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Perioperative Red Blood Cell Transfusion: Harmful or Beneficial to the Patient?

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Summary
Although the transfusion of red blood cells (RBCs) is safer than ever regarding infections, it is still associated with several adverse reactions and therefore should only be used on the basis of evidence-based triggers. However, prevention of RBC transfusion and subsequent substitution of blood losses with acellular solutions will inevitably result in dilutional anemia. Acute dilutional anemia can be compensated by the body over a wide range of hemoglobin concentrations without a critical restriction of tissue oxygenation. On the other hand, chronic anemia is known to be a potent cause of morbidity and mortality. As a consequence, the impact of perioperative anemia on mortality is difficult to describe, because anemia, as well as the transfusion of RBCs, can influence the clinical outcome. The resulting 'Gordian knot' cannot be cut easily, and this circumstance forces clinical physicians to make a daily trade-off between transfusion-associated and anemia-associated risks. This review focuses on the physiology of oxygen transport, the hazards of acute anemia, the hazards of RBC transfusion, and the literature putting these problems into perspective.

Zusammenfassung
Obwohl die Erythrozytentransfusion in Bezug auf Infektionen sicherer denn je ist, muss festgehalten werden, dass sie nach wie vor mit schweren Nebenwirkungen assoziiert ist und daher nur auf der Basis evidenzbasierter Trigger Anwendung finden sollte. Die Vermeidung von Erythrozytentransfusionen und die anschließende Substitution von Blutverlusten mit Hilfe azellulärer Lösungen wird aber unvermeidlich eine Verdünnungsanämie verursachen. Eine akute Verdünnungsanämie kann vom Organismus ohne kritische Einschränkung der Gewebeoxygenierung über einen weiten Bereich von Hämoglobinkonzentrationen kompensiert werden. Andererseits ist bekannt, dass eine chronische Anämie eine bedeutende Ursache für Morbidität und Mortalität ist. Der Einfluss einer perioperativen Anämie auf die Mortalität ist daher schwer zu beschreiben, weil sowohl die Anämie als auch die Erythrozytentransfusion das klinische Ergebnis beeinflussen können. Der resultierende «Gordische Knoten» kann nicht so einfach gelöst werden; dieser Umstand zwingt den Kliniker in einen täglichen Zielkonflikt zwischen transfusionsassoziierten und anämieassoziierten Risiken. Diese Übersicht fokussiert auf die Physiologie des Sauerstofftransports, die Gefahren der akuten Anämie, die Bedrohungen durch eine Erythrozytentransfusion sowie auf die Literatur, die sich mit diesem Problem auseinandersetzt.

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Introduction

Within the last 3 decades, an extensive amount of measures have been developed in order to reduce the perils of blood transfusion [1]. The first tests to prevent contagion of blood recipients were introduced in the early 1970s. Various laboratory methods have been employed from this time onwards. The use of blood donor history and serological and nucleic acid testing (NAT) assays has greatly reduced the probability for transfusion-associated transmission of several pathogens such as the human immunodeficiency virus or the hepatitis viruses (hepatitis A, B, C) [2–4]. As a consequence, bacterial contamination of platelet concentrates is the greatest remaining risk of infection in blood transfusion [5, 6]. Other risks include transfusion-associated lung injury (TRALI) and an increase in the number of postoperative infections [7, 8]. It has been speculated that the transfusion-associated risks might essentially depend on the age of the erythrocytes transfused [9]. However, one of the most important problems in transfusion medicine is still administrative error which accounts for most hemolytic transfusion reactions and ABO incompatibilities resulting in death in many cases. The incidence of this event is estimated to be between 1:12,000 and 1:135,000 units of red blood cells (RBCs) [10]; the risk of mortality due to administrative error is estimated to add up to 1:800,000 transfusions [11]. Overall, one might judge blood transfusions to be safer than ever before, and in fact the probability of being able to link unfavorable outcomes to a specific erythrocyte concentrate is negligible. Surprisingly, however, the opposite is true as well: it is also very difficult to attest that a specific erythrocyte concentrate was necessary to ensure the survival of a patient, and up to now it is impossible to describe the specific beneficial effects of an erythrocyte concentrate in terms of outcome. Therefore, the question whether a specific blood transfusion is harmful or beneficial for a specific patient cannot be determined easily [12].

