher storage temperature (22°C) in comparison to other blood components (Blajchman 2006). Between 1996 and 2009, for example, the UK's Serious Hazards of Blood Transfusion (SHOT) registry reported that 50% (33/66) of all TTIs in the UK were the result of bacterial contamination of platelet products and that 33% of these cases resulted in death (Taylor 2010). While the overall incidence of clinically significant TTIs is likely to be underreported and underestimated, US data from 2006 suggest that the mortality risk due to bacterial sepsis from platelet products is one case per 911,500 packs transfused for apheresis platelets and one case per 2,396,000 units transfused for pooled platelet concentrates (Whitaker 2007).

Description of the intervention

A number of interventions currently aim to reduce the risk of post-transfusion sepsis from contaminated platelets. These include improved donor screening, registries of previously deferred donors, single-donor apheresis platelets, improved laboratory testing including the use of nucleic acid amplification testing, optimised skin preparation, removal of the first 10-30 mL of donated blood and limited storage duration of platelet units. Some countries also carry out routine bacterial screening. These methods have reduced but not eliminated the risk of both bacterial and viral TTIs from platelet transfusion. However, viral contamination can still occur during the "window period" when the pathogen load is low enough to escape detection. The appearance of new blood-borne viruses, such as West Nile Virus (WNV) and severe acute respiratory syndrome (SARS), has highlighted the ongoing need to prevent the transmission of emerging pathogens.

It is against this background that photochemical pathogen-reduction technologies have been developed and tested over the past decade. Although solvent detergent-treatment of pooled plasma for fractionation and transfusion has effectively eliminated the transmission of HIV, HBV and HCV (Goodnough 2003; Pelletier 2006), these methods are cytocidal and therefore incompatible with cellular blood components. Pathogen-reduction technology uses photochemical processes to entirely inactivate or significantly reduce a broad spectrum of infectious agents such as viruses, fungi, bacteria and parasites within cellular blood components, including platelet concentrates. In addition, pathogen-reduction should increase the availability of platelet concentrates by retarding bacterial growth, thereby extending platelet storage life from five to seven days and reducing costs.

How the intervention might work

Pathogen reduction uses photochemical methods to prevent replication of nucleic acid-containing microbes whilst aiming to preserve cellular function and minimising toxicity. Two pathogen-reduction systems for the treatment of platelet concentrates are currently available commercially. These utilise either a synthetic psoralen compound (amotosalen) or riboflavin (vitamin B2), both in the presence of UV light.

Amotosalen

Amotosalen acts by selectively binding to nucleic acids within DNA and RNA and forming cross-links upon photoactivation by exposure to long-wave UVA light. Such cross-links render nucleic acids, and thus pathogens and white blood cells, incapable of replication (Grass 1998; Pelletier 2006). Amotosalen additionally binds to ribosomal RNA, inhibiting synthesis of proteins such as cytokines, and thus may also reduce the incidence of platelet transfusion reactions (McCullough 2007).

Amotosalen has been shown to inactivate 10^3-10^6 of enveloped viruses (HIV, WNV, HBV, HCV), both gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*) and gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*), plus protozoa commonly implicated in TTIs (Lin 2004; Lin 2005). However, inactivation of non-enveloped viral pathogens, including parvovirus B19, has been seen to be more variable (Lin 2005). In vitro data have demonstrated that following treatment with amotosalen plus UVA, platelet function is comparable following storage for five and seven days despite transient platelet activation (Lin 1998; van Rhenen 2000; Janetzko 2002; Moog 2004). Although platelet viability was found to be significantly reduced in vivo in terms of recovery, survival and corrected count increments, it has not led to a significant difference in correction of bleeding time and transfusion interval in two phase II studies (Snyder 2004; Slichter 2006). The INTERCEPT® blood system (Cerus Corporation, Concord, CA, USA) achieves pathogen- reduction through a combination of amotosalen and UVA light. It also employs a compound absorption device (CAD) to scavenge unwanted post-production residual amotosalen and photoproducts. The INTERCEPT pathogen-reduced products have demonstrated sufficient safety in terms of genotoxicity, carcinogenicity and phototoxicity in single and repeated doses in both in vivo and in vitro studies (Ciaravino 2003; Tice 2007).

