Transfusion Triggers in Surgical Patients

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The primary reason for blood transfusion should be the maintenance of an oxygen delivery (D02) sufficient to meet tissue oxygen demand. Convective D02 can be determined as the product of the blood flow and the arterial oxygen content. A change in hematocrit induces a proportional change in arterial oxygen content and often an opposite chancre in blood flow (related to alteration in blood viscosity). In the perioperative period, experts have considered a hematocrit of 30% as optimal but their recommendations were based primarily on theoretical calculations of maximal D02 to peripheral organs. Awareness of the risks associated with transfusion has brought this threshold into question. Clinical studies on Jehovah's Witness patients have reported that elective surgery can be done safely in patients with a preoperative hemoglobin level as low as 6 g/dL, if estimated blood loss is kept below 500 mL [1]. Hemoglobin level alone was a significant predictor of outcome only at levels below 3 g/dL, the strongest independent factors influencing outcome being sepsis and active bleeding [2].

The decision to transfuse a given patient should not be taken based only on a hemoglobin level [3]. A better knowledge of the physiologic adjustments occurring during anemia and of the clinical factors which can limit the ability of the body to maintain adequate D02 to the tissues would allow the clinician to determine the minimal hemoglobin level for each patient.

Physiologic Adjustments During Anemia

To maintain adequate tissue oxygenation when hemoglobin is reduced, several mechanisms come into play, at both systemic and microcirculatory levels, provided that circulating blood volume is preserved. An increased cardiac output is commonly observed during acute anemia; its degree depends on the level of hemodilution. This augmented cardiac output is mainly due to an elevated stroke volume as long as normovolemia is maintained [4]. The development of tachycardia during anemia indicates hypovolemia, an insufficient hematocrit or an increased tissue 02 demand. The rise in stroke volume during normovolemic anemia is intimately related to the reduction in blood viscosity, leading to an increased venous return and a decreased ventricular afterload. Several experimental observations tended to indicate that the sympathetic innervation of the heart is required to increase cardiac output to a sufficient level during acute anemia.

Although cardiac output increases as hematocrit is reduced, systemic D02 reaches a peak value of about 110% of pre-anemic D02 for a hematocrit of about 30% indicating an optimal compromise between reduced 02-carrying capacity and increased blood fluidity. As hematocrit declines to a level of 20-25%, D02 begins to decrease, and falls below normoxic pre-anemic levels. Therefore, total D02 varies minimally over a wide range of hematocrit values between 25% and 45%, but decreases above and below this range.

During normovolemic anemia, the compensatory increase in cardiac output is also associated with a redistribution of blood flow to areas of high demand, such as the

myocardium and the brain. Indeed, coronary and cerebral blood flow increase out of proportion to the rise in cardiac output, which can be explained only by a regional vasodilatation in these organs [5,6]. The increase in myocardial blood flow is even more important than the increase in cerebral blood flow as myocardial oxygen demand increases during normovolemic anemia. Coronary vasodilatation becomes maximal when the hematocrit is reduced to 10-12%. Below this value, coronary blood flow can no longer match the increased energy demand of the cardiac pump, myocardial hypoxia develops and cardiac output decreases. This is consistent with the decrease in systemic oxygen consumption (V02) that occurs at hematocrit values of 10% [7].

The excess perfusion of the brain and the heart during anemia occurs at the expense of other organs. Several studies have demonstrated that relative vasoconstriction develops in some tissues during acute anemia, so that hepatic, renal and mesenteric blood flows are proportionately less than the total cardiac response [5,6]. This regional circulatory response during normovolemic anemia does not seem to be altered in the presence of significant beta-adrenergic blockade.

In addition to increased cardiac output and redistribution of blood flow to areas of high demand, other compensatory mechanisms come into play in the microcirculation to maintain adequate tissue oxygenation when hemoglobin level is reduced. First of all, during acute normovolemic anemia, the ratio of the microcirculatory to systemic hematocrit is increased, This phenomenon, associated with an increased capillary blood flow velocity allows the maintenance of the net red blood cell flow until the systemic hematocrit falls to 15% [8]. Second, the decreased viscosity associated with anemia results in a better spatial and temporal distribution of the red blood cells in the capillary network, improving cellular 02 extraction [9,10]. Third, during severe anemia (hematocrit below 15%), a shift to the right of the oxygen dissociation curve, related to a rise in red blood cell 2,3-diphosphoglycerate (2,3 DPG), may decrease hemoglobin affinity for 02 and thereby improve 02 delivery to the cells. Van Woerkens et al. recently reported the case history of a Jehovah's Witness patient with extreme hemodilution and D02-dependent V02 due to excessive blood loss during surgery [11]. In this anesthetized patient, V02 started to decline at a D02 of 184 mL/min (4.9 mL/kg/min), which corresponded to a hemoglobin level of 4 g/dL (hematocrit ± 12%). The authors observed a right shift of the oxyhemoglobin dissociation curve, but only when the hematocrit reached 8%.

