

Transfusion vs. alternative treatment modalities in acute bleeding: a systematic review

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Background and methods: The practice of transfusion varies a great deal between countries and hospitals. Therefore, a systematic literature review was performed to evaluate the evidence underlying practice of transfusion and alternative treatment modalities in acute bleeding. After a stepwise evaluation, 79 out of 2438 abstracts were approved as the evidence base.

Results: Albumin for volume therapy is not better than artificial colloids or crystalloids and may be detrimental in trauma patients. No outcome difference has been proved between artificial colloids and crystalloids. Use of hypertonic solutions remains controversial, as do the concepts of delayed and hypotensive resuscitation. Healthy individuals tolerate acute, normovolaemic anaemia at 5 g haemoglobin/dl, but pre-operative haemoglobin < 6 g/dl gives increased mortality from surgical interventions. Keeping haemoglobin higher than 8–9 g/dl has not been associated with any positive effect on mortality or morbidity, even in patients with cardiovascular disease. The changes induced in erythrocytes by storage may be clinically insignificant. No alternative to erythrocyte transfusion was established. Evi-

dence underlying the practice of thrombocyte and plasma transfusion is scarce. Available evidence on recombinant coagulation factor VIIa is insufficient to define its future role in acute bleedings. Antifibrinolytic drugs in general seem to reduce the need for transfusion.

Conclusions: Intravenous volume replacement and transfusion policies seem largely based on local tradition and expert opinions. As a result of the difficulties in performing controlled studies in patients with acute bleeding and the large number of patients needed to prove effects, other scientific evidence should be sought to better define best practice in this important field.

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TRANSFUSION of blood components and plasma products is a prerequisite for modern surgery, anaesthesia and intensive care. However, the use of transfusion products varies considerably even between countries with similar disease patterns and levels of health service (1,2). Major differences in transfusion policies have also been found between comparable hospitals and for similar therapeutic procedures (3–6). On the other hand, surgical procedures with a high risk of extensive blood loss have been performed successfully in patients who refuse any kind of transfusion, e.g. members of Jehovah's Witnesses (7,8).

Even when all available prophylactic measures are taken, there remains a small, but real, risk of infection

transmission or other serious complications with any transfusion (9,10). This risk should always be weighed against the presumed health gain of transfusion for the patient. Furthermore, when transfusing, the clinician also has an obligation to meet the presumption of the voluntary, unpaid donor that her or his gift is used appropriately to save the lives or improve the health of fellow human beings.

Against this background, it would seem of interest to examine the scientific evidence underlying current practice of transfusion. In 2004, the Norwegian National Knowledge Center for the Health Services (NOKC) decided to perform a systematic review of the relevant literature in this respect. However, as the spectrum of clinical indications for transfusion is

wide and many different blood and plasma products are applied, it was decided to concentrate on the role of transfusion and alternative treatments in acute bleedings only. The complete report has been published in Norwegian (11). The purpose of this report is to summarize the literature search strategies and major findings of our systematic review.

Methods

A review team was established by the NOKC in 2004 to assess the evidence base for transfusion vs. alternative treatment modalities in acute bleeding, defined as treatment instituted within 24 h after the bleeding started.

The team performed a Health Technology Assessment (HTA) according to internationally accepted principles by doing a systematic review of the published literature (12). A literature search was done to identify literature on acute bleeding in trauma and surgery within 24 h after the start of bleeding. The detailed search strategy is given in (11). Literature published in English, French, German, Italian, Spanish and the Scandinavian languages were included. No groups of patients were excluded. The studies included interventions to:

- replace lost blood volume (volume replacement),
- ensure sufficient oxygen delivery to the tissues (oxygen transportation), and
- achieve good hemostasis.

Outcomes were length of hospital stay, survival, complications and use of blood products. A second literature search was made on the 13 January 2005 in order to secure adequate updating of the evidence base. A specific, additional search was performed on 'post-transfusion survival', on 'haemoglobin solutions' and on 'Platelets AND haemostasis AND temperature AND haemorrhage'.