Riboflavin

Mirasol® pathogen-reduction technology (CaridianBCT, Lakewood, CO, USA) reduces pathogens in platelet concentrates by utilising UV light in the presence of riboflavin (vitamin B2). This combination introduces intercalations with nucleic acids which, through photolysis upon exposure to UV light, promotes guanine oxidation and single-strand breaks of nucleic acids (Kumar 2004). Pathogens and white blood cells are thereby rendered inactive and effectively incapable of replication (Kumar 2004; Goodrich 2006). Riboflavin is a naturally occurring compound that does not require post-production removal, and the breakdown products resulting from photolysis have been demonstrated to be satisfactorily safe (Hardwick 2004; Reddy 2008). In vitro studies have shown that riboflavin inactivates viruses including HIV, WNV, parvovirus B19 and a number of bacteria commonly implicated in causing TTIs, including *S. epidermidis*, *S. aureus* and *E. coli* by 10^3-10^6 (Ruane 2004; Goodrich 2006).

Why it is important to do this review

Although current pathogen-reduction technologies have demonstrated that they are very effective at reducing viruses and bacteria in platelet concentrates, concerns remain about the haemostatic effectiveness of platelets treated in this way. While some studies have suggested that cell quality and platelet function are largely comparable between pathogen-reduced and standard platelets (Lin 2004; AuBuchon 2005; Perez-Pujol 2005; Goodrich 2006; Picker 2009), other studies have reported that current methods of pathogen-reduction appear to significantly reduce post-transfusion platelet recovery and survival in vivo when compared to standard platelets (Snyder 2004; AuBuchon 2005; Slichter 2006). Moreover, a recent randomised controlled trial found amotosalen pathogen-reduced pooled platelets to be less clinically effective at preventing bleeding than standard pooled platelets (Kerkhoffs 2010). As pathogen-reduced platelets must be found to be safe and effective at achieving haemostasis in thrombocytopenic patients prior to their introduction into routine clinical use, a systematic review of randomised controlled trials in this area is urgently required.

OBJECTIVES

To determine the effectiveness and safety of pathogen-reduced platelets for the prevention of bleeding in all patients requiring platelet transfusion(s).

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials (RCTs), irrespective of language or publication status.

Types of participants

We will include all patients requiring platelet transfusion(s).

Types of interventions

We will include the following comparisons.

- Pathogen-reduced platelets (either amotosalen-CHL/ultraviolet A or riboflavin/ultraviolet A or other pathogen-reduction technologies) versus standard platelets in patients requiring platelet transfusion(s).
- Amotosalen-CHL/ultraviolet A versus riboflavin/ultraviolet A versus other pathogen-reduced platelets in patients requiring platelet transfusion(s).

Types of outcome measures

Primary outcomes

- Number, type and severity of bleeding episodes.
- All-cause mortality. Of particular interest will be deaths from platelet transfusion-related complications such as haemorrhage, infection, thromboembolism or transfusion reactions.

Secondary outcomes

- Recognised complications of platelet transfusions - e.g. mild transfusion reactions (rigours, fever, skin rash, urticaria) and platelet refractoriness.
- Other adverse events - e.g. anaphylaxis, transfusion-related acute lung injury (TRALI), infection, arterial or venous thromboembolism.
- Laboratory assessment of response to platelet transfusion by post-transfusion platelet count increment.
- Platelet and red cell transfusion requirement and interval.

