Transfusion-Associated Immunomodulation: Experimental Facts and Clinical Reality – New Perspectives

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Key Words

Blood transfusion · Infectious complications · Cancer recurrence · Immunomodulation · Leukofiltration · Gene polymorphism

Summary

Blood component transfusion may be required in association with emergency and chronic disease to improve hemodynamics and tissue oxygenation. Due to the risk of microbial transfection from donor to recipient, the blood is undergoing vigorous testing to improve safety. It is well known, however, that blood component transfusion may lead to certain acute side effects with a frequency of 0.5–2% depending on the specific component transfused. In addition, homologous blood component transfusion seems to be associated with increased frequency of bacterial infectious complication after operation in a variety of diseases. If patients have been operated on for malignant diseases, emerging evidence has accumulated that suggests a combination of blood component transfusion, postoperative bacterial infectious complications and subsequent poor long-term survival even in patients who have been curatively resected. The mechanisms leading to such side effects are not known in detail, but bioactive substance accumulation during preparation and storage may play an important role. Such substances may also explain why side effects are also observed after autologous blood transfusion. Institution of universal leukofiltration in most European countries has led to improvement in patient treatment, with reduction of a variety of side effects. Future research should be focused on patient genetic polymorphisms that may play a role in the development of side effects to blood component transfusion.

Schlüsselwörter

Bluttransfusion · Infektiöse Komplikationen · Tumorrezidiv · Immunomodulation · Leukofiltration · Genpolymorphismus

Zusammenfassung

In der akuten und chronischen Krankheitssituation kann eine Blutkomponententransfusion erforderlich sein, um die Hämodynamik und die Gewebeoxygenierung zu verbessern. Um eine mikrobielle Transfektion vom Spender zum Empfänger zu vermeiden und die Transfusionssicherheit zu verbessern, wird gespendetes Blut einer intensiven Prüfung unterzogen. Allerdings führt die Blutkomponententransfusion in 0,5–2% der Fälle – abhängig von der transfundierten Komponente – zu akuten Nebenwirkungen. Darüber hinaus scheint die homologe Blutkomponententransfusion bei einer Reihe von Erkrankungen die Häufigkeit des Auftretens bakterieller infektiöser Komplikationen nach Operation zu erhöhen. Bei Patienten, die wegen maligner Erkrankungen operiert werden, gibt es zunehmend mehr Hinweise für eine Verbindung zwischen Blutkomponententransfusion, postoperativen bakteriellen, infektiösen Komplikationen und einem daraus resultierenden schlechten Langzeitüberleben, sogar bei solchen Patienten, bei denen eine kurative Resektion durchgeführt werden konnte. Die Mechanismen, die diesen Nebenwirkungen zugrunde liegen, sind im Detail noch unbekannt, aber die Akkumulation von bioaktiven Substanzen während der Präparation und Lagerung spielt möglicherweise eine bedeutende Rolle. Derartige Substanzen könnten auch erklären, warum die Nebenwirkungen auch nach autologer Bluttransfusion auftreten. Die Einführung der Leukofiltration hat in den meisten europäischen Ländern durch die Reduzierung einer Reihe von Nebenwirkungen zu einer Verbesserung der Patientenbehandlung geführt. Zukünftige Untersuchungen sollten genetische Polymorphismen der Patienten und deren Bedeutung für die Entwicklung von Nebenwirkungen nach Blutkomponententransfusion in den Mittelpunkt stellen.

Introduction

It is well established that homologous blood component transfusion is a life-saving therapy, particularly in patients with acute anemia due to trauma, surgery or childbirth. In addition, blood components may also improve quality of life and even prolong the life of certain persons with chronic anemia. Transfused blood components may maintain the overall hemodynamics, lead to optimal tissue oxygenation, and improve blood coagulation capacity. Due to potential presence of contaminating microbial agents in the donor's blood [1–3], blood component safety has been considered for decades. At least in the industrialized part of the world such considerations have led to development of screening procedures to guarantee the safety and quality of blood components for transfusion [4]. At present transmission of microbial contaminants including HIV and hepatitis viruses are limited, and blood components are considered to have optimal safety for transfusions to patients.