The literature search was done in the following bibliographical databases:

- Medline (1966–2004)
- Embase (1974–2004)
- HTA-database (1992–2004)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Library:
 - Cochrane Database of Systematic Reviews (CDSR)
 - Cochrane Controlled Trials Register (CCTR)

Three pairs of reviewers evaluated the literature. The assessment was done stepwise starting with 2438

abstracts, each being evaluated by one pair. From the abstracts, 618 studies were deemed relevant by at least one reviewer and read as full text. They were evaluated for internal validity according to (11) and for relevance to Norwegian health care (external validity). This left 214 studies for further evaluation, according to the following grading of level of evidence (13):

Level 1: Meta-analysis, systematic review of randomized controlled trials or randomized control trial (RCT).

Level 2: Case-control study or cohort study.

Level 3: Non-analytic studies, e.g. case reports, case series.

Level 4: Expert opinions, guidelines.

Furthermore, the quality of studies of levels 1 and 2 was graded as ++, + or – according to probability of causal connection and risk of bias. Only studies of quality ++ and + were approved. Altogether, 79 out of the 214 studies were approved for inclusion in the evidence base, while 133 were excluded or only used for background information. The approved studies were supplemented with a RCT (14) known only as abstract at closure of the formal review (15). Thus the finally approved evidence base comprised 80 studies. As one study was deemed relevant for both oxygen transportation and haemostasis, the evidence database comprised 81 quotations.

Results

The 80 studies forming the evidence base are summarized in Table 1. The results were split into three sections according to purpose of the treatment:

- volume replacement,
- oxygen transportation,
- haemostasis.

Volume replacement

Treatment strategy. One patient series was found in which the authors claimed that low mortality was as a result of their emphasis on keeping the patients continuously normovolaemic (16). By contrast, two meta-analyses of intravenous volume treatment in seriously injured patients concluded that there is insufficient scientific support for the hypothesis that early (pre-hospital) and liberal volume treatment is generally advantageous; however, good documentation was also lacking for the opposite view (17,18). One of the RCTs included in both meta-analyses

Table 1

Numbers of studies approved for inclusion in the evidence base, ranged by level and quality (see *Methods* for definitions).

Purpose	Level	Level 1		Level 1		Level 2		Level 3	Level 4	Animal studies
		Meta-analyses or systematic reviews		Randomized clinical trials						
		Quality	++	+	++	+	++			
Volume replacement		7 (17,18, 24–26, 31,33)	0	7 (19,22, 23, 27–30)	0	1 (20)	0	2 (16,32)	0	1 (21)
Oxygen transportation		2 (49,54)	0	0	11 (38,40,41, 43,44,46, 48,55,57, 59,62)	1 (45)	3 (47,50, 52)	10 (7,8, 34–37, 51,53, 56,60)	0	4 (39,42, 58,61)
Haemostasis		6 (63,67, 69,72, 78,86, 106)	3 (68,72, 79)	5 (70,74, 81,83, 84)	12* (64,71,73, 75,76,80,81, 85,89,91, 93,94)	0	1 (95)	2 (51,90)	0	1 (78)

Numbers in parenthesis are numbers in References list. *One more study (14), previously known as an abstract (15), was added after closure of the formal literature search.

indicated that early crystalloid fluid therapy in penetrating trauma was associated with increased mortality (19), but the study has been criticized because a long time elapsed until haemostatic surgery was initiated, despite brief transportation time. Furthermore, the study excluded patients with traumatic brain injury, in whom it is considered important to avoid hypotension (20). A meta-analysis of animal studies (21) showed that in models with ongoing bleeding, none as well as excessive fluid treatment were associated with increased mortality. In an RCT of hypotensive resuscitation, the authors found no difference in survival, but power analysis showed that such a difference would be very difficult to demonstrate (22).

Choice of resuscitation fluid. A recent study from Australia and New Zealand compared isotonic saline and 4% albumin as a volume expander in 7000 intensive care patients and found no differences in survival or complications. In this study, acute bleeding was only one of many reasons for volume therapy, but for trauma patients there was a nearly significantly increased mortality in the albumin group ($P = 0.06$) (23). A separate meta-analysis also failed to suggest any superiority of albumin as a resuscitation fluid (24).

