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**ABSTRACT**

Anemia, which occurs commonly in ICU patients, is defined as a decrease in hemoglobin concentration to less than  $13 \text{ g} \cdot \text{dL}^{-1}$  for a male adult or  $12 \text{ g} \cdot \text{dL}^{-1}$  for a female adult [1]. Many patients admitted to an intensive care unit are anemic at the time of admission [2-4]; the majority of patients will become anemic during intensive care. Assuming normovolemia, the physiologic response to a decrease in hemoglobin concentration and oxygen content includes an increase of cardiac output and oxygen extraction by the tissues in order to meet tissue oxygen needs. If hemoglobin concentration is decreased below a critical value, tissue hypoxia occurs. Critically ill patients may present with 1) increased oxygen requirements (eg. due to impaired tissue oxygen utilisation) and/or with 2) a limited ability to adequately compensate for the low hemoglobin concentration. Not surprisingly, anemia is a risk factor for increased mortality in patients with preexisting cardiovascular disease or major blood loss. Consequently, it had been proposed that hemoglobin concentration in the critically ill should be maintained above a threshold of  $10 \text{ g} \cdot \text{dL}^{-1}$  to ensure sufficient oxygen supply to the tissues. Augmenting oxygen content by the use of allogeneic transfusion was assumed to be associated with improved tissue oxygenation and, thereby, survival. According to recent investigations, allogeneic red blood cell (RBC) transfusion to ICU patients is commonly performed. Recent evidence is controversial regarding the influence of allogeneic RBC transfusion on the outcome of ICU patients. Liberal transfusion regimens resulting in greater hemoglobin concentrations may be associated with decreased survival. The latter may be due to an increased risk of adverse effects in the critically ill or to lack of efficacy. Extended storage of packed RBCs may be associated with an impaired ability to improve tissue oxygenation. At present, symptomatic treatment is recommended. The decision to transfuse or tolerate anemia should be based on a patient's individual cardiovascular reserve and on physiologic signs of impaired tissue oxygenation.

**CAUSES OF ANEMIA IN PATIENTS RECEIVING INTENSIVE CARE**

In general, anemia results from an increased turnover or reduced production of red cells. In the critically ill, causes of anemia include: surgical blood loss; repeated phlebotomies; blood loss into extracorporeal circuits; decreased red cell production and an impaired erythropoietin response [4][5]. Acute post-traumatic and / or intraoperative blood losses account for one third of RBC transfusions [4]. Anemia has been reported to be pronounced during acute renal failure and considerable amounts of blood are lost in extracorporeal circuits during renal replacement therapy [5]. Chronic blood losses include those generated by frequent diagnostic blood sampling. A recent estimate attributes approximately 30% of transfused RBCs to repeated phlebotomy [4;5]. Another common cause of anemia in this setting is gastrointestinal bleeding. This may be due to stress ulceration, anticoagulation or impaired gut mucosal integrity. A decrease in RBC life span to less than 120 days may be due to the use of extracorporeal circuits in renal replacement therapy, cardiac surgery and cardiac assist-devices, as well as by massive transfusion and hemolytic transfusion reactions.

Inappropriate formation of new red cells in the bone marrow may be another cause for anemia in the ICU. Normally, erythropoietin is produced within the kidney and liver in response to low arterial oxygen content. Erythropoietin release is impaired in the presence of acute renal failure. Proinflammatory cytokines (Interleukin  $1 \beta$ , Tumor necrosis factor  $\alpha$ ) have been shown to inhibit erythropoietin production, but may also directly interfere with maturation of red cells. Systemic inflammation decreases iron availability for RBC formation. Folate and vitamin B 12 deficiencies may also account for anemia in critically ill patients [5].

**COMPENSATORY RESPONSE TO ACUTE ANEMIA**

If normovolemia is maintained by fluid administration during acute blood loss, dilutional anemia results. The principal mechanisms which maintain adequate oxygenation of tissues in these circumstances are 1) an increase in cardiac output, which temporarily augments oxygen delivery during moderate hemodilution ( $\text{Hb} > 10 \text{ g} \cdot \text{dL}^{-1}$ ) and 2) enhancement of tissue oxygen extraction [6] by redistribution of regional blood flow in according to regional oxygen requirements [6;7].

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In the awake patient, cardiac output is increased via a sustained increase in heart rate; in the anesthetized subject it is increased via an increase in stroke volume. The latter is due to a decrease in blood viscosity and systemic afterload, to an increased venous return and enhanced myocardial contractility. Under physiologic conditions, oxygen extraction is almost maximal in the myocardium and cannot be greatly increased during hemodilution. Therefore, myocardial oxygenation under the condition of increased myocardial work predominantly depends on an adequate increase in coronary blood flow. During hemodilution, an increase and redistribution of organ blood flow has been described between and within organs. Redistribution of bulk flow occurs mainly in favour of the heart to meet increased myocardial oxygen requirements and to maintain the circulatory response to anemia. Redistribution of microcirculatory flow serves to match regional oxygen delivery to local tissue oxygen demands [7-10].