Search methods for identification of studies

Electronic searches

The SRI's Information Specialist (CD) will formulate the search strategies used in collaboration with the Cochrane Haematological Malignancies Group. We will search the following databases for RCTs:

- Cochrane Haematological Malignancies Group's Specialised Register

- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, latest issue)
- MEDLINE (1950-present)
- EMBASE (1980-present)
- CINAHL (1982-present)
- British Nursing Index Database (BNID) (1985-present)
- Centre for Reviews and Dissemination (CRD) databases (1980-present)
- LILACS (1982-present)
- KoreaMed (1997-present)
- PakMediNet (1995-present)
- IndMed (1986-present)
- UKBTS SRI Transfusion Evidence Library (1980-present)
- ISI Conference Proceedings Citation Index - Science (CPCI-S) (1990-present)
- Ongoing trial databases: ClinicalTrials.gov, ISRCTN Register, WHO International Clinical Trials Registry Platform (ICTRP), TrialReach.

We will combine searches in MEDLINE, EMBASE and CINAHL with adaptations of the Cochrane RCT search filter as detailed in Chapter Six of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Please see Appendix 1, Appendix 2 and Appendix 3 for search strategies.

Searching other resources

Handsearching of reference lists

We will check references of all identified trials, relevant review articles and current treatment guidelines for further literature. We will limit these searches to the 'first generation' reference lists.

Personal contacts

We will contact authors of relevant studies, study groups and experts worldwide who are known to be active in the field to request any unpublished material, missing data or further information on ongoing studies. We will also contact the following experts associated with manufacturers of the relevant pathogen-reduction technology: Dr Raymond Goodrich (Mirasol, CaridianBCT Biotechnologies) and Dr Laurence Corash (INTERCEPT, Cerus Corporation).

Data collection and analysis

Selection of studies

One review author, Susan Brunskill (SB), will initially screen all search results for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two other reviewers, Caroline Butler (CB) and Carolyn Doree (CD), will independently screen all the remaining hits for relevance against the full eligibility criteria. We will retrieve full text papers for all those references where we are unable to decide on eligibility based on title and abstract alone. If necessary, we will seek further information from the authors where articles contain insufficient data to make a decision about eligibility. We will resolve differences of opinion through discussion and consensus, where necessary with reference to a third author, Lise Estcourt (LE). We will detail studies which do not meet our eligibility criteria in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (CB and CD) will independently extract data onto standardised forms and cross-check. We will pilot the forms on two included RCTs. We will agree on changes to be made to the data extraction form where appropriate. Throughout the data extraction process we will resolve any disagreements by consensus. If we cannot reach agreement, we will consult a third author (LE). The review authors will not be blinded to names of authors, institutions, journals or the outcomes of the trials. We will extract the following data for each trial:

1. General information
Review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, objectives of the trial.

2. Trial details
Trial design, location, setting, sample size, power calculation, methods of treatment allocation, randomisation and blinding, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, method of statistical analysis used and funding.

3. Characteristics of participants
Age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of underlying condition(s), losses to follow-up, drop-outs (percentage in each arm) with reasons, protocol violations, current treatment, previous treatments, prognostic factors.

4. Interventions
Experimental and control interventions, type of platelet given, method of platelet production (apheresis or pooled, buffy-coat derived), type and dosage of platelet given, timing of intervention, compliance with interventions, additional interventions given (especially in relation to red cell transfusions), any other differences between interventions.
5. Outcomes
Mortality due to haemorrhage. Long-term morbidity due to haemorrhage (e.g. stroke, myocardial infarction, pulmonary embolism). Number and severity of bleeding episodes. Laboratory assessment of response to platelet transfusion by post-transfusion platelet

count increment. Platelet and red cell transfusion interval. Platelet and red cell transfusion requirement. Recognised complications of platelet transfusion (e.g. transfusion reaction, transfusion-transmitted infection, platelet refractoriness, thromboembolism, development of platelet antibodies). Any other serious adverse event (e.g. anaphylaxis, acute lung injury).

Assessment of risk of bias in included studies

Two review authors (CB and CD) will assess all included studies for possible risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). They will assess the design, conduct and analysis of the trial using a three-point scale: yes (low risk of bias), no (high risk of bias) or unclear. To assess risk of bias, the authors will include the following questions in the risk of bias table for each included study.

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented (i.e. blinded) throughout the study?
- Were incomplete outcome data adequately addressed for every outcome?
- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias?