Newer meta-analyses have detected no survival benefit with colloids instead of crystalloids (Ringer's lactate, isotonic saline) for fluid resuscitation (25,26). Some evidence was found that a starch-based artificial colloid of low molecular weight has better volume effect, lower influence on coagulation and

can be given in larger amounts than starch-based colloids of higher molecular weights (27–29). Nevertheless, no decisive evidence exists that one artificial colloid is more effective and/or secure than are others (26,30).

A meta-analysis from 2002 found no clear advantages of hypertonic saline solutions over isotonic saline in trauma and post-operative patients (31). However, data does not exclude that some subgroups of patients, notably those with serious head injuries, may benefit from the use of hypertonic solutions.

Other methods. Pneumatic anti-shock garments have been applied in traumatology to reduce bleeding and centralize remaining blood volume (32). A meta-analysis from 1999 (33) identified two studies of sufficient quality including approximately 1200 patients. The analysis concluded that there is no clear evidence that such devices reduce mortality, length of intensive care or hospital stay. However, the effect of properly applied anti-shock garments remains to be clarified in certain subgroups of patients, e.g. pelvic fractures with massive venous bleeding or ruptured abdominal aortic aneurysms.

Oxygen transportation

Effects of acute normovolaemic anaemia in healthy volunteers. Acute, normovolaemic reduction of haemoglobin concentration to 7 g/dl induces no measurable changes of human cognitive functions. Further reduction leads to slightly increased reaction times and reduced short- and long-time memory (34). In healthy individuals with normovolaemic anaemia at

5 g/dl concentration of haemoglobin there were no signs of critically low oxygen transport capacity (DO_2). Oxygen consumption and plasma lactate concentration remain unchanged. However, pulse rate increased, and so did cardiac output (35,36). Sense of weakness and increased pulse rate as a result of normovolaemic anaemia of about 5 g/dl were reversed by transfusion of autologous erythrocytes stored briefly outside the body (37).

Significance of erythrocyte transfusion and lung function. In moderately anaemic cardiac surgery patients (hgb concentration 7.5–8.5 g/dl), transfusion of 1 or 2 units of blood bank erythrocytes failed to increase the oxygen consumption index and tissue oxygenation, although the oxygen delivery index increased significantly (38). By contrast, ventilation with 100% oxygen increased all these endpoints. It therefore seems that lung function is more critical to oxygen delivery to the tissues than is the concentration of haemoglobin. This view is supported by an animal study (39) in which piglets with impaired lung function needed much higher oxygen concentrations in the ventilation gas than did otherwise healthy piglets with normovolaemic anaemia. Accordingly, when lung function is impaired, the organism has reduced DO_2 capacity, and the critical concentration of haemoglobin is higher than at normal lung function.

Normalization of reduced blood volume also increases DO_2 (40).

The clinical significance of the storage-related reduction of 2,3-diphosphoglycerate in erythrocytes remains controversial, even though the reduction leads to a firmer binding of oxygen to haemoglobin. This might be expected to reduce tissue liberation of oxygen (41,42).

Lowest acceptable haemoglobin concentration – ‘transfusion trigger value’. In a study from 1988 of patients denying transfusion, mortality increased from 8% at a blood loss < 500 ml to 43% at blood loss > 2000 ml (8). In an enlarged group of similar patients, the same authors later found a somewhat lower mortality, but they concluded that mortality increases with increasing blood loss, especially if the patient has cardiovascular disease (7). The results indicated that the loss of blood volume was of greater significance to mortality than reduction of haemoglobin concentration in patients with a pre-operative haemoglobin concentration > 6 g/dl.

In a large RCT, it was found that non-bleeding, haemodynamically stable intensive care patients generally did as well with a restrictive erythrocyte transfusion trigger (i.e. haemoglobin concentration =

7 g dL⁻¹, mean hgb value 8.5 g dL⁻¹) as with a liberal one (i.e. = 10 g/dl, mean hgb value 10.7 g/dl), with the possible exception of patients with acute myocardial infarction and unstable angina pectoris (43,44).