In summary, the maintenance of adequate tissue oxygenation despite the decreased 02carrying capacities of the blood results from compensatory mechanisms acting at both the systemic (increase and redistribution of the cardiac output) and the microcirculatory level (increased extraction capabilities). These mechanisms allow V02 to remain constant until hematocrit falls to about 10%, at which point it becomes dependent on D02.

Clinical Limits of Anemia

The efficacy of the mechanisms maintaining adequate tissue D02 when blood 02 content is reduced depends first on the maintenance of normovolemia and on the integrity of myocardial function. Hypovolemia blunts the effects of the decreased blood viscosity on venous return, and a depressed myocardial function, even in the presence of an adequate blood volume, prevents the increase in stroke volume associated with the augmented venous return. Animal studies have demonstrated that anemia is not as well tolerated when cardiac function is decreased, as after myocardial infarction or chemically induced myocardial depression [12].

Coronary artery disease (CAD) can also limit the tolerance of the patient to normovolemic anemia. More than 15 years ago, Geha [13] observed that coronary vascular reserve is significantly compromised during progressive hemodilution, indicat-

ing cardiac vulnerability at this level, especially if coronary artery disease should coexists. The lowest tolerable hematocrit in CAD patients is not known, and experimental data on animals with extrinsically applied coronary stenoses remain conflicting. From a theoretical point of view, it has been recently demonstrated that coronary artery disease patients may tolerate some hemodilution intraoperatively although they will require a higher hematocrit during the early postoperative period to meet the increased tissue, especially cardiac tissue, 02 demand. In 27 coronary artery disease patients, Nelson demonstrated that a postoperative hematocrit below 28% was significantly associated with myocardial ischemia and morbid cardiac events [14]. Although the small sample size and case-control nature of the investigation limited the interpretation of these results, this study shows the need for larger clinical studies to better define the tolerance and thus the appropriate management of anemia in patients with coronary artery disease.

Respiratory insufficiency will also limit the tolerance of patients to anemia. Obviously, patients with chronic respiratory failure develop polycythemia in an attempt to maintain adequate tissue D02. However, there is no available data on optimal hematocrit during respiratory insufficiency.

Anesthesia has dual effects on the patient's tolerance of anemia. On one hand, the use of anesthetic agents can decrease tissue 02 demand, essentially by a decrease in sympathetic activity related to the elimination of pain and stress. Moreover, tissue 02 metabolism is also decreased during anesthesia by the presence of moderate hypothermia and the use of mechanical ventilation, which also allows the maintenance of high inspired fractions of oxygen increasing the amount of 02 carried by the plasma. On the other hand, anesthetic agents could alter the increase in cardiac output commonly observed during normovolemic hemodilution [15]. This effect could be attributed to the sympatholytic properties of these agents and to their effects on venous tone and myocardial contractility. These observations also stress the need for adequate monitoring to avoid the development of tissue hypoxia when hemodilution is performed during anesthesia using agents with potent negative inotropic properties.

Controlled hypotension is frequently used during surgical procedures to decrease intraoperative blood losses. However, the combination of controlled hypotension and normovolemic hemodilution could be associated with a decrease in D02 in some organs such as the kidneys and the splanchnic area, which could occasionally be associated with an impaired tissue oxygenation [16]. These observations strongly suggest the need for extensive clinical monitoring of patients in whom hemodilution and controlled hypotension are combined. Higher degrees of hemodilution cannot be recommended in this setting.

Carson has recently performed a retrospective cohort study to determine the effect of perioperative transfusion on 30- and 90-day postoperative mortality [17]. In 20 US hospitals between 1983 and 1993, a total of 8787 consecutive hip fracture patients, aged 60 years or older, who underwent surgical repair were included in the study. Primary outcome was 30-day postoperative mortality; secondary outcome was 90-day postoperative mortality. The «trigger» hemoglobin level was defined as the lowest hemoglobin level prior to the first transfusion during the time period or, for patients in the nontranfused group, as the lowest hemoglobin level during the time period. Overall 30-day mortality was 4.6% (n=402; 95% confidence interval (CI), 4.1%-5.0%); overall 90-day mortality was 9.0% (n=788; 95% CI, 8.4%-9.6%). A total of 42% of patients (n=3699) received a postoperative transfusion. Among patients with trigger hemoglobin levels between 80 and 100 g/L (8.0 and 10.0 g/dL), 55.6% received a transfusion, while 90.5% of patients with hemoglobin levels less than 80 g/L (8.0 g/dL) received postoperative transfusions. Postoperative transfusion did not influence 30- or 90-day mortality after adjusting for trigger hemoglobin level, cardiovascular disease, and other risk factors for death: for 30-day mortality, the adjusted odds ratio (OR) was

0.96 (95% CI, 0.74-1.26); for 90-day mortality, the adjusted hazard ratio was 1.08 (95% CI, 0.90-1.29). Similarly, 30-day mortality after surgery did not differ between those who received a preoperative transfusion and those who did not (adjusted OR, 1.23; 95% CI, 0.81-1.89). Carson et al. concluded that perioperative transfusion in patients with hemoglobin levels 80 g/L (8.0 g/dL) or higher did not appear to influence the risk of 30- or 90-day mortality in this elderly population. At hemoglobin concentrations of less than 80 g/L (8.0 g/dL), 90.5% of patients received a transfusion, precluding further analysis of the association of transfusion and mortality.