Side Effects of Blood Transfusion

Transfusion of blood components may infrequently lead to acute side effects in 0.5–2% of cases, including febrile non-hemolytic transfusion reactions, acute hemolytic transfusion reactions, transfusion-related acute lung injury, and graft-versus-host reactions [5, 6]. In addition, transfusion of homologous components should be considered as transplantation with white cells that express various tissue type antigens not compatible with recipient tissue types [7] may even lead to acute leukocytosis [8]. During recent years it has been investigated whether or not white cells in blood components may lead to transferral of donor genetic material to the recipient, a phenomenon well-known from organ transplantation [9] where it leads to impaired protein synthesis and subsequent risks for the recipients [10]. It has been shown that transfusion of male blood to female recipients may lead to y-chromosome accumulation that may last for weeks, months and infrequently even years [11]. Subsequently, it was shown that donor genes could be traced in more than half of a trauma patient cohort receiving blood component transfusion [12]. At present it is not known in detail whether transfusion of donor genes may lead to a long lasting impairment in recipient protein synthesis. However, blood component contamination with viruses that may be related to cancer development, such as cytomegalovirus, Epstein-Barr virus, herpes simplex virus, papillomavirus, HAV, HBV, HCV, human parvovirus, etc. [13] might be considered a potential risk for recipients. It has been shown in animal models and in humans that contamination of transfused blood components with cancer-related virus frequently lead to cancer development [14, 15]. Subsequently, a variety of results concerning blood transfusion to patients with benign diseases and long-term risk of development of malignant diseases such as renal cell carcinoma,

non-Hodgkin's lymphoma and various skin cancers have been presented [16–22]. It has to be highlighted, however, that two other publications focusing on blood component transfusion offered to women after childbirth could not show any association between the transfused blood and increased lifetime risk of malignant disease development [23, 24]. In summary, the majority of current results suggest that blood transfusion to patients with transient impaired immune competence due to trauma or major surgery may enhance the lifetime risk to develop certain malignant diseases. However, presumably due to the increased immune tolerance associated with pregnancy, blood transfusion offered after childbirth does not seem to increase the risk of subsequent development of malignant diseases.

Immunomodulation and Postoperative Infectious Complications after Blood Transfusion

Emerging evidence has led to the overall agreement that blood component transfusion cause recipient immunomodulation with stimulation of certain immune responses and suppression of others, resulting in an impaired immune competence [25, 26]. Patients with Crohn's disease, patients undergoing organ transplantation and patients with recurrent rheumatoid arthritis may benefit from blood transfusion-induced impaired immune competence [27] while this may be of disadvantage in patients with trauma or undergoing major surgery [28], due to its relation to development of postoperative infectious complications [29–34]. However, the interpretation of the association of blood transfusion and postoperative infectious complications may be complicated because various other factors in addition to blood component transfusion also play significant roles. Thus, at least bacterial contamination, circumstances under which the operations are performed (e.g. acute versus elective operations), the preoperative host immune competence, the nature of the disease (benign or malignant), alcohol and tobacco abuse are factors that might be considered [28]. There are considerable differences in bacterial contamination between large bowel and hip or knee joint replacement surgery, with a higher risk of infectious complications among patients undergoing surgery for large bowel diseases. Furthermore, patients undergoing emergency surgery for large bowel diseases may have a much higher risk of subsequent infectious complications than patients undergoing elective operations for similar diseases [28]. Finally, there is emerging evidence suggesting that patients with malignant diseases have pronounced impairment of immune competence before, during and after surgery compared with patients with benign disease of the same organ [28, 35]. Therefore, the awareness of the association of blood component transfusion with increased risk of postoperative infectious complications should be differentiated and related to the specific surgical situation.