Physiological Principles

Oxygen (O_2) transport in the blood is mainly ensured by erythrocytes transporting hemoglobin-bound O_2 from the lungs to the cells. Under resting conditions, the amount of O_2 transported to the cells exceeds the tissue O_2 demand. This margin of safety for O_2 transport is needed in situations where the body's O_2 demand abruptly increases to such a degree that a sole increase in cardiac output is not sufficient to fulfill the metabolic needs. Under resting conditions, this redundant amount of hemoglobin-bound O_2 is insignificant for tissue oxygenation.

The most important cornerstone in the compensation of acute anemia is the increase in cardiac output due to an increase in stroke volume and heart rate. Furthermore, the O_2 extraction ratio can be expanded in order to improve cellular O_2 delivery. One consequence of these compensatory mechanisms is that low hemoglobin levels (< 5 g/dl) can be tolerated by young healthy individuals at rest [13, 14], and that even extremely low hemoglobin levels (< 1 g/dl) can be survived without sequelae [15]. Since most of the compensatory mechanisms of acute anemia depend on sufficient cardiovascular compensatory mechanisms and with that on efficient cardiac function, it is not surprising that the limits of acute anemia are determined by myocardial O_2 supply. Hence, adequate coronary perfusion is believed to be one of the main determinants of the potential of compensatory mechanisms of acute anemia [16]. However, it has to be kept in mind that to date no study exists that can doubtlessly prove the concept that the limits of acute anemia are mainly determined by the limits of myocardial O_2 delivery. It has been speculated that other organs might achieve their individual limit of compensatory mechanisms at an earlier time point than the myocardium [17, 18]. Therefore, studies describing the limits of acute anemia in terms of critical myocardial O_2 supply probably neglect silent tissue hypoxia of other organs that occurs at an earlier time point in the course of anemia development.

Hazards of Anemia

One of the most feared risks of anemia is a critical restriction of O_2 delivery and subsequent insufficient tissue oxygenation resulting in severe tissue hypoxia. Although maintenance of adequate tissue oxygenation is one of the cornerstones of peri-interventional patient care, no guidelines exist that specify the optimal approach to monitor O_2 delivery and tissue oxygenation globally. Furthermore, no universally valid therapeutic corridors for typical physiologic parameters regarding tissue oxygenation have been established yet.

Surprisingly, although the outermost limits of extreme anemia have been extensively described in the literature [19, 20], little is known about the effects of moderate anemia on long-term survival of a specific patient as long as tissue oxygenation is ensured. As a consequence, it is very difficult to judge whether moderate anemia influences outcome. However, some studies exist that suggest anemia to be one important risk factor of periinterventional morbidity and mortality. Carson et al. [21] were one of the first to demonstrate that perioperative mortality is inversely correlated with the hemoglobin concentration rising from 7.1% for patients with levels above 10 g/dl to 61.5% for those with levels below 6 g/dl. In this relatively small investigation (125 participants), it was also shown that none of the patients with a hemoglobin level above 8 g/dl died. Hence, one could speculate that a hemoglobin concentration of 8 g/dl may be considered a reasonable conservative threshold for a potential transfusion trigger. This study was repeated in 1996 by the same group with more patients, and again it was shown that a low preoperative hemoglobin level increased the risk of death or serious morbidity.

Furthermore, it was demonstrated that this effect was more pronounced in patients with cardiovascular disease than in those without [22].

