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Haemostasis and Transfusion

Perioperative Management in Elderly Patients

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Guest-Editors

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Foreword

With the proportion of older adults in the population of Western countries continuing to grow, the number of geriatric surgical patients has increased dramatically. Anemia is very frequently found in these patients, because of their higher incidence of comorbidity and because of the often necessary surgery. Although low hematocrit levels appear, surprisingly, to be well tolerated in the perioperative period, they are, in fact, a significant risk factor for morbidity and mortality, particularly in the post-operative period as well as in normal daily life. The simple transfusion of erythrocytes only partly reduces these risks, if at all; in some cases the risks are even increased. We therefore need to develop effective, patient-friendly, and economically defensible strategies to reduce the perioperative risk of anaemia.

Furthermore, it is not clear what the prognostic significance of age-related coagulation disorders is. Because of the danger of cardiovascular complications and thromboembolism, older patients as a rule receive antithrombotic agents, which can make perioperative coagulation management more difficult, increase perioperative blood loss and thereby heighten the risk of anemia. To facilitate making acute diagnoses – which are so important in the perioperative period –, several new methods specifically for testing at ‘point of care’ are being investigated or are already part of clinical routine.

The goal of this ‘Expert Meeting’ which was organized by the Department of Anaesthesiology and Intensive Medicine of the University of Graz and the Department of Anaesthesiology of the University of Munich, was to discuss and develop standards in order to further reduce perioperative complications in the older patient.

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Incidence and Risk of Perioperative Anemia in Elderly Patients

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Introduction

Perioperative anemia is common in elderly patients undergoing surgery. Red blood cell transfusions are an extremely common medical intervention. In the United States, 11 million units were transfused to 3.4 million patients in 1994. The indications for red cell transfusion are very controversial. For many years, the widely accepted standard was to transfuse patients when the hemoglobin level dropped below 10 g/dl. Most modern guidelines conclude that transfusion therapy should be individualized, and consider the patients symptoms rather than focusing on a specific hemoglobin level. Recent trends have been to use lower thresholds for allogeneic red cell transfusions because of fears of HIV and hepatitis. However the safety of allogeneic red cell transfusion has improved greatly during the past 20 years in countries with a well regulated blood supply. In the US, it is very difficult to even measure risk and statistical modeling is now being used to estimate safety. Given the dramatic improvement in safety, it is timely to reconsider risk associated with anemia and the evidence that allogeneic improves outcome.

Risk from Anemia

The risk associated with anemia can be estimated in an unbiased manner by examining outcome in surgical patients who decline blood for religious reasons. Analysis of case reports and case series suggest that patients tolerate anemia well with anemia related deaths occurring most commonly below 5 g/dl. We have performed a retrospective cohort study and included 1,958 adult consecutive surgical patients who refused transfusion for religious reasons. The primary analysis focused on the association between preoperative Hgb level and postoperative mortality. We found the mortality rose and hemoglobin level fell. Furthermore, we found a significant interaction between underlying cardiovascular disease (defined as a history of angina, myocardial infarction, congestive heart failure, or peripheral vascular disease) and preoperative Hgb level ($p = 0.03$). In patients with underlying cardiovascular disease the adjusted odds ratio for postoperative mortality began to rise sharply at Hgb level equal to 10 g/dl or less while in patients without underlying cardiovascular disease there was a subtler rate of increasing risk below 10 g/dl (fig. 1). Further analyses examining patients with perioperative hemoglobin levels below 7 g/dl found very high rates of mortality and morbidity.

Fig. 1.

Beside clinical studies, this question can be examined by human experimentation. A study of 32 normal volunteers undergoing acute isovolemic reduction of Hgb levels to 5 g/dl, critical oxygen delivery was not affected. However, 2 patients had electrocardiogram changes consistent with ischemia.

Beside mortality and morbidity, anemia may be associated with symptoms such as fatigue, weakness and diminished physical performance. These widely accepted clinical signs of anemia remain poorly characterized. There is scant medical literature characterizing severity of anemia and the subsequent development and severity of these symptoms. A recent study in 5 healthy adults aged 18–35 years old who underwent acute isovolemic hemodilution to hemoglobin levels from 5–7 g/dl reported increased fatigue and decreased energy levels. Perhaps more important, the relationship between functional status and anemia is poorly characterized.

Efficacy of Blood Transfusion

A systematic review of the literature identified only 16 studies which were controlled; 11 were randomized controlled trials, and 5 were observational studies. One randomized trial was confined to patients with sickle cell disease. The main limitation of observational studies is that there may be confounding by indication for transfusion. Only a randomized clinical trial can overcome this limitation.

The details of the 10 randomized clinical trials are summarized in Table 1. The clinical settings were variable. Five studies took place within the context of surgery – general, cardiac, vascular or orthopedic. Three small trials were in the context of acute blood loss and/or trauma, and 2 trials involved patients in critical care units. Only one clinical trial (Hebert et al. N Engl J Med 1999) in ICU patients had adequate power to examine clinical outcomes. This study suggested that a restrictive transfusion threshold of 7 g/dl did not adversely effect

Table 1. Clinical trials examining transfusion thresholds

Study	Clinical setting	Transfusion Protocol
Topley <i>et al.</i> (1956)	Trauma (n=22)	(1) <u>Liberal strategy</u> : to achieve red cell volume $\geq 100\%$ of normal (2) <u>Restrictive strategy</u> : maintain red cell volume 70-80% of normal
Blair <i>et al.</i> (1986)	Acute severe upper GIH (n=50)	(1) <u>Liberal strategy</u> : patients received at least 2 units of PRBC immediately on admission to hospital (2) <u>Restrictive strategy</u> : patients were not transfused PRBC during the first 24 hours unless Hb < 8.0 g/dl or shock persisted after initial resuscitation with colloid
Fortune <i>et al.</i> (1987)	Trauma / acute hemorrhage (n=25)	Patients were first resuscitated using crystalloid (1) <u>Liberal strategy</u> : Hct was brought up to 40% slowly over a period of several hours by the infusion of PRBC (2) <u>Restrictive strategy</u> : Hct was kept close to 30% by the administration of PRBC
Johnson <i>et al.</i> (1992)	Cardiac surgery (n=38)	(1) <u>Liberal strategy</u> : patients received blood transfusion to achieve a Hct value of 32% so long as autologous blood was available (2) <u>Restrictive strategy</u> : patients received transfusions only if the Hct value fell below 25%.
Hebert <i>et al.</i> (1995)	Critical care (n=69)	(1) <u>Liberal strategy</u> : patients were transfused PRBC if their Hb 10.0 to 10.5 g/dl or less; Hb concentration maintained at 10.0 to 12.0 g/dl (2) <u>Restrictive strategy</u> : patients were transfused PRBC only if their Hb 7.0 to 7.5 g/dl; Hb concentration maintained at 7.0 to 9.0 g/dL.
Bush <i>et al.</i> (1997)	Vascular surgery (n=99)	(1) <u>Liberal strategy</u> : transfused with PRBC to maintain Hb > 10.0 g/dl (2) <u>Restrictive strategy</u> : Transfused only if Hb level fell below 9.0 g/dl
Carson <i>et al.</i> (1998)	Orthopedic surgery (n=84)	(1) <u>Liberal strategy</u> : patients received 1 unit of PRBCs at the time of random assignment and then as needed to maintain Hb > 10.0 g/dl (2) <u>Restrictive strategy</u> : transfusion was delayed until the patient developed symptoms or consequences of anemia, or Hb value < 8.0 g/dl in the absence of symptoms
Hebert <i>et al.</i> (1999)	Critical care (n=838)	(1) <u>Liberal strategy</u> : patients were transfused with PRBC to maintain Hb concentration at 10.0 to 12.0 g/dl (2) <u>Restrictive strategy</u> : patients were transfused to maintain Hb concentration maintained between 7.0 and 9.0 g/dl.

outcome compared to a liberal transfusion threshold. All other studies were much too small. Only one study examined symptomatic transfusion.

A summary of the trials suggests that a restrictive transfusion trigger reduces the proportion of patients receiving red blood cell transfusion, the total number of units transfused, and the mean hematocrit levels. The currently published evidence suggests that restrictive transfusion triggers do not adversely effect mortality, cardiac morbidity, or length of hospital stay. Given the uncertain generalizability of the data across different clinical settings, the limited data from patients with underlying cardiovascular disease, and the absence of data on functional recovery, additional randomized clinical trials are needed. For the present, we recommend the use of a restrictive transfusion trigger, but suggest using caution in patients with cardiovascular disease.

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Erythropoietin, Iron, and Erythropoiesis

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Recent knowledge gained regarding the relationship between erythropoietin, iron, and erythropoiesis in patients with blood loss anemia, with or without recombinant human erythropoietin therapy, has implications for patient management. Under conditions of significant blood loss and/or erythropoietin therapy, iron restricted erythropoiesis is evident, even in the presence of storage iron and iron oral supplementation. Intravenous iron therapy in renal dialysis patients undergoing erythropoietin therapy can produce hematologic responses with serum ferritin levels up to 400 µg/l, indicating that traditional biochemical markers of storage iron in patients with anemia of chronic disease are unhelpful in assessment of iron status. Newer measurements of erythrocyte and reticulocyte indices using automated counters show promise in the evaluation of iron restricted erythropoiesis. Assays for serum erythropoietin and the transferrin receptor are valuable tools for clinical research, but their roles in routine clinical practice remain undefined. The availability of safer intravenous iron preparations allows for carefully controlled studies of their value in patients undergoing erythropoietin therapy and/or blood loss

Blood Conservation in Geriatric Patients

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Over the last years, it has repeatedly been advocated that the various methods of blood conservation should be implemented in a comprehensive blood management of the perioperative patient in order to minimize the manifold adverse effects of allogeneic blood transfusion. However, the target population for these techniques largely consists of elderly patients, and especially the patients > 75 years of age comprise the most rapidly growing population segment in the Western world. On the other hand, autologous methods are needed most in the very patient group where they are most difficult to perform (as in e.g. the geriatric patient scheduled for cancer surgery).