A cohort study from 1997 concluded that anaemia increases risk of death in critically ill patients with heart disease (45). Transfusing elderly, anaemic patients with serious injury and established heart disease to increase haemoglobin concentration 1 g/dl increased survival (odds ratio = 0.80). In patients operated on for coronary disease, no negative effect was found from a transfusion threshold of 8 g/dl post-operatively (46). Transfusion of 1–2 units of blood bank stored erythrocytes to moderately anaemic patients produced no change in oxygen consumption parameters, in contrast to ventilation with 100% oxygen (38,41). In patients with a hip fracture, higher pre- and post-operative haemoglobin concentrations were both associated with a more favourable in-hospital clinical course (47).

A pilot RCT from 1998 concluded that transfusion triggered from patient symptoms or a haemoglobin concentration of 8 g/dl, saves transfusion of erythrocytes compared with a transfusion trigger of 10 g/dl (48). In accordance with this RCT, a Cochrane report from 2002 (49) concluded that the effect of low transfusion triggers on functional status, morbidity and mortality should be studied in large trials, especially of patients with heart disease.

Two studies (43,50) indicate that transfusion is an independent factor associated with increased time in intensive care units and in hospital as well as an increased mortality. None of the studies used leucocyte-filtered blood products. Furthermore, a retrospective study from 1999 concluded that the prognosis of massively transfused patients had improved over a 10-year period, due probably to among others better damage control surgery, more efficient re-warming of the patients, and possibly to better blood banking procedures (51).

Retransfusion of the patient’s own erythrocytes with CellSaver® (intra-operative cell salvage, ICS). ICS involves collecting autologous shed blood, and adding anticoagulant for re-infusion in large bleeds. This procedure may save significant amounts of homologous transfusions in aortic, non-cardiac surgery (52). Others claim that blood loss in elective aneurysm repair is too small to justify ICS (53). A meta-analysis on 27 studies of post-operative collection of shed blood and retransfusion from 1999 (54) showed that the effect was only marginal in heart surgery, while considerable numbers of homologous

transfusions could be saved in orthopaedic surgery. It should be emphasized that this does not concern the indisputable blood saving effect of reintroducing into the circulation via the cardiotomy filter all shed blood during cardiopulmonary bypass in fully heparinized patients. In a more recent, randomized clinical trial from 2004 a significant reduction of homologous erythrocyte transfusion in patients operated upon for abdominal aortic aneurysm was demonstrated (55).

Artificial oxygen carriers

Perfluorocarbons (PFC). Fluosol DA[®] (Green Cross, Osaka, Japan) was found to be ineffective in treating anaemia in 23 surgical patients with serious blood loss (56). In a multicentre trial in 330 patients with a blood loss > 20 ml/kg it was concluded that PFC could reduce the need for erythrocyte concentrates, but with several quite serious side-effects (57).

Haemoglobin solutions. A multicentre RCT of diaspirin cross-linked haemoglobin was stopped because an intermediary analysis showed increased mortality in the study group. Later, an experimental study in sheep concluded that this substance is not effective as a substitute for erythrocyte concentrates (58). Use of polymerized human haemoglobin (PolyHem[®], Northfield Laboratories Inc., Evanston, IL, USA) was reported in 1998 to lead to reduced use of erythrocyte concentrates (59). In 2002, the same group reported reduced mortality compared with historical controls using PolyHem[®] in patients with serious bleeding when erythrocytes were not available for transfusion (60). The company producing PolyHem[®] employed all the authors. Other studies of PolyHem[®] were not identified. Polyethylene-glycol-haemoglobin has been found to normalize blood pressure, oxygen tension and liberation of dopamine in the brain of severely anaemic piglets (61), but clinical studies of this substance were not identified.

Solution of cattle haemoglobin was studied in a multicentre RCT from 2000 in elective patients operated on for aneurysm of the abdominal aorta (62). Consumption of erythrocyte concentrates was reduced by 27%, with good tolerance and unchanged mortality. These promising results have apparently not been pursued, probably because of the danger of transmission of prion diseases with products from cattle. Similar studies were not identified for solutions of human haemoglobin.

Haemostasis

Blood products: fresh frozen plasma (FFP) and thrombocyte concentrates (TC). A systematic review of 57 RCTs (63) included 14 on its use in

elective surgery and only one on massive transfusions. No conclusions could be drawn on blood-saving or haemostasis-promoting effects of FFP. Thus documentation on clinical effect of FFP in acute bleeding is lacking, and recommended practical guidelines are not supported by RCTs.