In 2004, Herzog et al. [23] investigated more than 1 million patients from the Medicare database from the time period of 1996–1997. They found out that the annual mortality rate for patients without congestive heart failure, chronic kidney disease, or anemia was 4%. Anemia was associated with an annual mortality of 8% which was the same as chronic kidney disease (8%). The annual mortality for congestive heart failure was 13%. The highest annual mortality was found in patients with all 3 comorbid conditions; mortality in these patients was 23%. From this data, it can be deduced that chronic anemia has to be judged a potent multiplier of mortality.

This is even more true in patients suffering from significant coronary stenosis. Nelson et al. [24] demonstrated in 1993 that anemia is disproportionately dangerous in patients with significant cardiovascular comorbidities. In this investigation, a hemoglobin concentration of < 9.3 g/dl was significantly associated with myocardial ischemia and morbid cardiac events in patients undergoing infra-inguinal arterial bypass procedures. This could be due to the fact that critical coronary stenosis impairs coronary vascular adjustment to acute anemia and significantly reduces the tolerance of the left ventricle to anemia [25]. These findings underscore the importance of recruitment of coronary vasodilator reserves in preserving total and regional myocardial oxygenation during compensation of acute anemia [25]. In the case of acute ST elevation, myocardial infarction anemia is known to be an independent risk factor for mortality and complications in the intensive care setting. Moreover, the development of anemia during myocardial infarction is associated with a higher mortality rate and incidence of complications with respect to patients who maintain normal hemoglobin values [26]. One reason for myocardial infarction-associated anemia might be the fact that inflammation-sensitive proteins are induced by myocardial infarction, which are associated with lower hemoglobin concentrations in the patients. Therefore, at least part of the hemoglobin drop after myocardial infarction is related to anemia of inflammation [27]. The incidence of myocardial infarction-associated anemia is high. About 40% of patients develop hospital-acquired anemia after the onset of myocardial infarction [28].

One of the largest studies that investigated the correlation of peri-interventional hemoglobin concentrations and mortality was conducted by Wu et al. [29] in 2007. They were able to verify that even mild degrees of preoperative anemia were associated with an increased risk of 30-day postoperative mortality and cardiac events in older, mostly male, veterans undergoing major non-cardiac surgery. The authors furthermore showed that supranormal hemoglobin concentrations will also result in increased mortality.

Although anemia has been repeatedly accused of being an important risk factor of perioperative morbidity and mortality in patients with coronary artery disease [30], a more recent investigation failed to determine whether preoperative anemia represents an independent risk factor for 30-day mortality and nonfatal myocardial infarction in patients undergoing major orthopedic arthroplasty surgery [31]. Furthermore, in more than 6 million patients undergoing hip and knee arthroplasty, anemia has also not been associated with a higher mortality rate [32].

In summary, it has to be stated that there are good reasons for preventing perioperative anemia, since there is a sufficient amount of data that identifies acute anemia as an independent risk factor of perioperative morbidity and mortality. However, there also exists some data that puts these results into perspective. In particular, the studies mentioned above are not qualified to justify transfusion at higher hemoglobin concentrations, since transfusion per se has some dangerous perils.

Hazards of Blood Transfusions

Infection has been the most feared side effect of blood transfusions for a long time. The measures necessary to reduce contagious risks of RBC transfusions are getting more and more laborious. Nobody can anticipate whether this level of monitoring can be maintained in the future with a large number of new pathogens arising, although one possible solution of this problem might be pathogen inactivation. However, new data have gained more attention within the last few years. For example potential immunomodulatory effects of blood transfusions have lately been identified which might be responsible for an increase in mortality of septic patients [8]. It has been speculated that these immunomodulatory effects are mediated by mononuclear cells, white blood cell-derived soluble mediators [33], and/or soluble human leukocyte antigen (HLA) peptides circulating in allogeneic plasma [34]. However, not only septic patients might be threatened by this phenomenon. Transfusion-associated immunomodulation (TRIM) is an ubiquitary pathology resulting in a general increase in the post-transfusion infection rate [35–37]. Surprisingly, it does not take a large number of erythrocyte concentrates to notice these changes; 1 or 2 could be effectual in influencing the incidence of postoperative infections [37, 38]. Furthermore, these transfusion-associated infections do not necessarily occur within a short time period after transfusion. The limited data suggests that the incidence of postoperative infections is increased with a lag of as much as 4 weeks after application of the last erythrocyte concentrate [39], and therefore in daily clinical practice the onset of infection is rarely traced back to an erythrocyte concentrate administered weeks ago. Besides these risks, Castillo et al. [40] discussed a hypothesis that there might be an association between blood transfusions and consecutive non-Hodgkin's lymphoma (NHL). In their meta-analysis of observational studies, blood transfusions were associated with a 20% increase in the risk of NHL.