#### **LIMITS OF COMPENSATION FOR ACUTE ANEMIA**

A limit exists to peripheral, microcirculatory, and coronary compensation for anemia. This limit may be defined by a "critical" hemoglobin concentration which depends on species, body temperature, age and cardiac compensatory reserve. When this limit is exceeded, ischemic myocardial failure and peripheral tissue hypoxia will occur [11;12]. According to previous experimental data, the critical hemoglobin concentration varies between 2 and 5 g•dL<sup>-1</sup> ( corresponding to an oxygen delivery of 5 to 15 mL•min<sup>-1</sup>•kg<sup>-1</sup> ) [11-15]. The critical hemoglobin concentration for different organ systems may also vary due to the described redistribution of blood flow between organs, mainly in favour of heart and brain [8].

The critical hemoglobin concentration in humans has not been defined. A decline in oxygen consumption secondary to decreased oxygen delivery has been observed at an hemoglobin concentration of 4 g•dL<sup>-1</sup> in an anesthetized patient that refused allogeneic transfusion for religious reasons [16]. During profound hemodilution in human volunteers, slight changes in cognitive function have been observed at hemoglobin concentrations of 5 - 6 g•dL<sup>-1</sup> [7;9;10;17]

#### **CHANGE IN PHYSIOLOGIC RESPONSE**

Critically ill patients may present with factors limiting their ability to cope with a low hemoglobin concentration. A decrease in circulating blood volume limits the magnitude of a compensatory increase in stroke volume, as do congestive heart failure or coronary artery disease. Impaired pulmonary gas exchange further decreases arterial oxygen content. Many intensive care patients suffer systemic inflammation and sepsis which are associated with impaired myocardial contractility. These patients suffer impaired tissue oxygen utilisation mostly due to microvascular oxygen shunts [18]. Consequently, tissue oxygenation cannot be maintained via an increase of tissue oxygen extraction. For these reasons, the historical practice of attempting to ensure supranormal oxygen delivery in patients was established and patients received blood product transfusions liberally. The beneficial effect of increasing oxygen content using RBC transfusion on oxygen delivery is well documented [19]. But increased oxygen delivery is not the ultimate objective of a RBC transfusion. The aim should be not to increase merely oxygen delivery but also to improve tissue oxygenation, evidenced by a parallel increase in O<sub>2</sub> consumption.

#### **EFFICACY OF RED CELL TRANSFUSION TO IMPROVE TISSUE OXYGENATION**

There is experimental evidence that transfusion of RBCs improves oxygenation of hypoxic tissues. Powell acutely withdrew 30% of rats' blood volumes and resuscitated the animals with fresh autologous whole blood, albumin or Ringer's lactate [20]. Subcutaneous pO<sub>2</sub> and mixed venous O<sub>2</sub> saturation were most effectively restored in the whole blood group. Nolte et al acutely withdrew 54% of hamsters' blood volume and resuscitated the animals using either 1:1 fresh whole blood or the same volume of 6% dextran [21]. Following therapy, the tissue pO<sub>2</sub> was greater in the whole blood group. Fitzgerald hemodiluted conscious septic rats until supply dependency of oxygen consumption occurred [22]. Transfusion of fresh RBCs resulted in an increase in oxygen consumption indicating the presence of supply-dependency prior the start of transfusion. In patients, there are numerous studies in patients which report an increase of oxygen delivery following red cell transfusion. However, in contrast to the large amount of animal data (cited), RBC has rarely been shown to increase oxygen consumption, in patients(Overview in [19]).

#### **INFLUENCE OF STORAGE**

The duration of packed RBC storage may be associated with a lack of efficacy of transfusion in terms of restoring tissue oxygenation. Fitzgerald transfused supply-dependent septic rats either with fresh (3 days) or