No study was identified on haemostatic effect of TC in acute bleeding. A level 3 study was found which, in addition to data relevant for oxygen transportation, also reported on the average use of TC in massive bleeding (51). However, the results were insufficient for conclusions to be drawn. A RCT of cardiac surgery patients was identified in which a transfusion algorithm based on on-site coagulation data led to fewer transfusions, irrespective of surgical blood loss (64).

No study was identified indicating a specific haemostatic effect of transfusing fresh whole blood.

Pharmaceuticals

Fibrinolysis inhibitors. These drugs inhibit the decay of fibrin. Tranexamic acid (Cyclokapron[®], Pfizer Manufacturing, Puurs, Belgium) and aminocaproic acid (Amicar[®], Pfizer Manufacturing) inhibit the activation of plasminogen to plasmin, which disintegrates the fibrin of thromboses. These drugs are lysine analogues, substituting for lysine in plasminogen. Their mode of action is similar, the only difference being that aminocaproic acid is less potent than tranexamic acid and has a shorter half-life (65). Aminocaproic acid is not available for routine use in Norway. Aprotinin (Trasylol[®], Pfizer Manufacturing) is a bovine-derived fibrinolysis inhibitor, which is excluded from clinical use in Norway. Studies on aminocaproic acid or aprotinin without simultaneous comparison of tranexamic acid were therefore excluded from this systematic review.

In 1983, it was found that tranexamic acid reduces mortality in upper gastrointestinal bleeding (66). A meta-analysis from 1997 (67) found that tranexamic acid decreased the exposure of patients to allogeneic transfusion peri-operatively in relation to cardiac surgery. A major systematic review from 1999 (68) showed that tranexamic acid reduces bleeding in many clinical settings, including post-operative bleeding after various surgical procedures. Increased risk of thrombotic side-effects has not been shown in clinical studies. A meta-analysis from 2003 showed that tranexamic acid reduces the need for allogeneic transfusions in installation of hip and knee prostheses (69). Two randomized clinical studies from 2003 showed reduced need of allogeneic transfusion in installation of hip prosthesis (70) and in caesarean

section (71) using tranexamic acid. A meta-analysis from 1999 showed that lysine analogues reduce blood loss in cardiac surgery (72). A randomized clinical trial from 2001 concluded that tranexamic acid reduces post-operative blood loss and need for allogeneic transfusion in aortic valve replacement (73). Thus, extensive documentation exists on the blood saving effect of tranexamic acid in various surgical interventions. Only one randomized controlled study, in primary coronary by-pass surgery, found no reduction in post-operative bleeding (74). Furthermore, aminocaproic acid has been found to reduce blood loss in paediatric heart surgery (75). A systematic review from 2004 concluded that there is insufficient evidence from RCTs of antifibrinolytic agents in trauma to either support or refute a clinically important treatment effect (76).

Extensive documentation was found on the blood saving effect of aprotinin in several surgical interventions. As examples, two meta-analyses (72,77) showed reduced peri-operative blood loss and need for transfusion in cardiac surgery patients. However, as articles on this drug were not reviewed systematically, the evaluation of aprotinin in the present report is incomplete.

Desmopressin. Desmopressin is a synthetic analogue of vasopressin. Desmopressin increases plasma levels of coagulation factor VIII and von Willebrand's factor upon intravenous or intranasal administration (65). A Cochrane analysis from 2005 concluded that there is no scientific documentation that the use of desmopressin will reduce peri-operative blood loss and need for allogeneic transfusion in patients with no haemostatic abnormalities (78). Eighteen RCTs with 1295 patients were included in this Cochrane analysis. A meta-analysis from 1995 concluded that desmopressin reduced blood loss in cardiac surgery patients with large blood loss, but there was no significant effect on the number of blood units required for transfusion (79). A RCT from 2002 showed the blood-saving effect of desmopressin combined with the somatostatin analogue octreotide and the acid pump inhibitor omeprazol in bleeding because of portal vein hypertension (80). A RCT from 1999 concluded that a point-of-care haemostasis test would contribute to the optimal use of desmopressin and hence reduce the need for an allogeneic transfusion post-operatively in elective cardiac surgery patients (81).