Although retrospective meta-analyses should not be used to prove causality, and the study design had certain scientific flaws, these results warrant awareness of yet unidentified long-term effects of blood transfusions.

It has been speculated, that leukocyte-depleted packed RBCs have the potential to reduce immunomodulatory effects and thus transfusion-associated morbidity. However, it was shown recently by 2 different groups that perioperative transfusion of leukocyte-depleted RBCs does not decrease immunomodulatory effects and morbidity of surgical patients [41, 42].

At the moment, one of the most dangerous hazards of blood transfusion is TRALI [43]. TRALI is defined as a new acute lung injury occurring within 6 h of a transfusion, and hence clearly coinciding with that transfusion, in patients without risk factors for acute lung injury other than transfusion. TRALI is typically manifested by shortness of breath, fever, and hypotension [44]. Antibody-mediated TRALI (immune TRALI) is now recognized as one of the most common causes of transfusion-associated major morbidity and death in the Western world [45].

Although TRALI can be induced by all types of blood products, it has been demonstrated that a higher incidence of TRALI is found with plasma and pooled buffy coat-derived platelet products than with RBC products (fatal TRALI incidence: plasma, 1:200,000–300,000; platelets, 1:300,000–400,000; RBCs, 1:2,500,000–2,900,000), as well as an association with donor leukocyte antibodies (approximately 80% of cases) [46]. The underlying mechanisms of TRALI are still not fully understood. Nowadays, the so-called 2-hit hypothesis is believed to describe TRALI most comprehensively: antibodies, as well as alternate substances in blood products, directed against a HLA or another neutrophil antigen result in neutrophil activation which induces TRALI [46]. It is believed that plasma components from female donors are responsible for most cases of TRALI, since TRALI-associated alloantibodies are formed when the immune system of an individual with blood cells negative for an antigen is exposed to blood cells carrying that antigen. This happens especially in women with prior pregnancies. However, HLA class I and II antibodies are also detectable at a low prevalence in male donors regardless of transfusion and in female donors without known immunizing events. However, the prevalence of HLA antibodies increases significantly with the number of pregnancies [47]. As a consequence, plasma products are tested for HLA and HNA antibodies, and donors with antibodies are excluded from apheresis platelet donations. Although first data suggests efficacy of these measures, further studies are needed to elucidate whether they are effective in reducing the incidence as well as the mortality of TRALI.

Another important side effect of RBC transfusion is transfusion-associated circulatory overload (TACO). The primary differential diagnosis between TACO and TRALI can be very difficult, especially since the vigilance for TACO is low. The first article dealing with this phenomenon was published in the 1990s, and up to now less than 100 articles have been released on this topic [48]. Therefore, it is sometimes difficult to judge whether an aggravation of pulmonary function is induced by immunomodulatory effects or by circulatory overload [49].

The Trade-Off between Anemia and Blood Transfusion

An emerging body of evidence has been published within the last decade convincingly demonstrating that both anemia and transfusion of RBCs have specific limitations, and as a consequence a trade-off has to be made between the effects of anemia and the side effects of blood transfusion. Surprisingly, the number of studies elucidating an adequate approach to this problem is rather low. One reason for this phenomenon is the fact that it is quite difficult to identify blood transfusion as an independent risk factor of morbidity and mortality. If patients from a cohort are separated by whether or not they have been transfused, it is very likely that the older, sicker, and more restricted patients will be stratified into the transfusion group due to their underlying disease. As a consequence, it seems logical that these patients will suffer from a higher morbidity and mortality than the patients that have not been transfused. However, this increase in mortality is most likely predetermined by the underlying disease and not by the fact that patients were transfused. This way, the demonstration of causality is impossible since one question remains unanswered: Is morbidity higher due to transfusion, or is the number of transfusions higher due to morbidity?