The lack of a clear definition of the 'elderly' patient seems less important when we consider that it is not the amount of years that precipitate a higher perioperative risk, but rather the fact that these patients frequently suffer from a variety of coexisting diseases, especially of the cardiovascular system. Thus, advanced age is merely associated with a higher incidence of risk factors because of comorbidity, but not the age per se.

Special Issues of the Elderly

In order to adapt existing autologous methods for the use in the elderly, it seems necessary to consider several special problems that are typical for the geriatric patient. Table 1 shows a compilation of issues that have to be assessed first before blood saving techniques may be applied in this special patient group. The biggest problem that substantially restricts or even precludes the application of blood saving techniques is the prevalence of preexisting anemia. Preoperative anemia is known to be associated with an increased perioperative mortality and morbidity, irrespective of a subsequent increase of hemoglobin by transfusion of allogeneic blood (1–7). Furthermore, it is the single most important predictor for the likelihood of perioperative allogeneic blood transfusion, thus adding the potential adverse effects of blood transfusion to the perioperative risk. Unfortunately, due to a dramatic decrease of the average hemoglobin level in patients older than 70 years, the incidence of anemia is particularly high in the geriatric population (1,2,8). This is partly caused by an increased incidence of non-surgical bleeding as well as surgical procedures in this population, but it is also precipitated by concomitant factors such as iron deficiency, imbalanced nutrition intake, the prevalence of Anemia of Chronic Disease (ACD), cancer (+ chemotherapy, radiation), chronic drug intake (e.g. non-steroidal antiinflammatory agents) and a generally impaired ability of the

Table 1

High incidence of anemia
ACD, iron deficiency, NSAI, cancer
Comorbidity
diabetes, hypertension etc.
Cardiovascular/pulmonary diseases
increased anemia risk, decreased anemia tolerance, narrow safety margins
Impaired nutritional state
iron, B12, impaired blood loss compensation
Chronic drug intake (non-steroidal etc.)
Mobility
Cognitive functions, fatigue
Cost/benefit
Life expectancy – ethical considerations

hematopoietic system to compensate for perioperative blood loss. The anemia problem in the elderly population becomes even more relevant in preoperative patients where the incidence of preoperative anemia may rise to 15–28 % of all patients presenting for surgery (9).

Apart from a generally increased comorbidity, it is especially the cardiovascular system of the elderly patient that may be affected by disease. Coronary artery disease or other severe heart conditions multiply the perioperative anemia-associated risk, substantially restrict the level of anemia tolerance and thus lower the safety margin towards a decrease in circulating hemoglobin. For these reasons, the use of autologous methods may be severely restricted in these patients.

Anemia and Cognitive Function

A decrease of hemoglobin may influence the cerebral performance. In young healthy volunteers, hemodilution beyond hemoglobin levels of 5–6 g/dl produce a substantial decrease in cognitive function that is reversible upon retransfusion of the collected blood (10). For geriatric patients, such a relation has not yet been established. Thus, it is not known whether cerebral functions may be susceptible to the same effect at perhaps different – higher – hemoglobin levels. However it could be shown that elderly people are generally more susceptible to a postoperative decline in cognitive functions (11), that the incidence of these dysfunctions is linked to an intraoperative decrease in cerebral oxygenation, and that the incidence of postoperative delirium – another well-established problem of the elderly patient – is particularly high when a hematocrit of less than 30% was observed intraoperatively (12). Taken together, these findings point towards a crucial role of oxygen transport capacity, and that elderly patients may react in a more sensitive way to a relative lack of oxygen carriers, which may substantially limit the usefulness of some autologous methods.

Blood Conservation Strategies

Extensive review of autologous techniques can be found elsewhere (13,14). Since these methods are mostly used in an elderly patient population, many of the findings generally apply to the geriatric patient. A great part of the risks associated with autologous methods are presumably not enhanced by advanced age, which means that their use is as ‘safe’ or ‘unsafe’ as in younger patients.

Autologous Blood Donation

Preoperative autologous blood collection may be associated with a few problems that are specific to the elderly: Because of comorbidity, the tolerable degree of anemia necessary for an erythropoietic stimulus may not be sufficient to adequately compensate for blood loss by donation. Furthermore, the capacity of the hematopoietic system may be impaired, due to a variety of factors (nutritional, drug intake etc.). Anemia caused by preoperative blood donation may be particularly harmful in elderly due to coexisting cardiovascular diseases,

and because anemia is the most important predictor for transfusion probability (13). Thus, a potential overcollection of autologous blood units should be avoided at all costs.

For geriatric patients, it may also become a substantial problem to perform ABD, due to restricted mobility or inadequate venous access. Because of these various additional impediments, the cost-benefit relation of ABD may be less rewarding in this patient group.

Most of the studies analyzing adverse effects in blood donation agree that autologous donation is no more harmful than homologous donation (15). Due to the high incidence of coexisting diseases, it has been assumed that elderly patients have a higher risk of ABD than younger, healthy people. However, it could be shown that the incidence of adverse effects is substantially higher in young donors, even when compared to high-risk elderly patients (16,17). While the overall incidence of adverse effects is less in elderly patients (mainly due to vasovagal dysregulation), the relative percentage of cardiovascular events seems to be higher in this group (17).

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Strategies to Reduce the Risk of Perioperative Anemia

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There are numerous sequelae of anemia in the perioperative period. A primary concern relates to cardiovascular disease and the potential for anemia to lead to coronary supply/demand mismatches. Two published studies have addressed this issue specifically with respect to noncardiac surgery, and another study evaluated cardiac surgery. In a small retrospective cohort study involving patients undergoing infrainguinal bypass surgery, Nelson et al. demonstrated a significant increase of myocardial ischemia and myocardial infarction in patients with hematocrits less than 27% on postoperative day number 1.¹ Hogue et al. studied a cohort of patients undergoing radical retropubic prostatectomy and similarly demonstrated an increased incidence of myocardial ischemia in patients with hematocrits of less than 28%, but there were no perioperative myocardial infarctions in any patient.²

There have been several large scale epidemiologic trials, which address this issue. Hebert and colleagues studied 4,470 critically ill patients and reported that hemoglobin values were significantly higher than those who survived compared to those who died.³ In the subgroup of patients with cardiac disease, increasing hemoglobin values in anemic patients were associated with improved survival with an odds ratio 0.80 for each 1 g/dl increase. In contrast, Carson and co-workers reported that 30 day mortality in 8,787 hip fracture patients was not influenced by perioperative transfusion if hemoglobin levels were 8 g/dl or higher.⁴ The authors were unable to comment on lower hemoglobin levels because of the high incidence of transfusion in this population. Importantly, they did not stratify by the presence of cardiac disease.

In reviewing the studies by both Hogue and Nelson, hemodynamic data suggest that the ischemia is more frequent when anemia is associated with tachycardia. In fact, in a cohort of 100 patients undergoing infrainguinal surgery (similar to the Nelson study), ischemia related to a hematocrit less than 28% was first observed on postoperative day 2. Heart rate was well controlled in this trial on the first postoperative day using pharmacologic management, which was discontinued on postoperative day 2. Taken together, these studies suggest that high risk patients may be at risk for developing perioperative myocardial ischemia and infarction depending upon the other determinants of coronary supply and myocardial demand.

Pathophysiology of Perioperative Ischemia and Potential Treatment

The determinants of myocardial oxygen supply/demand and its potential to cause myocardial ischemia is shown in figure 1.

Ischemia is multifactorial

Fig. 1.

Decreased myocardial supply can be the result of decreased O₂ from either anemia or decreased oxygen saturation. At the same time, there is evidence to suggest that the decrease in hemoglobin leads to decreased viscosity of the blood that may in fact lead to increased tissue perfusion. Other determinants of decreased supply include coronary vasoconstriction. Coronary vasoconstriction can be seen with coronary vasospasm or may be related to abnormal response to catecholamines in areas of coronary atherosclerosis and denuded endothelium. Another potential cause of coronary vasoconstriction, potentially related to denuded endothelium, is hypothermia.⁵ Treatment for supply related anemia would involve transfusion; however, it is important to realize that increasing viscosity could lead to decreased tissue perfusion as the hematocrit rises. Prevention of hypothermia can reduce myocardial ischemia and cardiac events. In a cohort of 300 patients, randomized active warming vs. routine care, perioperative cardiac events were significantly lower in those patients who were actively warmed.⁶ Treatment of abnormal vasoconstriction related to denuded endothelium is easily treated using nitroglycerin, although the hypovolemia associated with anemia may be compounded with infusion of this agent. Importantly, prophylactic nitroglycerin has not been shown to reduce the incidence of perioperative myocardial ischemia.⁷

With regard to increased myocardial demand, tachycardia is the most commonly seen hemodynamic perturbation associated with the development of myocardial ischemia and infarction. Numerous studies have associated tachycardia with myocardial ischemia, particularly in the presence of anemia.^{1,2,8} Increased contractility may also lead to myocardial ischemia, but has not been shown to be a major determinant in any study. Treatment for increased demand from tachycardia is best accomplished with beta blockade. Several studies have demonstrated the value of prophylactic beta blockade in high risk patients for reducing both perioperative and long term outcomes.^{9,10} Therefore, the strategy which appears to have the best therapeutic effect is control of heart rate particularly with beta blockade.