The indications for transfusion have never been evaluated in a prospective adequately sized clinical trial. A pilot study was conducted to plan larger clinical trials [18]. Hip fracture patients undergoing surgical repair who had postoperative hemoglobin levels less than 10 g per dL were randomly assigned to receive 1) symptomatic transfusion: that is, transfusion for symptoms of anemia or for a hemoglobin level that dropped below 8 g per dL or 2) threshold transfusion: that is, patients receive 1 unit of packed RBCs at the time of random assignment and as much blood as necessary to keep the hemoglobin level above 10 g per dL. Outcomes were 60-day mortality, morbidity, functional status, and place of residence. Among 84 eligible patients enrolled, (mean ± SD) prerandomization hemoglobin was 9.1 ± 0.6 g/ dL. The median number of units transfused in the threshold transfusion group was 2 (interquartile range, = 1-2), and that in the symptomatic transfusion group was 0 (6; interquartile range, = 0-2) (p 0.001). Mean hemoglobin levels were approximately 1 g per dL higher in the threshold group than in the symptomatic group: for example, on Day 2, 10.3 ± 0.9 g / dL versus 9.3 ± 1.2 g / dL, respectively (p 0.001). At 60 days, death or inability to walk across the room without assistance occurred in 16 (39.0%) of the symptomatic transfusion group and 19 (45.2%) of the threshold transfusion group. Death occurred by 60 days in 5 (11.9%) of the symptomatic transfusion group and 2 (4.8%) in the threshold transfusion group (relative risk = 2.5; 95% CI, 0.5-12.2). Other outcomes were similar for the two groups. Symptomatic transfusion may be an effective blood-sparing protocol associated with the transfusion of appreciably fewer units of RBCs and lower mean hemoglobin levels than are associated with the threshold transfusion policy. However, it is unknown whether these two clinical strategies have comparable mortality, morbidity, or functional status. A definitive trial is needed.

In the critically ill patient, most of the compensatory mechanisms for anemia are altered by the presence of hypovolemia, hypoxemia, depressed myocardial function and/or altered tissue 02 extraction capabilities. Moreover, the 02 demand of the critically ill patient is often increased simultaneously, due to fever, pain or stress. The current clinical guidelines recommend that in at-risk patients, hemoglobin level be maintained between 7.0 and 10.0 g/dL [16]. In septic patients, there is no current evidence for an optimal hematocrit although the maintenance of an hemoglobin level greater than 10 g/dL has been recently recommended. All authors emphasize the need to justify each unit of blood transfused by clinical judgment using a goal-oriented approach.

To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, Hebert et al compared the rates of death from all causes at 30 days and the severity of organ dysfunction [19]. They enrolled 838 critically ill patients with euvolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned 418 patients to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter, and 420 patients to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter. Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, P= 0.11).

However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill — those with an Acute Physiology and Chronic Health Evaluation II score of or =20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group; P=0.03) — and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; P=0.02), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.3 percent vs. 28.1 percent, P=0.05). Hebert et al concluded that a restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

Monitoring of Tissue Oxygenation During Normovolemic Anemia

The adequacy of any hemoglobin concentration in a given clinical situation depends on whether a sufficient amount of oxygen is carried to the tissues to meet 02 needs. In the absence of good clinical signs of inadequate tissue oxygenation, mixed venous 02 saturation (SV02) is frequently used to detect the development of an imbalance between 02 supply and demand. Trouwborst et al. [20] and Rasanen [21] assessed the potential value of monitoring SV02 as an indicator of tissue oxygenation during progressive acute normovolemic hemodilution in anesthetized pigs. They found a significant correlation between changes in SV02 and02 extraction ratio. They determined that the critical hemoglobin value, i.e. the value of hemoglobin below which V02 starts to decline, was around 4.0 g/dL, which corresponded to a SvO2 of 44% and an02 extraction ratio of 57%. In anesthetized animals with or without limited coronary vascular reserve, significant myocardial lactate production reflecting anaerobic metabolism occurred only when systemic 02 extraction ratio exceeded 50%[22]. In a Jehovah's Witness patient dying from massive bleeding, critical hemoglobin level was found around 4 g/dL corresponding to aSV02of 56% and an02extraction ratio of 44% [11]. These experimental and clinical observations tended to indicate that SV02 and02 extraction ratio could be reliable physiologic guide to transfusion. In eight ASA class I anesthetized patients undergoing idiopathic scoliosis correction, Fontana et al. [23] performed profound intraoperative normovolemic hemodilution using a SvO2 of 60% as a «transfusion trigger". In their patients breathing 100% 02, hemoglobin decreased from 10.0 g/dL to a nadir of 3.0 g/dL, while SV02 decreased from 90.8% to 72%. No patients suffered clinically adverse outcome. Despite the very small number of patients (healthy adolescents) included, this study tended to indicate that profound level of normovolemic hemodilution could be performed in some patients using SV02 as the transfusion trigger, without any adverse outcome. Other studies have now tended to confirm these observations [24].

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