Table 1. White cell- and platelet-derived bioactive substances

Cell type	Bioactive substance	Target
Basophils	histamine, serotonin, tryptase, plasminogen activator, peroxidase,	immunomodulation, inflammation, cancer growth
Eosinophils	eosinophil protein X, cationic protein, peroxidase, basic protein	inflammation, tissue damage, cancer growth
Neutrophils	myeloperoxidase, YKL-40, elastase, vascular endothelial growth factor, vascular endothelial growth factor receptor-1, matrix metalloproteinases	inflammation, tissue damage, hyperpermeability, cancer growth, cancer invasion and cancer dissemination
Platelets	plasminogen activator inhibitor-1, tissue inhibitor of metalloproteinases-1, vascular endothelial growth factor, tissue factor	inflammation, hyperpermeability, hypercoagulation, apoptosis inhibition, cancer growth, cancer invasion, cancer dissemination

The debate concerning the association between perioperative blood component transfusion and reduced recurrence-free and long-term survival of patients with solid tumors has been running for decades without a final consensus. As shown by retrospective and prospective observational studies, it is well recognized that patients undergoing intended curative resection for colorectal cancer who are perioperatively in need for blood component transfusion have a worse prognosis than patients undergoing similar operations without receiving transfusion [26, 36]. However, results from clinical studies of patients with various other solid tumors are more difficult to be used in an overall evaluation of the significance of blood component transfusion and poor survival after intended curative surgery. In some of these studies, including breast, esophageal, liver, lung and head and neck cancer, such an association has been shown while in other studies including breast, lung, brain and gynecologic cancer, it could not be confirmed. A variety of important factors and the specific biology of a certain malignant disease may play a significant role for the recurrence risk after intended curative operation. Thus, hereditary or acquired genetic polymorphisms, presence of minimal residual disease including micrometastases, tumor location within a specific organ, acute operation as well as the level of surgeon education and training are parameters that also should be included as significant determinants of recurrent disease and long-term survival [37–40]. Due to release of cancer growth-related substances in inflammation and infection, development of postoperative infectious complications might be included as an additional parameter influencing the long-term outcome of cancer patients. Considering the variety of solid malignant diseases included in the evaluation of the negative survival impact of blood component transfusion, at least three cancerous diseases – colorectal cancer, esophageal cancer, and head and neck cancer – are known to be associated with a relative high risk of developing postoperative infectious complications. Recent results from a major clinically controlled, prospective observational study including 740 patients undergoing elective resection for colorectal cancer showed that patients receiving perioperative blood component transfusion

and who subsequently developed postoperative infectious complications ($n = 134$) had a significant and stage-independent reduced recurrence-free and long-term survival [41]. It should be noted that patients receiving blood transfusion ($n = 296$) without subsequent development of postoperative infectious complications had a prognosis similar to non-transfused patients. These findings confirm previous studies and are confirmed by subsequent studies [42–44], indicating that postoperative infectious complications play an important, additional role for the prognosis of cancer patients. In summary, variations in the studies evaluating the effect of blood component transfusion on prognosis after resection for a malignant disease may explain some of the discrepancies between previous and current results. Perioperative blood component transfusion may play a role in reducing the prognosis in some patients, in particular in those with gastrointestinal and head and neck tumors, while it does not have a pronounced effect on patients with a variety of other tumors.

Autologous Transfusion – a Step Forward?

Due to e.g. the risk of transmission of virus from donor to recipient, postoperative infectious complications, cancer recurrence, microchimerism, and exposure to foreign tissue type antigens by transfusion of homologous components, preoperative autologous blood deposition has been introduced in most European countries. In elective surgery for benign diseases including hip and knee replacement surgery this approach has reduced the overall infectious complication rates significantly [45]. In surgery for solid, malignant tumors, however, results from studies comparing homologous blood component transfusion with predeposit autologous blood transfusion indicate that patients receiving autologous blood have a similar poor prognosis as patients receiving homologous blood [46]. While blood donation does not adversely affect the immune competence of healthy blood donors, blood donation in patients with malignant diseases lead to impaired immune competence that may play a negative role for the patients during and after

surgery [27]. This may partially explain why patients receiving their own predeposit blood have a similar poor prognosis as those patients receiving homologous blood component transfusion.

It is indicated, at least in patients with malignant diseases, that side effects to blood component transfusion using homologous or autologous blood components may be similar. One explanation for this phenomenon may be the presence of white cells and platelets in the blood components. Various white cell- and platelet-derived bioactive substances well known as being involved in posttrauma complications, immunomodulation, development of infectious complications, and cancer cell growth, invasion and dissemination are stored in granules of white cells and platelets (table 1).