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“old” (28 days of storage) RBCs [22]. Whereas transfusion of fresh RBCs increased O<sub>2</sub> consumption, the transfusion of “old” red cells was not. In a similar protocol, Sielenkämper also induced supply dependency by hemodiluting septic rats [23]. Due to a lesser survival in the group receiving “old” red cells, changes in O<sub>2</sub> consumption could not be analysed. Marik and Sibbald investigated the influence of the transfusion of three units of packed RBCs on gastric mucosal oxygenation in septic patients, who presented with a hemoglobin concentration of 9 g dL<sup>-1</sup> and an increased serum lactate concentration [24]. The greatest improvement in gastric mucosal oxygenation was significantly correlated with the age of the RBC units. Several reasons may account for the lack of efficacy of “old” red cells. Acidosis and loss of high energetic phosphates lead to changes in shape, membrane deformability, and surface antigen patterns. As a result, sludging of red cells in the microcirculation occurs. The loss of 2,3- diphosphoglycerate leads to a reduction of the p50 value of the hemoglobin within the transfused red cell and a leftward shift of the hemoglobin oxygen dissociation curve. These factors may decrease convective O<sub>2</sub> transport within the microcirculation and unloading of O<sub>2</sub> from transfused RBCs to hypoxic tissues.

## EFFECT ON OUTCOME

Current evidence does not unequivocally indicate a beneficial effect from RBC transfusion on the outcome of intensive care patients [25][4;26;27]. Several large studies conclude that a preoperative hemoglobin concentration < 9-10 g•dL<sup>-1</sup> or major intraoperative blood loss are associated with an increased risk of death or serious morbidity [2;26] This finding was even more obvious in patients with preexisting cardiovascular disease. A perioperative hemoglobin concentration < 9.5 g•dL is associated with an increased risk for myocardial ischemia during and after non-cardiac surgery. In a large combined retrospective and prospective analysis in 4470 critically ill patients, Hébert examined the effect of blood product transfusion on patient survival [26]. In patients with an hemoglobin concentration < 9.5 g•dL<sup>-1</sup> and an Apache II Score < 20, overall mortality increased with the number of transfused red cell units. In patients with the same hemoglobin concentration, and with an Apache II score > 20, patient mortality was inversely correlated to the number of transfused red cell units as long (as the total number was less than 6 units). The authors concluded that anemia increases the overall mortality risk. However, these data do not support the conclusion that maintaining the hemoglobin concentration > 10 g•dL by means of a packed RBC transfusion improves survival.

In a more recent multicenter trial, two matched groups of patients were compared. In one group, a liberal transfusion regimen was applied and hemoglobin concentration was maintained > 10 - 12 g•dL<sup>-1</sup>. In the other group, hemoglobin concentration was allowed to decrease to 7-9 g•dL<sup>-1</sup> [27]. The incidence of in-house mortality was less in the group to whom the more restrictive transfusion regimen was applied. This difference was most marked in young patients, who were less severely ill.

It is clear that transfusion of packed RBCs does not necessarily improve tissue oxygenation. [19] or improve patient outcome. The adverse effects of allogeneic transfusion contribute to the increased mortality associated with a more liberal transfusion practice. These include transfusion-transmitted infections, allergic and immunologic reactions, transfusion related immunomodulation, transfusion related lung injury and post-transfusion purpura.

Under certain preconditions, anemia in critically ill patients is associated with an increased mortality. Patients' abilities to compensate for anemia is differs based on the actual oxygen requirements, cardiovascular reserve, depth of analgesia and sedation and coexistent inflammation. An individual, symptomatic indication for allogeneic transfusion might be a more reasonable approach than searching for a numeric transfusion trigger. Ideally, this indication would be based reliable, immediately available evidence that tissue hypoxia is present.

## SYMPTOMATIC TRANSFUSION TRIGGERS INSTEAD OF HEMOGLOBIN-LEVEL DRIVEN TRANSFUSION ?

As outlined, tissue hypoxia as well as myocardial ischemia may occur if the critical hemoglobin concentration is reached in a patient. Reliable clinical parameters indicative of a critical level of acute isovolemic anemia, (so called symptomatic transfusion triggers), have been used in clinical studies [28]. Changes in hemodynamic parameters such as blood pressure, heart rate or cardiac output may indicate variations in the compensatory response to anemia. They are not specific indicators of the presence of tissue hypoxia. Surrogate parameters for tissue oxygenation like venous pO<sub>2</sub> or mixed venous O<sub>2</sub> saturation are sensitive to changes in tissue oxygenation. They are not reliable markers of regional tissue hypoxia eg. in the heart and the intestinal mucosa. The same is true for the ECG: ST-segment deviations indicate a disturbed myocardial oxygen balance. Inadequate analgesia or sedation or systemic inflammation may cause such a disturbance in presence of an unchanged hemoglobin concentration. It has been proposed that a beneficial effect of red cell transfusion

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is related to a preexisting decrease in oxygen consumption [29]. As patients with jeopardized tissue oxygenation will mostly be ventilated using high FiO<sub>2</sub> concentrations (> 60%), determination of oxygen consumption with a metabolic monitor is technically impossible. In this situation, the only access to O<sub>2</sub> consumption is calculation using the reversed Fick principle. However, at least in the presence of experimental oxygen supply dependency, calculation of oxygen consumption is unreliable and imprecise [30]. This limited accuracy prevents valid determination of changes in oxygen consumption, < 20-30% when using the Fick principle. The inherent limitations to calculating oxygen consumption need to be considered when deciding on the need to transfuse RBCs.