Recombinant factor VIIa (rFVIIa). This drug enhances clot formation at the site of injury through interaction with exposed tissue factor (82). Accordingly, the drug is inactive outside the damaged area.

Initial studies on this new drug were performed in elective surgery, where unexpected excessive blood loss may occur. In a RCT from 2003, rFVIIa reduced peri-operative blood loss and the need for transfusion in retropubic prostatectomy (83). However, only 36 patients were included. No thromboembolic or other serious complications were observed. In a RCT with 204 patients undergoing liver resection, rFVIIa did not change the number of patients or the number of units transfused (84). Another RCT from 2005 revealed no effect of rFVIIa on peri-operative blood loss in 48 patients with traumatic pelvic fracture (85). A large RCT showed significantly reduced bleeding and need for allogeneic transfusion in blunt trauma after the administration of rFVIIa (14,15), but the study has been criticized as fresh frozen plasma was given at random.

Other methods

A Cochrane report from 2004, updated late in 2005, concluded that locally applied 'fibrin sealants' will reduce post-operative bleeding and allogeneic transfusion (86). However, the studies were generally small and insufficiently blinded, and a need for studies of higher quality was pointed out. 'Dry fibrin sealant dressing' was found to have a good effect on survival, bleeding control and need for volume therapy in a study of hypothermic pigs with serious liver damage (87).

A level 3 study concluded that upper gastrointestinal bleedings not coming from varices were controlled more rapidly with increasing use of acute haemostatic endoscopy (88). A randomized clinical trial concluded that sclerotherapy is more effective for the control of bleeding from oesophageal varices than compression therapy with a balloon (89). A level 2 study indicated that acute sclerotherapy gives fewer needs for transfusion, better bleeding control and better survival than delayed sclerotherapy for oesophageal varices (90). A RCT from 2000 concluded that infusion of the somatostatin analogue octreotide seemed as effective as sclerotherapy in this situation (91). A level 1 review from 2001 concluded that the infusion of the somatostatin analogue octreotide is a valuable adjunct to sclerotherapy (92), but additional studies were called for to reach a firm conclusion.

In a level 1 study from 2000, drugs that increase the tension of the uterus (misoprostol and syntocinon) have been found to reduce blood loss in elective caesarean section (93). Furthermore, a level 1 study was identified which claimed that ultrafiltration to

remove inflammatory mediators significantly reduced post-operative bleeding and the need for allogeneic transfusion in adult cardiac surgery (94).

A level 2 study indicated that a treatment algorithm based on 'near patient haemostatic testing' might reduce the number of transfusions in cardiac surgery patients with normal haemostasis parameters prior to surgery. Controls were historical and based on clinical evaluation (95). Furthermore, a retrospective level 3 study suggested that a more aggressive correction of coagulopathy, including effective re-warming of the patient, would lead to a significantly reduced need for allogenic transfusion (51).

Discussion

No transfusion measure has come into general use based on controlled clinical trials. However, in recent years, important parts of transfusion practice have been tested in controlled clinical trials. Most of these have been undertaken in intensive care patients, many of whom did not suffer from acute bleeding. Thus, only few high quality data have been obtained from studies in patients with acute bleeding. Nevertheless, the review team feels that some of the results from intensive care patients also may apply to the treatment of acute bleeding.

Three important points should be considered by the clinician treating the individual patient with acute bleeding:

1. The primary aim of treatment is bleeding control by compression, local wound treatment and surgical procedures.
2. In parallel with this, lost blood volume should be replaced to reduce the chance of hypoperfusion and organ failure at a later stage.
3. If bleeding control is not easily achieved, the aim of treatment is to keep the patient alive and prevent later complications by judicious use of volume therapy and transfusions until bleeding control can be achieved.

In this context, transfusion and its alternatives are used in order to obtain three effects:

- volume replacement,
- sufficient oxygen transportation, and
- adequate haemostasis.