We will use the assessment of risk of bias in each trial to explore heterogeneity among included trials and to perform subgroup analyses.

Measures of treatment effect

We will present dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CI).

For continuous outcomes, we will record the mean and standard deviations. For continuous outcomes measured using the same scale, the effect measure will be the mean difference (MD) with 95% CI. We will use the standardised mean difference (SMD) for outcomes measured using different scales.

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

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster-randomised trials are unlikely to be included in this review, but if any arise we will treat these in accordance with the advice given in Chapter 16 of the *Handbook* (Higgins 2008).

Dealing with missing data

We will contact study authors in order to obtain information that is missing or unclear in the published report. We will record the number of patients lost to follow-up for each trial. Our preferred analysis will be by intention-to-treat (ITT), but if insufficient data are presented in the included studies, we will present per protocol analyses.

Assessment of heterogeneity

The decision to combine the results of individual studies or not will depend on an assessment of heterogeneity. If we consider studies to be sufficiently homogeneous in terms of their clinical and methodological characteristics, we will carry out a meta-analysis and assess the statistical heterogeneity of treatment effects between trials by using a Chi² test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify the degree of possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity). In the presence of heterogeneity we will conduct a random effects meta-analysis and present the results of both the fixed and random-effects analysis. We will also explore potential causes of heterogeneity through pre-specified sensitivity and subgroup analyses and examine changes in the effect size. (Please see below.)

Assessment of reporting biases

In meta-analyses with more than 10 trials, 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 to be significant for this test (Lau 2006; Sterne 2008).

Data synthesis

We will perform analyses according to the recommendations of The Cochrane Collaboration. We will use aggregated data for analysis. For statistical analysis, we will enter data into the Cochrane statistical package Review Manager 5.0.2. One author (CD) will perform data entry into software. A second author (CB) will then check for accuracy. If meta-analysis is possible, we will use a fixed-effect model. If there is unexplained statistical heterogeneity, we will also undertake a random effects meta-analysis and report both. Where data does not allow for meta-analysis, we will report outcome data descriptively for each outcome within the Results section of the review.

We will use the GRADE profiler to create a Summary of Findings table, as suggested in Chapters 11 and 12 of the *Handbook* (Schünemann 2008), based on our primary outcome and harms outcomes.

Subgroup analysis and investigation of heterogeneity

We will perform a subgroup analysis if data are available for the following.

- Length of platelet storage.
- Patients' underlying condition(s).

Sensitivity analysis

We will assess the robustness of our findings by the following sensitivity analyses (where appropriate).

- Including only those trials at low risk of bias.
- Including only those trials in which 25% participants or less were lost to follow-up.

ACKNOWLEDGEMENTS

None.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. Blood Platelets/
2. Platelet Transfusion/
3. Blood Component Transfusion/
4. Blood Transfusion/
5. Plateletpheresis/
6. Antigens, Human Platelet/
7. Blood Borne Pathogens/
8. (platelet* or thrombocyte* or blood product* or blood component*).ti.
9. ((platelet* adj5 (transfus* or concentrate* or product* or component*)).tw.
10. (septic transfusion* or (transfus* adj2 transmit*)).tw.
11. or/1-10
12. Blood Preservation/
13. Virus Inactivation/
14. Decontamination/
15. Disinfection/
16. Photochemistry/
17. Photosensitizing Agents/
18. Ultraviolet Rays/
19. exp Ultraviolet Therapy/
20. Psoralens/
21. Riboflavin/
22. (photochemical* or photoinactivat* or photosensiti* or intercept* or amotosalen* or s-59 or riboflavin or vitamin b2 or ultraviolet or ultra violet or UV light* or UV therap* or actinotherapy or mirasol* or eurosprite* or hovon* or sprint trial).tw.
23. (photo adj (chemical* or inactivat* or sensiti*)).tw.
24. ((pathogen* or virus* or viral* or infect*) adj3 (inactivat* or reduc*or remov*)).tw.
25. or/12-24
26. 11 and 25