One way to partially overcome this confinement is the statistical method of 'propensity score matching'. This makes it possible to differentiate 2 cohorts from a basic population that are similar to each other except for 1 specific attribute, in this case transfusion. Comparing the 2 cohorts, it is then possible to link differences in morbidity and mortality to blood transfusions, since all other attributes of the 2 cohorts are similar [50]. In transfusion medicine, 3 large studies have been performed using propensity score matching in the last few years: the ABC study [51], the CRIT study [52], and the SOAP study [53]. ABC and CRIT were able to determine blood transfusion as an independent risk factor of mortality, whereas SOAP demonstrated that transfusion of RBCs is associated with increased survival. The reasons for these conflicting results are not completely understood, but it has been speculated that the initiation of leukocyte-depleted RBCs might be responsible for the improved outcome in the SOAP study [53].

It has to be pointed out that propensity score matching can be used to generate hypotheses but is an inappropriate strategy to verify causal relationships. This is only possible by large randomized controlled trials. However, to date, only 3 prospective, adequately powered, randomized controlled trials exist that have investigated the impact of a restrictive ver-

sus a liberal transfusion strategy on mortality [54–56]. Although all of these studies demonstrate restrictive transfusion regimes to be at least as effective as liberal transfusion strategies, the results provided have to be interpreted cautiously. While all 3 studies are very well designed and fulfill the prerequisites of randomized controlled trials, they were performed in very specific study populations: one in intensive care patients [54], one in children [55], and one in patients undergoing cardiac surgery [56]. As a consequence, the results of these studies have to be interpreted and analyzed with regard to the specific study population, and it is difficult to transfer these results into daily clinical practice. Other populations might have other specific problems not covered by the study protocols. However, since none of these studies demonstrated superiority of a liberal transfusion strategy, one could speculate that other populations may also benefit from a restrictive transfusion regimen.

In 2008, Marik et al. [57] published a meta-analysis including 45 articles that investigated whether the risks of RBC transfusion outweigh the benefits. In 42 of the 45 studies, RBC transfusions were associated with unfavorable outcome, 2 studies found the risk to be neutral, and in a subgroup of 1 single study the benefits outweighed the risks. This analysis demonstrated that there is sparse evidence that routine RBC transfusion in the non-bleeding patient with a hemoglobin concentration greater than 7.0 g/dl leads to improved outcome, which justifies transfusion triggers above 8 g/dl only in patients with restricted cardiac function.

Conclusion

Are perioperative RBC transfusions harmful or beneficial to the patient? This question cannot be answered easily. Like all medical procedures, the initiation of an RBC transfusion has to be made based on an established indication and after weighing up possible benefits and specific risks and drawbacks. Taking into account the investigations published so far, transfusion alternatives seem reasonable to reduce the number of allogeneic blood transfusions. One cornerstone of modern blood-sparing techniques is the tolerance of acute anemia. However, anemia per se increases morbidity and mortality, especially in older people. Although a limited number of outcome studies exists, it has not yet been completely elucidated in which situation the acceptance of blood transfusions or the acceptance of low hemoglobin levels is more dangerous for a patient. In summary, it has to be stated that neither the hazards of anemia nor the hazards of RBC transfusions can be neglected. New concepts are needed to enable physicians to make a reasonable trade-off between RBC transfusion and the acceptance of low hemoglobin levels. However, the outcomes of several clinical studies published so far favor a more restrictive transfusion regimen.

Disclosure Statement

The authors did not provide a conflict of interest statement.

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