Transfusion Medicine Reviews 29 (2015) 127–137

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Transfusion Interventions in Critical Bleeding Requiring Massive Transfusion: A Systematic Review

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ARTICLE INFO

Available online 7 February 2015

Keywords:
Blood transfusion
Hemorrhage
Gastrointestinal hemorrhage
Injuries
Recombinant FVIIa
Prothrombin complex concentrate
Fibrinogen
Perioperative

ABSTRACT

Critical bleeding (CB) requiring massive transfusion (MT) can occur in a variety of clinical contexts and is associated with substantial mortality and morbidity. In 2011, the Australian National Blood Authority (NBA) published patient blood management guidelines for CB and MT, which found limited high-quality evidence from which only 2 recommendations could be made. The aim of this systematic review (SR) was to update these guidelines and identify evidence gaps still to be addressed. A comprehensive search was performed for randomized controlled trials (RCTs) and SRs using MeSH index and free text terms in MEDLINE, the Cochrane Library (Issue 11, 2012), EMBASE, CINHAL, PUBMED, and the Transfusion Evidence Library up to July 15, 2014. The evidence was grouped according to 4 questions based on the original guideline relating to transfusion interventions: (1) effect of dose, timing, and ratio of red blood cells (RBCs) to component therapy on patient outcomes; (2) effect of RBC transfusion on patient outcomes; (3) effect of fresh frozen plasma, platelet, cryoprecipitate, fibrinogen concentrate, and prothrombin complex concentrate on patient outcomes; and (4) effect of recombinant activated factor VII (rFVIIa) on patient outcomes. From this search, 19 studies were identified: 6 RCTs and 13 SRs. Two of the RCTs were pilot/feasibility studies, 3 were investigating rFVIIa, and 1 compared restrictive versus liberal RBC transfusion in upper gastrointestinal hemorrhage. Overall, limited new evidence was identified and substantial evidence gaps remain, particularly with regard to the effect of component therapies, including ratio of RBC to component therapies, on patient outcomes. Clinical trials to address these questions are required.

Contents

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http://dx.doi.org/10.1016/j.tmrv.2015.01.001
0887-7963/

Critical bleeding (CB) requiring massive transfusion (MT) can occur in a variety of clinical contexts and is associated with substantial mortality and morbidity. Blood component transfusion is an essential element of the management of patients with CB. As with any therapeutic intervention, the decision to transfuse should be guided by the evidence for efficacy balanced against the potential risks. However, despite the crucial role transfusion plays in the management of patients with CB, there have been few studies to inform their optimal use. In 2011, Australia's National Blood Authority (NBA) published patient blood management (PBM) guidelines for CB and MT [1]. These were developed by clinical experts from 11 colleges and societies, including the Australia and New Zealand Society of Blood Transfusion, and patient representatives. The guideline was developed using the 2007 Australian National Health and Medical Research Council (NHMRC) guideline development methodology [2] and was approved by the NHMRC. The results of the systematic review (SR) indicated a paucity of high-quality evidence and the need for further research. Only 2 recommendations could be made: institutions should develop an MT protocol (MTP) that includes the dose, timing, and ratio of blood component therapy for use in trauma patients with, or at risk of, CB requiring MT; and (2) the routine use of activated recombinant factor VII (rFVIIa) in trauma patients with CB requiring MT was not recommended because of its lack of effect of mortality and variable effect on morbidity. However, no recommendations could be made on the dose, timing, or ratio of blood components or use of individual blood components.

The aims of this SR were to identify whether any new studies (randomized controlled trials [RCT] or SRs) had been published addressing the evidence gaps identified in the PBM guidelines for patients with CB and MT, with particular reference to transfusion interventions and to identify which evidence gaps remain.

Methods

A study protocol was developed that outlined the participants, interventions, comparators, and outcomes of interest, inclusion and exclusion criteria, and search strategy as outlined below.

Search Strategy

We searched for RCTs and SRs using MeSH index and free text terms in MEDLINE, the Cochrane Library (Issue 11, 2012), EMBASE, CINHAL, PUBMED, and the Transfusion Evidence Library from the period May 2009 to November 2012. An updated search (from November 12, 2012, to July 15, 2014) was performed prior to publication and involved a review of all RCTs and SRs listed on the UKB SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com).

Selection Criteria

To be eligible for inclusion in the review, studies were required to meet all of the following criteria: (1) be an SR that had included at least 1 RCT or be an RCT; (2) include a patient population who had CB and had received, or were anticipated to receive, an MT in any clinical setting; (3) have at least 1 relevant transfusion intervention of interest (red blood cell [RBC], fresh frozen plasma (FFP], platelets, cryoprecipitate, prothrombin complex concentrate (PCC), fibrinogen concentrate, rFVIIa); and (4) measure at least one of the following outcomes—mortality, hospital length of stay (LOS), serious adverse events, transfusion-related adverse events, morbidity, and transfusion rate. Studies were excluded if the patient population was exclusively obstetric or paediatric, or if the clinical setting was planned CB during surgery, as these clinical scenarios were not included in the original PBM guideline [1]. The definition of CB used for this SR was the same as that used in the PBM guideline: a major hemorrhage that is life threatening and likely to result in the need for MT [1]. As in the original guideline, studies on hemorrhage of smaller volume in a critical area or organ were not considered in this SR. Any definition of MT was accepted.

No restrictions were placed on language and any papers not published in English were translated.

Data Extraction and Quality Assessment

All electronically derived citations and abstracts of papers identified by the review search strategy were screened for relevancy by 2 out of 3 review authors. Full text of identified studies were reviewed by 2 reviewers against the inclusion and exclusion criteria. Potentially relevant trials were then formally assessed for eligibility against the criteria outlined above by 2 review authors. A third review author resolved disagreements or discrepancies.

Data Collection

A standard data extraction form was developed separately for SRs and RCTs. Data extraction was conducted by 2 review authors, and any disagreements were resolved by consensus or with discussion with a third review author. Details collected from each RCT were as follows: author, citation of paper, secondary citations, objectives of the trial, trial location, number of sites, clinical setting, study population, study design, dates of recruitment, sample size, power calculation, whether stopping rules were applied, numbers of participants randomized and analyzed, inclusion and exclusion criteria, experimental and control interventions, primary and secondary outcomes, co-interventions, compliance with interventions, loss to follow-up, results, statistical analysis, and aspects of study quality. For SRs, data collected included author, citation of paper, study objectives, clinical setting, study population, study design, dates and strategy for the literature search, method used for data screening and extraction, inclusion and exclusion criteria, nature of intervention, comparator population, outcomes examined, and results of any meta-analyses performed.