Appendix 2. EMBASE (Ovid) search strategy

1. Thrombocyte/
2. Thrombocyte Transfusion/
3. Blood Transfusion/
4. Blood Component Therapy/
5. Thrombocyte Concentrate/
6. Thrombocyte Antigen/
7. exp Blood Transfusion Reaction/
8. (platelet* or thrombocyte* or blood product* or blood component*).ti.
9. (platelet* adj5 (transfus* or concentrate* or product* or component*)).tw.
10. (septic transfusion* or (transfus* adj2 transmit*)).tw.
11. or/1-10
12. Thrombocyte Preservation/
13. Virus Inactivation/
14. Infection Control/
15. Phototherapy/
16. Photochemistry/
17. PUVA/
18. exp Photosensitizing Agent/

19. exp Ultraviolet Radiation/
20. Amotosalen/
21. Pathogen Reduction/
22. Psoralen/
23. Riboflavin/
24. (photochemical* or photoinactivat* or photosensiti* or intercept* or amotosalen* or s-59 or riboflavin or vitamin b2 or ultraviolet or ultra violet or UV light* or UV therap* or actinotherapy or mirasol* or eurosprite* or hovon* or sprint trial).tw.
25. (photo adj (chemical* or inactivat* or sensiti*)).tw.
26. ((pathogen* or virus* or viral* or infect*) adj3 (inactivat* or reduc*or remov*)).tw.
27. or/12-26
28. 11 and 27

Appendix 3. CENTRAL search strategy

1. Blood Platelets single term (MeSH)
2. Platelet Transfusion single term (MeSH)
3. Blood Component Transfusion single term (MeSH)
4. Blood Transfusion single term (MeSH)
5. Plateletpheresis single term (MeSH)
6. Antigens, Human Platelet single term (MeSH)
7. Blood Borne Pathogens single term (MeSH)
8. (platelet* or thrombocyte* or blood product* or blood component*):ti
9. (platelet* NEAR/2 (transfus* or concentrate* or component* or product*))
10. "septic transfusion*" or (transfus* NEAR/2 transmit*)
11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. Blood Preservation single term (MeSH)
13. Virus Inactivation single term (MeSH)
14. Decontamination single term (MeSH)
15. Disinfection single term (MeSH)
16. Photochemistry single term (MeSH)
17. Photosensitizing Agents single term (MeSH)
18. Ultraviolet Rays single term (MeSH)
19. Ultraviolet Therapy explode all trees (MeSH)
20. Psoralens single term (MeSH)
21. Riboflavin single term (MeSH)
22. photochemical* or photoinactivat* or photosensiti* or intercept* or amotosalen* or s-59 or riboflavin or vitamin b2 or ultraviolet or ultra violet or UV light* or UV therap* or actinotherapy or mirasol* or eurosprite* or hovon* or "sprint trial"
23. (photo NEXT (chemical* or inactivat* or sensiti*)
24. (pathogen* or virus* or viral* or infect*) NEAR/3 (inactivat* or reduc*or remov*)
25. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. #11 and #25

Appendix 4. Glossary

Apheresis The removal of blood from a patient for purposes of removing certain components (such as platelets) before transfusion back to the donor.
Cytocidal Causing cell death.
Haemostatic A haemostatic (also spelled hemostatic) agent is a substance that promotes haemostasis (stops bleeding). It may also be known as an antihaemorrhagic agent.
Pathogen A biological agent that causes disease or illness to its host (especially a virus, bacterium or other microorganism).
Photochemical Of or relating to or produced by the effects of light on chemical systems.
Psoralen A compound that sensitises mammalian cells to ultraviolet radiation.

HISTORY

Protocol first published: Issue 4, 2011

CONTRIBUTIONS OF AUTHORS

Caroline Butler is a content expert for this review and will undertake the screening and selection of trials, data extraction and assessment of risk of bias, analysis of results and initial preparation of the protocol and final report.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK.

External sources

- No sources of support supplied