Volume replacement

Monitoring blood volume status using clinical parameters is not straightforward (96). Age of the

patient, type and history of injury, concurrent diseases and general anaesthesia may all influence the patient's ability to compensate for ongoing blood loss. Securing normovolemia has been considered a standard of care in most situations. Not surprisingly, in-hospital supporting data in terms of RCTs for this well-established concept was absent. In trauma patients, there is an ongoing debate whether or not to allow both hypovolemia and hypotension prior to bleeding control (17–19,22). Some authors recommend hypotensive resuscitation, the principle of which is to avoid serious hypovolemia but also to avoid a systolic blood pressure increase, which may entail further bursts of bleeding. The recommendation is based on animal studies and pathophysiological theory (17,21). However, no clinical studies have been identified which show that this recommendation is clinically applicable and will improve survival (17,22,97). The tuning of early, pre-hospital volume therapy in trauma and acute bleeding therefore remains controversial.

Albumin is the only available blood product for volume replacement. Although widely used around the globe, no documentation exists of its superiority over artificial colloids or crystalloids. On the contrary, the so-called SAFE RCT failed to show any advantage of albumin for volume replacement in intensive care patients and even suggested an increase in mortality when albumin was used for resuscitation in patients with head injury (23). No evidence was found that artificial colloids are to be preferred over crystalloids in bleeding patients. The choice of resuscitation fluid may be more a matter of local tradition and costs than of scientifically based practice (98). The role of hypertonic solutions in bleeding patients also remains ill defined (31), as does the role of pneumatic antishock garments (32,33).

Oxygen transportation

Studies were identified which show conclusively that otherwise healthy human beings tolerate a loss of 2/3–3/4 of blood volume provided the loss of volume is compensated for by infusion of fluid intravenously. In accordance with this, studies of surgery in patients who deny transfusion show that morbidity and mortality increase when haemoglobin concentration sinks below 6–7 g/dl, especially in the elderly and if the patient has concurrent cardiovascular disease.

Available evidence fails to indicate a positive effect of increasing haemoglobin concentration in

non-bleeding patients above 8–9 g/dl, except possibly in patients with unstable angina pectoris or heart infarction. However, the relevant studies were carried out with leucocyte-containing erythrocyte concentrates, which are considered to induce a dose-related immunosuppression in the recipient and hence may contribute to increased morbidity and mortality in liberally transfused patients. Interestingly, however, in two other studies no effect on oxygen consumption parameters was found by transfusing 1–2 units of allogenic, blood bank stored erythrocytes to moderately anaemic patients (38,41). It seems that if haemoglobin concentration is maintained above 8 g/dl, lung function and blood volume is more critical to clinical outcome than is the concentration of haemoglobin.

The life-saving effect of transfusing erythrocytes to gravely anaemic, bleeding patients seems obvious and has support in the literature (7,8,99,100). At the same time, there is insufficient knowledge of the value of transfusion of erythrocytes to moderately anaemic, hemodynamically stable patients (i.e. with haemoglobin values exceeding 6–7 g/dl). As myocardial function is essential for the body's ability to increase cardiac output to compensate for acute bleeding (101), it seems rational to apply higher haemoglobin transfusion triggers in elderly than in young, otherwise healthy individuals. Prior to bleeding control, it would seem rational to apply a transfusion trigger of 8.5–9 g/dl haemoglobin in order to have a safety zone even in the young trauma victim.

A positive correlation has been observed between the number of erythrocyte units transfused and time in intensive care units as well as mortality (43,50). However, none of the studies used leucocyte-filtered blood products, which seem to give less immunosuppressive and other side-effects than non-leucocyte-filtered products (9,10). This side-effect of transfusion should be reassessed in patients given leucocyte-filtered products before conclusions are drawn. Interestingly, over the past years, survival of massively transfused patients may have improved (51). Factors contributing to this positive development were suggested to be among others improved damage control surgery including effective and efficient rewarming procedures, and better blood banking procedures.

As may seem surprising, the significance of increased binding of oxygen to haemoglobin in stored erythrocytes remains to be evaluated clinically. No results were found which justify the transfusion of only fresh erythrocytes to intensive care patients or to patients with acute bleeding.

Perfluorocarbon solutions seem unable to act as sufficiently efficient oxygen carriers and are associated with several unfavourable side-effects. Haemoglobin solutions have been found to have major side-effects, and their possible place in the treatment of acute bleeding remains unsettled. The association of cattle with prion disease renders the future of cattle-derived haemoglobin solutions dubious.