Although the development of myocardial ischemia may be a critical component in the pathophysiology of perioperative infarction, particularly if prolonged (e.g. greater than 30 minutes in duration) perioperative myocardial infarction may also result from thrombotic events.^{11,12} In the nonsurgical area, thrombosis is a primary cause of infarction.¹³ The relationship between the development of perioperative anemia and a pro-thrombotic state requires further evaluation.

Summary

In summary, the risks of decreased oxygen supply associated with anemia must be counter balanced by decreasing oxygen demand. The decision to transfuse must incorporate the baseline risk of the patient with the risks of infection and other sequelae of the use of blood products.

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The Use of Albumin

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Human albumin solutions were developed by Cohn for resuscitation of soldiers, and have been used for more than 50 years, without documented cases of virus transmission. However, a recent metaanalysis by the Cochrane Injuries Group Albumin Reviewers (*BMJ* 1998;317:235) came to the conclusion that there is 'no evidence that albumin reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia', and a 'strong suggestion that it may increase mortality'.

This paper was challenged by many other authors, who criticised e.g. the selection of quite heterogeneous studies, the small patient numbers of the trials (particularly of 'negative' trials), and the use of 'old' data, since the albumin use (e.g. dosage, monitoring) in several studies was not in line with current practice. The Cochrane metaanalysis conclusion of a 'strong suggestion that it [albumin] may increase mortality' was therefore not accepted. However, the paper greatly stimulated the discussion about the optimal use of albumin, and pointed to the weakness of existing evidence. There are still many clinicians, who are convinced of a benefit; however, there is no solid evidence for that; and we are left with considerable uncertainty. The question of the optimal use of albumin was addressed by two European expert meetings, and was also a subject of regulatory action by the Committee for Proprietary Medicinal Products (CPMP), the working arm of the European Medicines Evaluation Agency (EMA, London). The first of the two expert meetings mentioned above was entitled 'Blood Safety in the European Communities: An Initiative for Optimal Use'. It was organised under the German EU presidency in Wildbad Kreuth, Germany, May 20-22, 1999, and was chaired by W. Schramm. The proceedings were published (ISBN 3-00-005705-6) by the German Ministry of Health with permission of the EU commission. The experts stated that the benefit intended with albumin administration is volume replacement (not albumin replacement), and that its clinical benefit is not established by evidence from controlled studies with mortality as endpoint, but rather assumed on the basis of physiology and pathophysiological concepts, which also pertains to differential use of 'isooncotic' and 'hyperoncotic' preparations. The alternatives, e.g. artificial colloids like dextran, gelatine, or hydroxyethyl starch are far less expensive, but their dose may be limited by certain side-effects (e.g. enhanced bleeding). However, the experts saw also no clinical evidence from controlled studies for superiority of albumin over artificial colloids. Further studies were advocated.

The second expert meeting was a state-of-the-art conference sponsored by the Swedish Medical Research Council entitled

'The Scientific Evidence Base for the Use of Plasma Products', and took place in Stockholm, January 12–13, 2000. A proceedings volume is currently prepared. The experts confirmed that a systematic review of available randomised controlled clinical studies provides no evidence that albumin reduces the risk of death in critically ill patients, but the trials scrutinised in the Cochrane metaanalysis were of variable quality and the way albumin was used in these trials was partly not in keeping with current clinical practice. The widespread use of albumin was explained by the prevailing concept of maintaining physiologic variables within normal range, and the concentration of albumin in plasma was seen as an unspecific marker of disease, reduced levels seem being the result of pathological events – not the cause of them, and hypoalbuminaemia common in the critically ill patient. The experts furthermore pointed out that patients with critical illness constitute a wide plethora of alterations, background factors, underlying diseases, symptomatic and causal therapeutic interventions. Management of these patients should be based on current concepts of maintaining optimal physiologic conditions that give each individual patient the highest chance to survive. A need for further studies with mortality and quality of life as endpoints was identified

The CPMP, according to its responsibilities, had to decide on possible regulatory consequences. Since the Cochrane paper suggested an increased mortality due to the use of albumin, even a ban of the albumin preparations from the market was one of the options to be considered. However, the CPMP came to the following conclusions:

- There is insufficient evidence of hazard to warrant withdrawal of albumin products.
- The question of albumin and mortality will only finally be answered by conducting large, purpose-designed randomised controlled clinical trials.
- The CPMP Core Summary of Product Characteristics for human albumin should be updated in the light of this review to give a more specific indication and to highlight the risk of fluid overload by including appropriate warnings and precautions. In particular:
 - i. The indication for human albumin should focus on the use of albumin to replace lost fluids i.e. 'restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate'.
 - ii. Dose recommendations should be removed from the SPC because these vary depending on the clinical situation.
 - iii. The SPC should emphasise that haemodynamic parameters should be monitored in patients receiving albumin and should warn about the risk of hypervolaemia and cardiovascular overload.

The summary of product characteristics (SPC) is the basis e.g. for the package leaflet, and describes the essential information (e.g. indications, dosage, risks, precautions) about a medi-

cinal product. In the meantime, the core SPC was revised by the CPMP and its subgroups. The text can be found on the website of the EMEA at the address www.eudra.org/humandocs/humans/bpwg.htm under the documents of the Blood Products Working Group (BPWG).

In summary, albumin will continue to be available for volume replacement, provided proper monitoring of haemodynamic parameters is carried out. The existing literature provides insufficient data, an augmentation of evidence by further controlled studies would be highly desirable.

Is There a Specific Haemostasis in the Elderly?

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Advanced age is associated with a significantly increased risk for arterial and venous thrombosis and thromboembolism. Whereas the increased risk of arterial thrombosis seems largely to be related to arteriosclerosis, the occurrence of venous thromboembolism (VTE) is most probably due to an increased prothrombotic potential either primary or related to diseases known to increase the risk of thrombosis (e.g. malignancy, heart failure). Population based epidemiologic studies revealed a VTE risk of approximately 600/100,000 in subjects 70–90 years of age. In the overall adult population the risk for VTE has been found to be 117/100,000. Studies on the coagulation system revealed increased levels of fibrinogen, coagulation factors VII and VIII and coagulation activation markers such as prothrombin fragment 1+2 and thrombin-antithrombin complex. On the other hand an increase of the coagulation inhibitors antithrombin, protein C and protein S was found, but to a lesser extent as compared to the procoagulant factors. In very old subjects (> 100 years of age) free of thrombosis a striking increase of prothrombin fragment 1+2, thrombin-antithrombin complex and D-dimer was noticed. Hormone replacement with conjugated estrogens in postmenopausal women is associated with a two- to three-fold increased risk for venous thromboembolism, but at the long term most probably with a decreased risk for arteriosclerosis.

In patients at advanced age bleeding is mostly due to underlying diseases, such as malignancy or liver impairment. The risk for development of gastrointestinal bleeding/perforation secondary to medication with non-steroidal anti-inflammatory drugs is significantly increased in the elderly (risk ratio 9.2). Data on the peri-/post-operative bleeding risk in elderly compared to younger patients are scarce. The risk seems not to be excessively increased. In patients on oral anticoagulant treatment the bleeding risk is significantly increased in those older

than 70 years (relative risk 1.75) and this increased risk has to be weighed against the increased risk for thromboembolic events in this age group.

There are certain rare coagulopathies predominantly occurring in elderly subjects that may lead to very severe and life-threatening bleeding. These coagulopathies are acquired inhibitors against factor VIII (acquired haemophilia), factor V or von Willebrand factor or severe chronic disseminated intravascular coagulation secondary to malignancy. Specific treatment modalities have to be applied in patients with these abnormalities.

Coagulation Parameters as Risk Factors

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Several coagulation variables have been evaluated as risk predictors in several types of prospective study.

1) Healthy Persons (or Persons with Evidence of Arterial Disease) in Prediction of Thrombotic Events and Mortality

Systematic reviews have established that haematocrit, viscosity, fibrinogen, von Willebrand factor (vWF) and fibrin D-dimer are independent risk factors for coronary heart disease (CHD). Positive trends are also observed for these variables in prediction of stroke or total mortality. These findings suggest that viscosity, coagulation, endothelial disturbance (vWF) and platelet function (for which haematocrit, fibrinogen and vWF are cofactors) may be important determinants of thrombosis and cardiovascular mortality. Fibrinogen, vWF and D-dimer also correlate with the trans-European gradient of CHD risk. However, causal roles of these associations remain to be established by randomised controlled trials.

The predictive value of factor VII, factor VIII, tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1), coagulation activation markers, and thrombelastography remains to be established in further prospective studies.

2) Persons with Evidence of Arterial Disease in Prediction of Thrombotic Events and Mortality after Angioplasty, Bypass Grafting or Carotid Endarterectomy

There are conflicting reports for angioplasty, and little data for endarterectomy or coronary bypass grafting. Fibrinogen, vWF and D-dimer were predictive of graft occlusion or death in one study of peripheral bypass grafting. Fibrin D-dimer also predicted postoperative myocardial infarction in one study of peripheral bypass grafting. Further studies are required.