These substances have been shown to accumulate during preparation and storage of various blood components for transfusion in which white cells and platelets are present [47–50]. During storage the substances accumulate in a storage time-dependent manner, and the concentrations may increase by a factor of 65–70 for selected substances in whole blood components. The final concentration in a blood component may vary with the length of storage, ranging from 35 days in Scandinavia to 49 days in various other European countries for red cell components. Such factors should be considered to play an additional role in the development of posttransfusion side effects – particularly because results from experimental studies suggests that bioactive substances in blood components are associated with the side effects of blood [51, 52]. In addition, emerging evidence suggested that side effects to red cell blood component transfusion are associated with storage time of the components [53–58]. Such results may change the procedure for evaluation of side effects to blood component transfusion, and future prospective studies should include storage time as an independent and important parameter. Moreover, blood preparation and storage should be reconsidered as results from a variety of clinical prospective observational studies suggest that leukocyte filtration may be of benefit for the majority of trauma and surgical patients [59–62] to reduce various posttrauma complications. While the evidence for a benefit of leukofiltration is supported by results from a variety of specific surgical areas, including intraabdominal, cardiac, and hip replacement surgery, the benefit of leukofiltration of blood components transfused to cancer patients seem more diverging [63–65]. Obviously leukofiltration does not seem to have any beneficial effect on long-term survival of patients resected for colorectal cancer. The optimal timing of leukofiltration has been considered in various *in vitro* studies. It is suggested that prestorage leukofiltration, by avoiding accumulation of bioactive substances during storage of blood components, is superior to bedside leukofiltration. Bedside filtration performed at the time of transfusion will not inhibit bioactive substance release and accumulation during storage of blood from the time of donation and storage until the time of transfusion [66, 67]. This suggestion has been further under-

lined by experimental results showing blood component transfusion-associated, impaired immune reaction [67–69] and *in vitro* cancer cell growth stimulation [70] being attenuated by prestorage leukofiltration, while bedside leukofiltration appears to have no beneficial effect compared with non-filtered blood components. The introduction of universal leukocyte filtration in the majority of European countries at first sight increased the economic requirements, but the current reduction of the frequency of blood component transfusion-associated side effects may in the long run be of benefit for the patients and certainly for the economic capability as well. Subsequent change in the transfusion strategy aiming at reducing the ‘overuse’ of blood components, as shown by a European Community survey of blood usage at 43 university hospitals [71], may per se be of additional benefit for a variety of patients. Results from large multiinstitutional and multinational studies suggest that blood component transfusion can be substantially reduced with benefit for the patients [72–75]. In summary, introduction of universal prestorage leukofiltration is recommended to avoid side effects related to preparation- and storage-associated accumulation of white cell- and platelet-derived bioactive substances. But simultaneous reduction of the ‘overuse’ of blood components must be an additional requirement.

It should be considered that transfusion with homologous and predeposit autologous blood components may lead to similar side effects, due to mechanisms that cannot be explained by the well-known blood transfusion-associated immunomodulation. In particular, the relation between blood transfusion-associated development of postoperative infectious complications in patients operated for malignant diseases and subsequent poor prognosis should be reconsidered. Evidence has appeared that suggests blood transfusion per se to be without relation to poor prognosis in cancer surgery while the combination of blood component transfusion and development of postoperative infectious complications seems to be related to poor prognosis. The mechanisms are at present not known in detail but might be related to accumulation of bioactive substances in the blood components, release of similar bioactive substances in the patient due to bacterial contamination, and genetic polymorphisms in various parts of the immune system. In particular, polymorphisms in mannose binding lectin (MBL) genes, which is a prominent part of the innate immune system, may play a significant role in the development of postoperative bacterial infectious complications and resistance to cancer growth after resection for colorectal cancer [76, 77]. 10–15% of Caucasians have polymorphisms in the MBL genes, and such persons may be at risk during chemotherapy, trauma, major surgery and blood component transfusion where transient impairment of the overall immune competence is introduced [78, 79]. Future studies may be directed to explore the combination of genetic polymorphisms, blood component transfusion, infectious complications and long-term survival after resection for cancer.

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