Several studies indicate that the systematic use of cell savers for retransfusion of shed blood may contribute to the reduction of blood consumption in acute bleeding (52,54,55), but in acute bleeding the clinical situation may often restrict their use.

Haemostasis

Loss of 1–1.5 times blood volume is associated with reduced activity of the coagulation system (102). Exchange of 1–1.5 times plasma volume with fluid that contains no plasma reduces the fibrinogen concentration to about one-third of its normal value (103). It seems rational therefore to transfuse coagulation factors, and especially fibrinogen, by FFP if the patient loses more than 1 blood volume, but controlled clinical studies on this assumption are lacking. Several studies have been performed on the possible blood saving effect of FFP, but the studies are small and concern mostly elective procedures, permitting no clear conclusions to be drawn (63).

The review team did not identify any studies relevant to transfusion of thrombocytes in acute bleeding. This lack of knowledge is a serious problem, as the function of thrombocytes must be expected to be pertinent to the result of treatment of acute bleeding. In addition, the need for thrombocytes may possibly increase in the case of grave anaemia, as the reduction of erythrocyte content leads to rheological changes which reduce the shear flow stress that presses thrombocytes against the vessel wall (104). This may partly explain the surgical experience that gravely anaemic patients tend to bleed profusely.

The use of blood products to improve haemostasis in acute bleeding therefore rests on no firm evidence. Their use must be decided on the basis of clinical evaluation and on laboratory tests. Several methods exist for the *in vitro* evaluation of platelet and coagulation function, even 'on site' (thromboelastography, various variants of aggregometry, perfusion systems), but their place in the treatment of trauma and acute bleeding remains to be settled (105).

In contrast to blood products, many randomized control studies have been performed on drugs used to reduce bleeding. The blood-saving effect of the

fibrinolysis inhibitor tranexamic acid seems well documented in various elective surgical procedures, and there is apparently no increased risk of thromboembolic complications. Most of the studies focus on elective surgical procedures. The blood saving effect of fibrinolysis inhibitors in acute bleeding is more hypothetical, and evidence is still insufficient in trauma patients (76). These drugs do not seem to have come into general use, even in elective surgery (106). A blood saving effect of desmopressin has not been documented.

The recently developed drug rFVIIa represents a novel approach to haemostasis in acute bleeding, especially when caused by trauma, but the effect cannot yet be considered established by firm evidence. As the plasma protein prothrombin is the substrate of rFVIIa, consistent results on the effect of rFVIIa may be difficult to obtain until the use of FFP as a source of coagulation factors has been established more firmly. There is evidence that locally applied 'fibrin sealants' may reduce blood loss and need for transfusion, but their role is not yet sufficiently established.

Administration of the somatostatin analogue octreotide reduces the portosystemic gradient significantly (92). A blood-saving effect of octreotide in the treatment of acutely bleeding oesophageal varices therefore seems possible, but it remains to be firmly documented. Although available evidence supports the blood saving effect of uterus-contracting drugs in elective caesarean section, no documentation exists from RCTs for treatment modalities to reduce bleeding in relation to emergency caesarean section and post-partum bleedings.

Closing remarks

As shown in our systematic review, one of the difficulties with treatment strategies in acutely bleeding patients is the scarcity of published evidence for or against basic intervention strategies. Hence, the use of different volume replacement strategies and transfusion policies in bleeding patients is based more on experts' opinions or personal experience than on evidence from RCTs. It is uncertain to what extent this will change and to what extent new concepts, e.g. hypertonic fluid resuscitation, will play a clinical role. Moderate, normovolemic anaemia seems to be well tolerated by major patient groups, including those with cardiac disease, and the value of erythrocyte transfusions in such patients may be low. The role of FFP, rFVIIa and thrombocyte concentrates in achieving adequate haemostasis remains to be clarified. The lack of RCTs may possibly be compen-

sated for by multicentre studies of consumption of blood products in comparable patient populations linked to survival data (transfusion epidemiology). On the other hand, the significance of fibrinolysis inhibitors in reducing the need for an erythrocyte transfusion seems well established by RCTs in various elective procedures and should be studied further in patients with acute bleeding.

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