3) Preoperative Prediction of Postoperative Venous Thrombotic Events

Reviews of preoperative prediction of postoperative deep vein thrombosis have suggested that impaired fibrinolytic potential, fibrin D-dimer, short APTT/PTT and activated protein C resistance/factor V Leiden may be of predictive value.

4) Prediction of Mortality in Patients Admitted to Intensive Care Units (ICUs)

Small studies have suggested that vWF or t-PA antigen levels may predict ICU mortality. Further studies are required.

An obvious question for discussion is: what should the doctor do for patients with coagulation variables of proven risk prediction? Give extra general care? Give selective (or intensive) antithrombotic prophylaxis? Further studies (preferably large and powerful, which will require multicentre collaboration) are suggested.

Assessment of Global Haemostasis

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Plasma screening tests are of limited value to discover suspected dysfunction in the highly complex interaction between cells and plasma factors involved in haemostasis. In general it is of great importance to supplement laboratory results with acute clinical findings and information from the patient's medical history. For assessment of primary haemostasis in vivo bleeding time is still the golden standard to be performed. The methods used, however, lack sensitivity and precision and therefore are not recommended for screening. On the other hand many clinical signs coming up during intensive care (invasive procedures, operation site) give an immediate insight into patient's global haemostasis.

Automated whole-blood methods might be additionally helpful in emergency situations due to rapid and simple measurement procedures. However, specificity and sensitivity of global methods have to be pointed out. The platelet function for example focuses platelet collagen interaction in whole blood under high shear stress conditions. In general whole-blood methods are directly influenced by all ingredients of patient's sample which makes preanalytical standardization highly important.

Global methods like whole blood thrombelastography allow in particular the monitoring of specific haemotherapy with plasma factors or cellular blood components.

In conclusion new methods for measurement of global haemostasis have been proposed and partially shown effective. Old methods like thrombelastography have been improved. The most important prerequisite for standardized measurement is easy sample handling preferentially by use of anticoagulated whole blood in easy to handle devices.

Perioperative Monitoring of the Hemostatic System

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Geriatric patients undergoing surgical procedures are at risk for development of excessive bleeding necessitating transfusion support. Although excessive bleeding can be seen in patients undergoing complex surgical procedure, this discussion will summarize cardiac surgical studies since most of the published literature has focused on this setting based on the common occurrence of bleeding. Nevertheless, much of this information is applicable to any patient that develops excessive bleeding after surgery.

Excessive microvascular bleeding can result in hemodynamic consequences necessitating volume/vasopressor resuscitation along with an increase in transfusion requirements. Transfusion of allogeneic blood or blood components is potentially associated with a number of adverse events, such as blood-borne disease transmission, increased incidence of wound infections, hemolytic and non-hemolytic transfusion reactions and increased mortality (1–5), increased operative time (6) as well as increased cost. Excessive microvascular bleeding can result in reexploration which has been shown to be associated with a variety of negative outcomes such as an increased mortality, renal failure, sepsis, atrial arrhythmias, prolonged requirement for mechanical ventilatory support and longer length of stay (3;7).

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk for microvascular bleeding requiring perioperative transfusion of blood components. Acquired defects in the hemostatic system during cardiac surgery are quite common when compared to hereditary defects. Although excessive bleeding after cardiac surgery can be related to reduced circulating levels of coagulation factors, platelet-related abnormalities are considered the most important hemostatic abnormality in this setting (8–13). Exposure of blood to the extracorporeal circuit and hypothermia leads to impairment of the hemostatic system and excessive bleeding. Stimulation of both intrinsic (14) and extrinsic (15;16) pathways results in excessive thrombin (15;17–20) and fibrinolytic (21–27) activity which can lead to consumption of platelets and labile coagulation factors (18;19;28). The risk of development of ex-

cessive, non-surgical bleeding is influenced by the type of procedure (6;29) and the duration of cardiopulmonary bypass (CPB) (3;7;11;30). The introduction and use of new inhibitors of thrombin (*e.g.*, hirudin, argatroban, dermatan, Orgaran), factor Xa (*e.g.* LMWH, Orgaran) (31–34) and platelets (*e.g.*, abciximab (35–40), eptifibatide (41;42), tirofiban) as well as new fibrinolytic agents (*e.g.*, recombinant tissue plasminogen activator) (3;7) can potentially increase bleeding and complicate clinical management. The risk of bleeding related to these agents depends on their relative potency, pharmacodynamic half-life, time interval before surgery, and whether or not a reversal agent is available. Therefore, the exact association between these new agents and either bleeding or transfusion in patients undergoing cardiac surgical procedures is currently being defined. Accordingly, numerous pharmacologic and non-pharmacologic strategies are being utilized to prevent excessive bleeding and minimize transfusion requirements.

Blood component administration in patients with excessive bleeding after CPB is generally empiric. Thus, transfusion of RBC, platelets and FFP to cardiac surgical patients requiring CPB varies considerably among institutions, in part due to prophylactic administration of FFP and platelets (43–46), despite evidence that this practice is unwarranted (47;48). This variability has also been attributed to the empiric use of blood components such as FFP and platelets, which are administered in an attempt to distinguish between excessive MVB due to hemostatic system impairment or due to surgical bleeding (49;50). Although a panel of laboratory-based screening tests can provide a rational basis for diagnosis and treatment of excessive bleeding (51), the clinical utility of laboratory tests is often limited by long turnaround time (52) so that waiting for laboratory coagulation results can potentially prolong operative time and increase blood loss. This has led many investigators to study the role of point-of-care coagulation tests in this setting with respect to optimizing management of the bleeding patient.

Point-of-care tests should help physicians establish more appropriate management of excessive bleeding by targeting blood component therapy according to identified abnormalities in the coagulation system. Secondly, rapid test results may identify patients who could benefit from pharmacologic-based interventions. Thirdly, identification of patients who have a surgical source of bleeding can be expedited if coagulation tests reveal relatively normal results in the setting of excessive bleeding. Several studies have demonstrated that use of point-of-care and laboratory-based coagulation results (*i.e.* platelet count, PT, aPTT, fibrinogen) can result in reduced transfusion requirements, shorter operative times and reduced blood loss. The first, prospective, randomized trial compared empiric treatment of microvascular bleeding in cardiac surgical patients to therapy that was administered according to a transfusion algorithm linked to rapid, POC whole blood PT, APTT and platelet results was reported (6). The algorithm-treated patients (*n*=30) received fewer blood products, had shorter

operative times and had less blood loss after treatment of excessive MVB when compared to standard, empiric therapy (n=36) (6). In this trial (6), reduced transfusion requirements and blood loss may have occurred as a consequence of prompt, optimal management of bleeding, identification of patients with a surgical source of bleeding and/or a change in the transfusion trigger (53).

The usefulness of preset criterion for transfusion was confirmed in two other recent studies which demonstrated that preset transfusion triggers based on either laboratory or POC methods can dramatically affect transfusion requirements of patients undergoing cardiac surgery (2;54). The first study compared transfusion rates between 314 consecutive patients managed with preset transfusion criteria when compared to a retrospective group of 947 consecutive patients (2). A significant decrease in the percentage of patients receiving red cells (26% vs 41%) and plasma (13% vs 24%) was observed in the treatment when compared to control patients. In addition, the percentage of patients not receiving allogeneic blood products was significantly greater in the treatment group (69%) when compared to historical controls (48%). Two other algorithms that consist of laboratory-based tests (e.g. platelet counts and fibrinogen levels) and TEG-based measurements have been developed and utilized by Spiess (54) and Shore-Lesserson (55). Both the retrospective analysis (54) and prospective trial (55) revealed that use of this approach can reduce transfusion requirements (54).

DDAVP is an arginine vasopressin analogue (ADH) that results in shortened bleeding time results (56) most likely due to a marked increase in plasma levels of large molecular weight multimers of Willebrand factor (57) that are released by endothelial cells in response to secretion of PAF by monocytes (58). In an early randomized, prospective, double-blind study, DDAVP (0.3 mcg/kg IV infusion) administered immediately after protamine significantly reduced mean intra-, and early postoperative blood loss, without any untoward effects (59). However, in several subsequent studies a consistent beneficial of prophylactic administration of desmopressin could not be shown, as positive studies (60–65) were slightly outnumbered by negative studies (66;66–71).

More recently, studies have revealed that certain patient subsets at high risk for excessive bleeding as identified by tests of hemostatic function may benefit from desmopressin (65;72;73). The first study by Czer et al. demonstrated that desmopressin is beneficial when administered to patients with excessive bleeding and prolonged bleeding times (65). Monagan et al. studied the use of TEG for risk stratification of patients when evaluating post-CPB coagulation status. Patients were also randomly assigned to receive either normal saline (placebo) or 0.3 mcg/kg of DDAVP. A post-hoc analysis divided the patients into normal or abnormal TEG groups based on TEG MA measurements. The mediastinal chest tube drainage in the placebo-treated, abnormal MA (>50 mm) patients was substantially greater when compared with normal

(< 50 mm) MA patients, indicating that TEG could identify patients at risk for excessive bleeding. Of interest, the blood loss was similar in both DDAVP-treated patients with abnormal TEG values and placebo-treated patients who had normal TEG values. These findings indicate that DDAVP can improve hemostasis in patients who have abnormal TEG and who are at risk for increased blood loss.