## CONCLUSION

In conclusion, there is no numeric hemoglobin threshold below which an allogeneic RBC transfusion guarantees improvement in tissue oxygenation or patient survival. The decision to administer allogeneic blood to an individual patient should be based on the patient's underlying disease, the patient's cardiac reserve, and on careful interpretation of symptomatic transfusion triggers indicative of tissue hypoxia.

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In recent years, peripheral nerve block has become more widely used in Europe and the United States. Although single blocks are very effective for management of postoperative pain, their effectiveness is limited by their duration of effect, which does not exceed 14-18 hours. This is a major limitation as most upper and lower extremity procedures require more than 24 hours of postoperative pain control.

The first continuous nerve block was described in 1946 by Paul Ansbro [1] who performed repeated supraclavicular injections of the brachial plexus to prolong the duration of anesthesia in patients undergoing upper extremity surgery.

More than 30 years later Selander et al. [2] published a study on 137 patients, in whom an axillary catheter was placed for hand surgery. Tuominen et al. in 1987 [3] first reported on the use of continuous interscalene infusion with 0.25% bupivacaine at a rate of 0.25 mg/kg/hr for 24 hours for postoperative pain management after shoulder surgery. Although this technique was more effective than a single injection of 1.25 mg/kg of 0.5% bupivacaine, it was also associated with local anesthetic accumulation (plasma levels that increased from 0.7 ug/ml to 1.1 ug/ml) and symptoms of local anesthetic toxicity such as dizziness and confusion. The same group also evaluated the effects of a continuous interscalene block on the ventilatory function demonstrating paresis of the ipsilateral hemidiaphragm [4]. In 1997, Borgeat et al. [5] introduced patient controlled interscalene analgesia with 0.15% bupivacaine using a basal infusion rate of 5 ml/hr and bolus of 3 to 4 ml with a lock-out period of 20 min. This technique has proven to be safe and effective without symptoms of toxicity and superior to PCA morphine.

With the development of new technologies, the use of patient controlled infusion pumps has now become the gold standard, being associated with similarly effective analgesia as with a continuous infusion and much less requirement of local anesthetics both for upper and lower extremity blocks [6,7,8].

Probably because of the extensive use of spinal and epidural techniques for lower extremity anesthesia and analgesia, it was not until 1978 that Brands and Callanan [9] reported on the first lumbar plexus placement of an "epidural" catheter. In the following years several authors reported on the safe and effective use of continuous peripheral nerve blocks of the femoral [10,11], sciatic [12,13] and lumbar plexus [14] for knee, hip and foot procedures in both elective and trauma patients.

Singelyn et al. [10] compared the effects of continuous femoral infusions to PCA morphine and epidural analgesia for acute postoperative pain management in patients who underwent total knee replacement, and demonstrated that the use of continuous femoral infusions of a mixture of 0.25% bupivacaine, sufentanil and clonidine for 48 hours resulted in a 60% reduction of postoperative morphine consumption, and better immediate functional recovery as indicated by a greater range of passive motion using a continuous passive motion machine.

In 1999 Capdevila et al. [15] studied the postoperative outcome using either a continuous femoral block, epidural analgesia or morphine PCA after major knee surgery. The first two techniques were performed using a solution of 1% lidocaine, 0.03 mg/ml morphine and 2 microg/ml clonidine administered at  $0.1 \text{ ml} \times \text{kg}^{-1} \times \text{h}^{-1}$ . The continuous epidural infusion and continuous femoral block groups showed significantly lower VAS scores at rest and during continuous passive motion, better early postoperative knee mobilization and shorter durations of stay in the rehabilitation center compared with the PCA morphine group. Side effects were encountered less frequently in the continuous femoral block group.

In 2001, Chelly et al. [11] confirmed that continuous femoral infusions of 0.2% ropivacaine for 48 hours in patients undergoing total knee replacement provided better postoperative pain control than epidural analgesia or PCA morphine. They also confirmed that, using this technique, morphine requirement was greatly reduced and that immediate functional recovery was accelerated. Furthermore, they reported that the use of continuous femoral infusions was also associated with a 20% reduction of hospital length of stay and a 60% reduction of total postoperative blood loss as well as an 80% reduction of serious complications following surgery.