Two hundred and three patients scheduled for elective cardiac surgical procedures were enrolled. In another recent prospective, blinded, placebo-controlled trial which utilized the hemostatic blood products and 72 patients with normal clot ratio values, 101 patients with abnormal clot ratio values (i.e. % maximal < 60 in channel 5) after administration of protamine were randomly assigned to either placebo (n=51) or DDAVP (n=50) treatment arms. Desmopressin-treated patients had a 50% reduction in red cell (1.1 vs 2.2 U), 95% reduction in platelet (0.1 vs 1.9 U) and 87% reduction in fresh frozen plasma (0.1 vs 0.8 U) units transfused with an overall 69% reduction in total donor exposures (1.6 vs 5.2 U) when compared to placebo patients. When compared to placebo-treated patients, patients who received desmopressin also had a 39% (182 vs 297 ml), 42% (299 vs 513 ml) and 39% (624 vs 1028 ml) reduction in blood loss in the first 4, 8 and 24 postoperative hours, respectively (73).

In conclusion, use of point-of-care (POC) tests of hemostatic function can facilitate the optimal management of excessive bleeding and reduce transfusion. Accordingly, point-of-care tests that assess platelet function may also identify patients at risk for acquired, platelet-related bleeding. In addition, rapid acquisition of coagulation data can also allow physicians to better differentiate between microvascular bleeding and surgical bleeding. An ideal algorithm would encompass test systems that evaluate heparin, fibrinolysis, coagulation factor levels, qualitative and quantitative platelet abnormalities. The ability to reduce the unnecessary use of blood products and to decrease operative time or re-exploration rates has important consequences for blood inventory, and blood costs, and overall health care costs.

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Diagnostics and Treatment of Perioperative Disorders of Primary Hemostasis

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Introduction

Primary hemostasis is the first phase of hemostasis after vessel injury. The primary hemostasis is initiated by activation of the platelets. This is influenced by the blood flow, the hematocrit, the distribution of the blood cells in the blood stream, and especially the concentration and function of the platelets passing the injured vessel wall. The platelets are activated by the exposed collagen fibers and additionally by ADP released from the endothelia cells. The activated platelets bind via von Willebrand factor (vWF) to the subendothelium and release a variety of substances that enhance the whole process by including further platelets passing with the blood stream, thus causing platelet aggregation and formation of the platelet plug which is the reaction platform for the further coagulation (secondary hemostasis).

Perioperative Disorders of Primary Hemostasis

The following disorders of the primary hemostasis perioperatively have to be considered (roughly ordered by frequency):

Hemodilution (blood loss)

- ASA, NSAID, ticlopidine, antibiotics, inhibitors of GP IIb/IIIa, etc.
- Hypothermia
- Hypersplenism
- von Willebrand disease (vWD, 1–2%)
- Extracorporeal circulation
- Heart valves
- Uremia
- Liver failure
- Fibrinolysis
- Bone marrow hypoplasia
- Inherited platelet disorders

When examining patients with a bleeding history more extensively, the majority shows disorders of the primary hemostasis (Kussmann, personal communication). On the other hand, one has to consider that not all patients with platelet function disorders have a bleeding history until their first surgical exposure. This is particularly true in latent vWD that can be found in 1–2%. These patients often have no bleeding history as long as no further factors are effective to impair the primary hemostasis, e.g. platelet inhibitors and/or large blood loss. Therefore, at least before large or more complicated operations screening tests on the primary hemostasis are necessary.

Diagnostic Methods

The diagnostic methods to examine primary hemostasis include platelet count, in vivo bleeding time, TEG and several modifications of it as the resonance thrombography or the so-called rotation thrombelastogram (roTEG, Nobis, Endingen, Germany), the Platelet Function Analyzer (PFA-100), the standardized in vivo bleeding time (e.g. Simplate time) and the platelet aggregation test. The bleeding time shows high variability, low reliability and only little sensitivity even in the hands of experienced persons. The roTEG is less sensitive to shock than the classic TEG, uses electronic data processing and has the clear advantage to give conclusive and more specific results in at least half of the time the classic TEG needs. Latter is achieved by the use of inducers like thromboplastin and partial thromboplastin. Furthermore, aprotinin, heparin or antibodies against GPIIb/IIIa receptor may be added in order to distinguish between the various underlying disorders. The platelet function analyzer PFA-100 is generally available since a few years. We use this method of in vitro bleeding test routinely already since more than 10 years. The PFA-100 very closely simulates the primary hemostasis and is not influenced by plasmatic disorders or heparin. The platelet aggregation test is the most sensitive test, but represents no routine test.

Studies

Recently we started a study on various hemostatic disorders: Hypofibrinogenemia with or without hyperfibrinolysis ($n = 24$), complex deficiencies of plasmatic coagulation factors especially due to coumarin uptake ($n = 13$), isolated thrombocytopenia ($n = 30$), platelet function disorders ($n = 63$; vWD 28, storage pool disease 10, drugs/ASA 11, unspecified thrombocytopathia 14), other hemostatic disorders ($n = 33$), healthy donors ($n = 39$) and patients without hemostatic disorders ($n = 33$).

The preliminary results show a rather good correlation of the maximal amplitude in the roTEG to the platelet counts. Perioperatively relevant thrombocytopenia ($\leq 50,000/\mu\text{l}$) mostly was indicated by significant narrowing of the maximal amplitude in the InTEG (partial thromboplastin as inducer). The sensitivity of the roTEG regarding thrombocytopenia was almost comparable to the PFA-100 (with epinephrine and ADP): Platelets $\leq 100,000/\mu\text{l}$ 59.4% vs. 78.3%, $\leq 50,000/\mu\text{l}$ 92.3% vs. 84.6%, $\leq 20,000/\mu\text{l}$ both methods 100%. On the other hand, thrombocytopenia can be determined much easier, quicker and more reliable with less cost by counting.

However, platelet function impairment is a major problem for surgery with respect to detection and treatment. 90% of the patients had a pathological platelet aggregation test, but only 31.3% had significant alterations of the roTEG. RoTEG particularly failed in patients taking ASA. PFA-100 clearly proved to be superior in regard to platelet function disorders (57.9%). This is in line with our previous data showing high sensitivity of the PFA-100 (with epinephrine) in the detection of vWD [1, 2]. The Simplate bleeding test failed in 3 of 10

moderate forms (vWF 5 to 25%) of vWD and in 5 of 7 mild forms (vWF 25 to 45%) in contrast to the PFA-100 that was able to detect all of them. 4 h after ingestion of a single dose of 100 mg ASA 50% of the test persons ($n = 30$) showed significantly prolonged closure time (CT) of the PFA-100 (epinephrine) [3]. After ingestion of 100 mg ASA at 3 consecutive days even more than 80% showed abnormal CT.

Treatment of Disorders of Primary Hemostasis

Disorders of primary hemostasis often are artificial. Even in case of inherited platelet disorders manifest bleeding complications often only occur when further factors impair primary hemostasis. Therefore, the application of platelet inhibiting drugs before and shortly after surgery should be avoided or stopped in time. Platelet transfusion mostly can be restricted to thrombocytopenia. Most disorders of primary hemostasis due to impairment of platelet function can be successfully treated with desmopressin alone or in combination with antifibrinolytics. Even in mild thrombocytopenia (40 to 80,000 platelets/ μl) platelet transfusion sometimes can be prevented or delayed by administration of desmopressin. Desmopressin is used in a dose of 0.2 to 0.3 $\mu\text{g/kg}$ BW i.v., diluted in physiological saline solution, infused during 30 min about 60 to 90 min before operation. It is necessary to keep this time schedule, because the peak of the efficacy by release of vWF from the endothelial cells is reached at this time. If necessary, the application can be repeated every 12 h. However, the effect decreases because of the limited stores. Dose, frequency and duration of treatment should be dependent on the operation and the efficacy. Concerning the limited stores tests on efficacy should never be performed later than a week before surgery. Desmopressin has some fibrinolytic effect which may be disadvantageous in situations with tendency to generalized or localized fibrinolysis, e.g. in cardiac, oral and urogenital surgery. Then the combination with low dose antifibrinolytics (e.g. aprotinin 100,000 IU/h) is recommended. On the other hand, particularly in these cases antifibrinolytics alone can be even successful. Finally, increase of the hematocrit by red cell transfusion also may improve primary hemostasis.

Therapy Control

Treatment of disorders of primary hemostasis should be controlled before surgery. This is particularly requested when using desmopressin and/or antifibrinolytics. PFA-100 has proven to be suited for therapy control (fig. 1 and 2) [4-6].

Conclusions

Most hemostaseological perioperative bleeding problems arise from disorders of primary hemostasis. According to detection and treatment, functional platelet disorders are a greater problem than thrombocytopenia. Therefore, routine screening tests on primary hemostasis are even more important than those usually performed on plasmatic coagulation. Platelet count and PFA-100 with epinephrine allow sensitive

Fig. 1. Desmopressin (DDAVP) effect in 7 cases of vWD documented by PFA-100 (collagen/ADP)

Fig. 2. Desmopressin effect in 9 patients with ASA induced platelet function impairment

and specific detection of disorders of primary hemostasis. Furthermore, they are well suited to document the therapy effect. This is particularly important when alternative therapeutic means are administered as desmopressin and/or antifibrinolytics. Adequate use of these drugs can considerably reduce the need of platelet transfusion and prevent bleeding complications.

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Coagulation Disorders and Treatment: Drug Interactions

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Avoiding to compromise blood coagulation is a crucial aspect in our attempts to minimize, if not eliminate transfusion of allogeneic blood and blood products in the perioperative care of surgical patients¹. Thereby, we need to maintain normothermia, choose the fluid replacement adequately and may use specific drugs supporting blood coagulation in certain operations (table 1). In addition, it has been suggested to maintain a hematocrit of 30–35% in order not to compromise blood coagulation². This, however, cannot be supported based on scientific evidence³.

Normothermia

Prospective randomized studies indicate that avoiding hypothermia reduces blood loss and allogeneic RBC transfusions, decreases postoperative infections and shortens hospitalization^{4, 5}. In patients during total hip replacement, blood loss and allogeneic RBC transfusions were less in normothermic than in mildly hypothermic (35.0 ± 0.5 °C) patients⁶. Maintaining normothermia is beneficial because hypothermia compromises blood coagulation, in particular platelet function^{7–9}.

Fluid Replacement Therapy

Maintaining normovolemia in the perioperative period is of paramount significance¹⁰. Therefore, significant amounts of replacement fluids are necessary during operations with relevant blood loss, in particular when preoperative acute normovolemic hemodilution (ANH) is being performed. The choice of replacement fluid therefore becomes critical to compromise blood coagulation as little as possible.

Table 1. Measures to maintain perioperative blood coagulation

1. Maintain normothermia
2. Utilize a fluid therapy based on crystalloids
If colloids are needed, avoid large-molecular weight HES and use gelatin or low-molecular weight HES
3. Consider using aprotinin, tranexamic / e-amino capronic acid and desmopressin in selected patients in cardiac and major non-cardiac surgery HES = Hydroxyethyl starch.

During ANH, red blood cells as well as coagulation factors and platelets become diluted¹¹. It is therefore understandable to intuitively assume that blood coagulation becomes progressively compromised as well. This, however, may not be correct. It has been demonstrated that a 25% and 30% in vitro hemodilution with crystalloids may in fact accelerate blood coagulation, as assessed by thrombelastography^{12–13}. This was also observed in vivo^{14–16} and may be related to an over-proportional reduction in antithrombin III¹⁶. Moderate crystalloid ANH thus may accelerate rather than inhibit blood coagulation. Eventually, with advanced crystalloid ANH blood coagulation may become compromised but blood coagulation, will not be compromised by an isolated reduction of the hematocrit alone (40% to 10%)³.

In contrast, if colloids are being used during ANH, some degree of compromised blood coagulation is observed in most studies^{13, 17, 18}. In general, gelatin has a moderate effect, similar to using human serum albumin^{13, 17} or may even accelerate blood coagulation^{12, 19}. As a result, perioperative changes in hemostasis were found to be similar in hemodiluted and non-hemodiluted patients undergoing major orthopedic surgery when volume replacement was performed with a combination of gelatin and Ringer's lactate^{19, 20}. In contrast, even medium molecular weight (200 kDa) hydroxyethyl starch (HES) compromises coagulation significantly^{13, 17, 18}, and high molecular weight (450–480 kDa) HES compromises blood coagulation even more¹⁸. In contrast, low molecular weight HES (70 kDa) may compromise blood coagulation less than medium molecular weight HES²¹. A combination of generous amounts of crystalloids with some colloids thus may be optimal to maintain blood coagulation, and to avoid incremental blood loss due to coagulopathy offsetting the efficacy of other blood conservation strategies.

Specific Drugs for Selected Patients and Operations

The prophylactic use of aprotinin, ε-aminocaproic acid and tranexamic acid reduce allogeneic blood transfusions in cardiac surgery^{22–26}. Initial concerns that aprotinin might cause an increase in graft occlusion rate or myocardial infarction have been recently found to be unjustified^{24, 25, 27, 28}. In selected patients following cardiopulmonary bypass also desmopressin may improve blood coagulation resulting in a decreased transfusion need²⁹.

Aprotinin may also be used in non-cardiac operations such as in liver resections³⁰ or major orthopedic surgery^{31, 32} to reduce blood loss and thus to decrease allogeneic RBC exposure^{30, 32}. Furthermore, tranexamic acid has been successfully used in total knee arthroplasty to decrease allogeneic RBC transfusions³³. There are, however, also reports that allogeneic RBC transfusions were not decreased with prophylactic antifibrinolytic therapy despite antifibrinolytic efficacy^{34, 35}. The uncritical prophylactic use of antifibrinolytics in major non-cardiac operation thus may not be advisable due to an uncertain efficacy and extra costs²².

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Novel Applications of Recombinant Factor VIIa: The Effect of the Administration of Recombinant Activated Factor VII (NovoSeven) on Perioperative Blood Loss in Patients Undergoing Transabdominal Retropubic Prostatectomy: The PROSE Study

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Background

Bleeding in patients with hemophilia A and B is normally treated by supplementation of factor VIII and IX, respectively. However, in some patients, antibodies against factor VIII or factor IX abolish the hemostatic effect of the coagulation factor concentrates. In these patients, alternative treatment is required. A similar situation occurs in previously healthy subjects who develop auto-antibodies towards factor VIII or another coagulation factor (acquired hemophilia). Based on the present knowledge of the initiation of coagulation in vivo, it seems logical that such strategies are aimed at factor VIIa. Indeed, the first evidence that factor VIIa might actually play a key role in a new treatment strategy for hemophilic patients with inhibitors, was provided in 1983 by Hedner et al. who demonstrated efficacy of treatment with purified human FVIIa in two patients with hemophilia and a high-titer in-

hibitor who experienced bleeding. Based on these findings, recombinant coagulation factor VIIa (NovoSeven®, Novo Nordisk, Denmark) has been developed. In 1988, a patient with severe hemophilia A with a high-titer inhibitor underwent an uncomplicated synovectomy of the knee covered under rFVIIa, in combination with tranexamic acid. Since this first clinical use, several clinical studies and case reports have established the efficacy of rFVIIa for control of more than 2,400 bleeding episodes from various sites in more than 500 patients with hemophilia, most of whom had inhibitors to factors VIII or IX. As a consequence, NovoSeven is currently registered for treatment of bleeding and as prophylaxis during perioperative periods in hemophilic patients with inhibitors to factor VIII or factor IX.

The mechanism of action of rFVIIa has been a matter of extensive debate over the last years. Recent insights in the mechanism of the coagulation cascade have revealed that the process of hemostasis is initiated by the complex formation between activated factor VII (FVIIa) and tissue factor. Based on this new insight, a possible mechanism of action of rFVIIa has been proposed and consists of complex formation between tissue factor and recombinant FVIIa at sites where tissue factor is exposed, such as damaged vessel walls during surgical procedures. Subsequently, the tissue factor/rFVIIa complex generates thrombin by activation of both factors X and IX in the presence of activated platelets. This process appears to induce only local thrombin generation, since TF and anionic phospholipids do not normally circulate in the plasma. Moreover, the rFVIIa-mediated thrombin generation is probably short lasting due to the relatively short plasma elimination half-life of rFVIIa. Besides the extended experience with the use of the product in hemophilic patients with inhibitors, NovoSeven has also been applied to patients with other (non-hemophilic) bleeding disorders. Recent case reports have described successful treatment with NovoSeven of patients with bleeding episodes due to non-hemophilic coagulopathies such as Glanzmann thrombasthenia, factor VII deficiency or von Willebrand disease. The use of recombinant factor VIIa in patients without coagulation disorders, however, is limited to a small number of patients who experienced life-threatening bleeding due to trauma, that could not effectively be treated with conventional therapy. Based on the proposed mechanism of action of NovoSeven in which the product exerts its hemostatic function only at sites where tissue factor is exposed, we hypothesize that NovoSeven might induce a short lasting local hemostasis at sites where bleeding occurs. The present study was designed to provide the first proof of concept that recombinant factor VIIa might be applied in a safe and efficient manner to patients without preexisting coagulation disorders, but who experience major blood loss due to surgery.

Retropubic prostatectomy is a commonly performed surgical procedure for patients with localized prostate cancer or enlargement of the prostate due to other diseases like benign

prostate hypertrophy. Despite refinement in technique and greater surgical experience, retropubic prostatectomy remains associated with major perioperative blood loss and the need for blood transfusion. The administration of allogeneic blood and blood products still may be complicated by serious immunological or infectious complications. We hypothesize that improvement in the function of blood coagulation during prostatectomy might reduce the perioperative blood loss and number of blood transfusions needed. Recombinant activated factor VII may induce such a prohemostatic effect and has, as said before, been shown to be an effective and safe approach in (bleeding) patients with coagulation defects. The aim of the present study is to evaluate the effects on blood loss and number of blood transfusions needed after a single bolus infusion of rFVIIa in patients without a coagulation disorder undergoing retropubic prostatectomy. Furthermore, we investigate whether the administration rFVIIa contributes to an efficient and safe hemostasis in these patients

Patients and Methods

The study is currently performed as a randomized, double-blind, placebo-controlled, dose-escalation single center trial. A total number of 36 patients will eventually be included. Patients who meet the inclusion criteria will be randomized to 2 different dose level groups and receive either rFVIIa as a single bolus intravenously or saline. The dose level in the two groups will be 20 and 40 µg rFVIIa per kg body weight, respectively. At each dose level, a 2:1 randomization scheme will be applied (rFVIIa versus placebo). Perioperative blood loss will be assessed by measuring the volume of blood in suction containers, drains and as additional blood loss. Furthermore, the number of blood transfusions needed during and after surgery will be assessed.

During and up to 7 days after the operation, blood samples will be taken for assessment of coagulation parameters and hemoglobin levels. Further treatment will be completely according to standard care, including postoperative prophylactic administration of low molecular weight heparin. In the postoperative period of 7 days, daily history and physical examination will be performed, as well as electrocardiography. One week after the operation, a venous ultrasound of both legs will be performed. During the entire study period, (non-)serious adverse events will be monitored. If adverse events occur, appropriate action will be performed immediately.

Results

The trial is currently ongoing. Up until now, a total of 34 consecutive patients have been screened for participation in the study. Of these, 8 patients were not included in the study for the following reasons: patient refused to participate: 4; cancelled operation due to hypertension: 1; metastasized prostate carcinoma discovered during surgery: 1; and angina pectoris, class IV, 2 patients. A total of 26 patients have been included in the study. 10 patients underwent radical prostatectomy; 16

Fig. 1.

patients underwent a prostatectomy according to Millin. Blood loss varied between 630 ml and 4,455 ml, with a mean of 1,766 ml. An interim analysis was performed after the 24th patient by the independent safety committee that was not directly involved in the study. A positive trend was seen between the two different treatment groups. This trend, however, was not statistically significant, due to the small number of patients. Figure 1 represents the volume of mean blood loss expressed in ml per patient, subdivided to type of treatment. The mean total volume of blood loss was circa 1,400 ml in patients that were treated with NovoSeven versus 2,400 ml in placebo-treated patients. The number of blood transfusions in all patients varied between 0 and 4 units per patient with a mean of 0.7 units. In the placebo-treated patients, the mean number of blood transfusions was 1.8 per patient, whereas a mean of only 0.4 blood transfusions was given in patients who received NovoSeven. In the peri- and postoperative period, none of the patients developed complications such as venous thromboembolism. The average hospital stay was 13 days (range: 9–28 days) and was not influenced by the type of treatment.

Conclusion

The present study represents the first randomized clinical trial in which the safety and efficacy of recombinant factor VIIa is being evaluated in patients without preexisting coagulation disorders who undergo surgery associated with significant blood loss. Treatment of patients undergoing transabdominal retropubic prostatectomy with a single bolus injection of recombinant factor VIIa, (NovoSeven), seems a safe and effective method to decrease the number of blood transfusions and volume of perioperative blood loss. However, the study represents only a small number of patients. Therefore, more patient data are needed before definite conclusions can be drawn. Furthermore, larger multiple-center trials concerning other types of patients and other types of surgery are needed to provide additional data concerning the efficacy and safety of recombinant factor VIIa treatment in patients without preexisting coagulation disorders who experience bleeding. Hopefully, the final results of the present study will be available at the end of 2000.

Cerebral Complications from Perioperative Coagulation Disorders in the Elderly – Can We Predict the Risk?

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Neurological complications constitute a potentially significant peri- and postoperative risk of major surgical procedures. This risk is especially prevalent in the elderly patient. Evolving deficits of the central nervous system (CNS) may consist of diffuse and/or focal symptoms. Cerebral infarction from ischemia and bleeding into the brain parenchyma are the most frequent causes of focal symptoms like hemiparesis, hemihypesthesia, hemianopsia or aphasia. Usually such deficits are readily recognized. Seizures can result from both focal and diffuse damage to the brain. Neuropsychological disturbances appear to be the most frequent complication following major surgical procedures. They are readily recognized in the presence of reduced alertness, disorientation and confusion. However, subtle deficits in domains such as attention, speed of mental processing or memory may go undetected or can be substantiated only by detailed neuropsychological testing. The term *postoperative cognitive dysfunction (POCD)* has recently been coined for such disorders which appear to be a consequence of rather diffuse impact on the brain although the exact damaging mechanisms frequently have not yet been identified.

The frequency of both focal and diffuse peri- and postoperative complications of the CNS varies largely with the type of surgical procedure. A large multicenter study on the incidence of POCD in 1,218 patients ≥ 60 years reported a 25.8% frequency at 7 days after major abdominal, noncardiac thoracic or orthopedic surgery [1]. At 3 months, the frequency of POCD was still 9.9%. Reports on patients undergoing cardiac surgery such as coronary artery bypass grafting report an incidence of neurobehavioral changes of up to 85% at 1 week after the operation and in one study, some deficits were still detectable in 35% of operated patients even after 3 years [2]. Fortunately, the risk of major focal neurological deficits is much lower. The International Study on POCD gives a stroke complication rate far below 1% for major noncardiac surgery even for an elderly population [1]. The incidence of postoperative stroke in large recent series of patients undergoing cardiac surgery ranges from 1.4 to almost 10% [2]. In part, these differences in stroke rates are related to the various surgical procedures, e.g. mitral valve replacement has been shown to carry a higher stroke risk (3.2%) than coronary artery bypass-grafting (2.9%) or aortic valve replacement (1.8%). An even higher rate was observed following combined procedures [3]. Differences in patient selection and demographics also need to be considered in the comparison of individual study data. Altogether, the absolute number of postoperative strokes re-

ported may also underestimate the true rate of focal ischemic events because of the limited sensitivity of the clinical examination.

Searching for predictive variables of CNS complications various etiologic mechanisms and the contribution of demographic and clinical factors have been considered. All studies agree on a strong impact of age concerning neurological complications. Risk rates are further increased by comorbidity [4]. Especially all evidence for or indicators of pre-existing cerebrovascular damage indicate a higher risk of CNS complications. This evidence may be gained by the patient's history of a previous stroke, imaging findings of the brain consistent with infarcts, lacunes and extensive ischemic white-matter damage or vascular examinations which reveal higher grades of atherosclerosis [5]. The presence of known cerebrovascular risk factors such as hypertension, diabetes mellitus or atrial fibrillation also contribute to the frequency of perioperative neurological complications [4]. The specific risk of various surgical procedures especially in regard to intervention-related embolism deserves special attention. Cerebral embolism during the surgical procedure appears of major importance during some procedures such as cardiopulmonary bypass [2]. Such microembolism detected by continuous transcranial Doppler-sonographic monitoring has been related primarily to specific stages of cardiopulmonary bypass and the probability of neuropsychological dysfunction postoperatively was shown to increase with the number of embolic signals detected. New therapeutic strategies are discussed to reduce this risk [2]. Doppler-sonographic evaluation for atherosclerotic changes of the aorta and of the carotid arteries before and during surgery may also help to reduce embolism. Magnetic resonance angiography appears to be another technique which should be successfully used for such purpose in the future.

While multiple factors that increase the frequency of peri- and postoperative neurological complications of the CNS have already been identified there exists much less knowledge on how hemostatic factors might contribute to or precipitate such events. The optimal peri- and postoperative management of hemostatic factors in regard to CNS complications is also largely unknown. Future studies should address these issues especially in high risk patients. Modern morphologic imaging techniques such as diffusion-weighted magnetic resonance imaging may not only serve to identify such patients but should also help to increase our ability to define surgery-related brain changes with high enough sensitivity and specificity.

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Quality Management of Clinical Transfusion Practice

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Introduction

In a meeting of European experts held near Vienna in 1998 ⁽¹⁾ the following definition of quality management was agreed upon: 'Quality management is the sum of activities that together ensure the effective functioning of a quality system. It is an umbrella term that encompasses quality system development and implementation; quality assurance, good manufacturing practice and quality control; and continued quality improvement'. In this general definition no mention is made of patients, blood or transfusion, but the concept of quality can be applied also to the transfusion process, thus creating a link between quality management and blood transfusion. In a similar meeting held in Wildbad Kreuth in 1999 ⁽²⁾ the following definition of quality for blood transfusion was agreed upon: 'Quality in the clinical use of blood products implies administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of both the process and the outcome'.

If these implications were always satisfied there would be no need to introduce quality management of clinical transfusion practice, but everybody is now aware that the administration of the wrong quantity, or of the wrong blood product, or in the wrong way, or to the wrong patient, and lack of documentation are measurable events that affect negatively the outcome of the patients and the quality of healthcare.

The SANGUIS study, carried out in the early 1990s ⁽³⁾, was seminal in showing that there is a significant variability in the use of blood products in comparable clinical situations, which implies both overuse, entailing waste of resources as well as unnecessary risks for patients, and potential underuse. Another problem highlighted by the SANGUIS study is lack of documentation, entailing the absence or unavailability of data related to the process, needed for traceability of products and accountability of operators, and related to the outcomes, needed for the evaluation of effectiveness and safety (haemovigilance, pharmacovigilance).

More recently, the annual reports of the Serious Hazards of Transfusion (SHOT) scheme have spotted a very high rate of

mistransfusions among the severe adverse events reported to the British surveillance system ⁽⁴⁾; and the risk of mistransfusion, whether ABO incompatible or not, is currently estimated to be three times the aggregate risk of transfusion-transmitted HBV, HCV and HIV infections ⁽⁵⁾.

While overuse and underuse are related to deficiencies both in the definition of guidelines for optimal use and in their dissemination, misuse and lack of documentation are related to deficiencies in the organisation of the system. In other settings the implementation of a quality management system has proven to be a successful solution to these kind of problems. Quality management systems are now widely used in the pre-clinical phase of the blood transfusion process, i.e. in the collection and preparation of blood and blood components, and have greatly contributed, along with the introduction of more sensitive [and expensive] tests, to achieve high standards of quality and safety in blood units made available for transfusion, so that lack of quality in their use is unacceptable.

For all these reasons there is a strong need to provide a quality management system also to the clinical part of the blood transfusion chain, to close the loop. This need has been addressed during the meeting held in Wildbad Kreuth in May 1999, and the following paragraphs are a condensed version of the conclusions and recommendations issued by the convened experts ⁽⁶⁾.

Requirements for Establishing a Quality Management System

The establishment of a quality management system for the clinical use of blood products first requires the commitment of administrators and decision-makers since only with their support can the necessary human and economic resources be made available.

In many member states of the European Union, Hospital Transfusion Committees, comprising representatives of clinical specialities involved in the use of blood products, nurses, blood transfusion service, pharmacy, administration and eventually patients' representation, have been established, but they suffer usually of lack of power and have a poor impact on clinical transfusion practice.

A local quality manager for the clinical use of blood products, with responsibility for the implementation of the system and empowered to take the appropriate actions to ensure and improve quality, needs to be identified. The quality manager should be supported by the Hospital Transfusion Committee. Accepted standards for the use of blood products, which define the quality in terms of appropriateness, need to be made available. In many areas, such as the use of red cells in the surgical setting and the use of albumin, scientific evidence as regards the indications and non-indications are still lacking. This presents many difficulties in evaluating both appropriateness and efficacy and controlled studies to resolve these issues are urgently needed.

Finally, the implementation of a quality management system needs the strong co-operation and commitment of all opera-

tors involved in the process, such as clinicians, nurses and other healthcare providers.

Tasks and Responsibilities

The main tasks and responsibilities of the quality manager and the transfusion committee are:

- a) ensuring compliance with regulations;
- b) adapting, adopting and updating guidelines;
- c) defining standard operating procedures (SOPs), mandatory for healthcare personnel;
- d) disseminating adopted guidelines and SOPs;
- e) verification [internal audit] of the compliance to guidelines and SOPs;
- f) evaluating effectiveness and safety (haemovigilance);
- g) providing feedback to clinicians;
- h) conducting problem-oriented quality assurance.

Some of these tasks [c) to f)] have been analysed more in detail, with the following conclusions reached.

Definition of SOPs

While standard operating procedures should cover all steps in the process, the following are of particular relevance for ensuring quality in the clinical use of blood products:

- 1) blood sampling for pre-transfusion testing, focusing on identification of the operator, the patient and the samples;
- 2) patient's information, both before and after transfusion;
- 3) administration of blood products;
- 4) home transfusion;
- 5) follow up of transfusion;
- 6) management in case of adverse events;
- 7) emergency procedures;
- 8) collection of autologous blood;
- 9) handling of unused units;
- 10) storage of blood products outside the blood bank;
- 11) documentation of the above described steps and outcomes.

In defining SOPs, particular attention should be given to preventing transfusion errors, re-engineering the process, and introducing, if possible, information instruments, such as portable barcode readers, to assess the identity of the patient, the blood samples and the assigned unit.

Dissemination of Adopted Guidelines and SOPs

It is common experience that paper guidelines do not turn into installed guidelines simply by their distribution. Education of involved healthcare professionals, such as clinicians and nurses, through courses in transfusion medicine, should follow the definition of guidelines and SOPs. University courses should include transfusion medicine in order to educate clinicians in the optimal use of blood products.

More sophisticated means of dissemination can also be taken into consideration, such as the adoption of request forms with algorithms for appropriate use of blood products.

The most advanced and effective means of education is provided by computer reminders: the physician in the ward enters the request in a computerised programme, with pre-established algorithms, that guides the clinician to comply with the accepted guidelines, or asks for additional clinical reasons to override them. This approach has the advantage of providing also an online documentation, but can be implemented only in case an integrated hospital information system has been put in place.

Verification of Compliance with Guidelines

There are two ways to verify the compliance with the accepted guidelines: retrospective audit and concurrent audit:

Retrospective audit is based on the collection and statistical analysis of data related to the utilisation of blood products and to the outcome. Indicators should be agreed upon a national or at least regional level, in order to make possible a comparison between different hospitals. This is the most feasible approach, but its impact in improving clinical practice, based on a feedback to the clinicians, is delayed.

Concurrent audit is based on a 'second opinion' at the time of issuing the request of blood products and its impact in improving clinical practice is immediate, preventing inappropriate use. The 'second opinion' can be given either in the clinical ward by a clinician in charge of auditing all non-urgent blood requests, or by the transfusion service receiving the request. There are examples of both solutions (^{7, 8}): the first solution avoids conflicts between the clinicians in the wards and the staff of the transfusion service and contributes to the dissemination of the guidelines; the second solution can be realised by means of a computerised audit of blood request in the transfusion service and has the advantage of facilitating the collection and analysis of data related to optimal use. In any case, the indications for the use of blood products need to be documented on the request form.

Evaluation of Effectiveness

Once compliance with the guidelines has been achieved and documented, data on the outcomes can be used not only to verify their appropriateness and contribute to their improvement but also to carry out cost analysis of different strategies. Parameters to evaluate the efficacy of the blood products used, however, have to be defined and the collection of data needs to be facilitated without burdening clinicians with copying information that should already be in the medical records.

Conclusions

Quality management systems have been widely and successfully used in the industry to ensure and improve the quality of both the process and the products. These systems have been also applied to the collection and preparation of blood and blood components, so that their extension to the clinical transfusion process would complete their coverage of the blood transfusion chain and maximise their benefit for the patients.

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Health Economics and Use of Blood and Blood Products

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The use of health economics offers assistance to health care decision makers in the appropriate allocation of resources in the review of existing as well as the consideration of new health technologies. Health economics can thus offer guidance on the prioritisation of competing technologies by consideration of the costs and consequences of therapeutic decision making. In a limited economy once a decision has been made to use a health care technology then the resources cannot be reused. The value of this decision is represented by the resources which might have been allocated to another treatment. This is known as an *opportunity cost*.

Consideration of the clinical and socio-economic aspects of the use of blood and blood products within the EU was recently made at a multidisciplinary forum at Wildbad Kreuth¹. The European Union (EU) spends many million Euros each year on the collection, processing and use of blood and blood products. However this does not include the economic consequences of underuse, overuse and misuse. In addition it does not address the wider economic consequences of the use of these products which might include unwanted effects, loss of productivity and humanistic suffering which contribute to a lower quality of life.

Resources are scarce, and there is evidence of marked variations in practice within the EU and the less than optimal use of these products in certain areas. The high cost of some products can place burdens on the economies of some countries. Improving health care technologies can create cost demands

in the areas of safety, diagnosis and use. Justification for the allocation of scarce resources should be made after careful consideration of the clinical and economic assessments of such developments.

Economic evaluations can be viewed from a number of different perspectives: societal, payer, or provider. Most authorities consider the societal perspective to be the most important. It is important that whichever perspective is considered there is the ability to move resources between the various budgets.

In order to plan for the future needs of the EU and to ensure that current usage is supported by a strong evidence base there is a requirement to understand how and why these products are used. A number of recommendations were made at Wildbad Kreuth:

- The epidemiology of need of these products should be assessed in the EU by determining the likely number of units which ought to be required in the general population.
- The actual number of units of each product used for the treatment of patients should be recorded for each Member State on an annual basis.
- Consideration should be made for a linkage between the usage and clinical conditions for which products are being used. This might be optimally achieved by the use of automated databases, the use of electronic patient records and electronic prescribing.
- Utilisation reviews should be conducted on both a clinical and economic basis in order to determine the nature of usage, to enable whether this is appropriate and the effect of education programmes.
- Indicators should be developed to reflect optimum usage of these products.

A proposal for the undertaking of a series of economic evaluations linked to effectiveness studies was made. These included:

- A review of current publications.
- The optimal size of blood collection-processing-distribution services.
- A review of each Member State's unit costs of blood and blood products and the method for calculation.
- The use of recombinant vs plasma derived clotting factors.
- The use of primary prophylaxis of clotting factors in children and adults.
- The optimal use of PCR testing of blood and blood products.
- Leucodepletion of red cells vs buffy coat-free red cells.
- The overall economic implications of the failure of not using blood and blood products in an optimal fashion.

It is recognised that there are changes in the relative use of plasma derived albumin, immunoglobulins, factors VIII and IX. This will have important consequences on the costs and availability of these products in the future. In order to assess this need it was recommended that a forecast for the future needs of these individual products needs to be undertaken and an assessment of the economic factors which will determine the viability of collection and fractionation centres conducted.

In addition it was felt that consideration should be made to the rational distribution of these centres throughout Europe and the dependency and commercial viability of production sources.

In order to ensure that rational use of these products was promoted the educational needs of clinicians and health care decision makers in both health economics and the rational, safe and cost effective use of blood and blood products should be addressed. This could be achieved by undergraduate and post registration education and training of the various groups of clinicians who use these products. Additionally methods for the optimal impact of recommendations should be investigated.

The group encourages the use of economic tools and arguments for improving the efficiency of blood resourcing and optimal use while maintaining the principles of voluntary non-remunerated donations.

In the view of the continuing development of the EU the principle and the need of self sufficiency of products throughout Europe should be re-assessed in the context of safety, availability, ethics and economics.

It is recognised that the unwanted effects of medicines can contribute considerably to the morbidity of patients within society. The elderly as a group suffer from a disproportionate high number of adverse effects. In the UK studies have shown that up to 19% of elderly admissions to hospitals may be due to inappropriate drug therapy² and up to half of these might be preventable³. The economic burden associated with drug

related morbidity and mortality has been estimated to be at least \$30 billion annually⁵.

One of the ways by which the use of transfused blood can be reduced and with it the attendant risks of transmission of infective agents is by pre-operative autologous blood transfusion using epoetin alpha. A recent meta-analysis of 5 randomised trials demonstrated the ability of epoetin alpha to reduce the use of allogeneic blood transfusions during cardiac surgery⁴. However two studies of the economic analysis of the use of pre-operative autologous blood transfusion using epoetin alpha in orthopaedic surgery and cardiac surgery did not demonstrate that these were cost effective interventions^{6,7}.

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