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REVIEW ARTICLE/BRIEF REVIEW

Review article: Risks of anemia and related management strategies: can perioperative blood management improve patient safety?

Article de synthèse: Risques d'anémie et stratégies de prise en charge : la gestion périopératoire du sang peut-elle améliorer la sécurité du patient?

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Abstract

Purpose *Anemia in both acute and chronic conditions is associated with an increased risk of organ injury (brain, heart, kidney) and mortality. Thus, anemia is not "safe". Impairment of tissue oxygen delivery likely contributes as a central mechanism; however, the existing treatments for anemia (i.e., transfusion, erythropoiesis stimulating agents, blood substitutes) have not produced a demonstrable improvement in patient outcomes despite their efficacy to increase blood oxygen content. Indeed, transfusion of red blood cells (RBCs) has been attributed to increase mortality in non-bleeding patients. Thus, the pathophysiology of anemia-induced morbidity and mortality and its treatments are complex and incompletely understood. New knowledge continues to emerge regarding the cellular mechanisms that maintain oxygen homeostasis during anemia. Nevertheless, the application of this knowledge has not yet led to improvements in patient outcomes. As both anemia and transfusion are associated with increased mortality, utilization of multimodal patient blood management strategies may be effective in avoiding both of these predictors of adverse outcomes. We propose to review new strategies to avoid both anemia and transfusion with the goal of improving patient outcomes and safety.*

Principal findings *We reviewed several approaches that utilize patient blood management to improve patient outcomes, including 1) characterization of biomarkers of anemia-induced tissue hypoxia to identify appropriate patient-specific treatment thresholds or hemoglobin (Hb) triggers; 2) development of adequately powered clinical trials that will help to define appropriate guidelines for the perioperative treatment of anemia and optimal Hb thresholds for transfusion of RBCs in specific patient populations; and 3) demonstration that an established blood conservation program (ONTraC) can reduce RBC transfusion and its associated adverse outcomes.*

Conclusions *Anemia is associated with increased morbidity and mortality. Ongoing initiatives to treat anemia and optimize patient blood management may improve patient outcomes. A broader application of these approaches may improve the overall safety of anesthesia and surgery for patients with anemia.*

Résumé

Objectif *L'anémie, qu'elle soit aiguë ou chronique, est associée à un risque accru d'atteinte des organes (cerveau, cœur, reins) et à une mortalité plus élevée. Ainsi, l'anémie n'est pas « sans risques » . Un déficit d'apport d'oxygène aux tissus est probablement un mécanisme contributif majeur. Cependant, les traitements actuels de l'anémie (c'est-à-dire les transfusions, les agents stimulant*

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l'érythropoïèse, les produits de substitution du sang) n'ont pas apporté une amélioration démontrable du pronostic des patients en dépit de leur efficacité pour augmenter le contenu en oxygène du sang. En fait, on a attribué aux transfusions de globules rouges un accroissement de la mortalité chez les patients non hémorragiques. Ainsi, la physiopathologie de la morbidité et de la mortalité induites par l'anémie est complexe et n'est pas encore complètement élucidée. De nouvelles connaissances continuent à apparaître concernant les mécanismes cellulaires qui maintiennent l'homéostasie de l'oxygène au cours de l'anémie. Néanmoins, la mise en œuvre de ce savoir n'a pas encore mené à des améliorations en termes de pronostic. L'anémie et la transfusion étant toutes deux associées à une augmentation de la mortalité, l'utilisation de stratégies multimodales de gestion du sang des patients peut s'avérer utile pour éviter ces deux éléments prédictifs d'évolution défavorable. Nous proposons d'analyser de nouvelles stratégies pour éviter, à la fois, l'anémie et les transfusions dans le but d'améliorer le pronostic et la sécurité des patients.

Constatations principales *Nous avons examiné plusieurs approches faisant appel à la gestion du sang des patients pour améliorer leur pronostic, y compris 1) la détermination de biomarqueurs d'hypoxie tissulaire induite par l'anémie pour identifier des seuils de traitement spécifiques aux patients ou des niveaux d'hémoglobine (Hb) critiques, 2) l'élaboration d'études cliniques ayant une puissance suffisante pour contribuer à définir des directives appropriées pour le traitement périopératoire de l'anémie et la définition de seuils optimaux d'hémoglobine pour la transfusion de globules rouges dans des populations particulières de patients, et 3) la démonstration qu'un programme organisé de conservation du sang (ONTraC) peut limiter les transfusions de globules rouges et les conséquences néfastes qui lui sont associées.*

Conclusions *L'anémie est associée à une augmentation de la morbidité et de la mortalité. Les initiatives en cours pour traiter l'anémie et optimiser la gestion du sang des patients peuvent améliorer l'évolution de ces derniers. Une application plus large de ces approches peut améliorer la sécurité globale de l'anesthésie et de la chirurgie pour les patients ayant une anémie.*

Since the inception of our specialty, improving the quality and safety of perioperative care has been a central goal of anesthesiologists.[1,2] While diverse and multifactoral components are included in the definition of quality, an integral part of all assessments of quality improvement in medicine is the element of improved safety.[1,2] Accordingly, improving patient safety is one of the cornerstones by which we can assess the level of the quality of care we provide. Within the practice of medicine, the definition of safety usually includes the avoidance of events or circumstances that cause harm or injury (i.e., morbidity and mortality). In this paper, we review data that suggest anemia is an unsafe condition associated with increased adverse outcomes. We also explore a number of approaches to treat anemia and minimize anemia-induced morbidity and mortality with the long-term goal of improving patient safety.

Why is anemia unsafe?

As recently reviewed, anemia is a global health problem affecting an estimated 25% of the world's population.[3] Iron deficiency is the contributing etiology in about 50% of cases.[4] In surgical patients, the prevalence of anemia is estimated to be as high as 20-30% for non-cardiac surgery[5,6] and more than 50% for cardiac surgical patients.[7] About 30% of these anemic patients have either iron deficiency anemia or anemia of chronic disease.[8] In these patients, even mild to moderate degrees of anemia have been associated with adverse outcomes, including renal injury, stroke, and death.[5,7,9,10] Furthermore, our basic science studies[11,12] and new translational clinical data support the hypothesis that the risk of anemia-induced organ injury (myocardial infarction and stroke) and mortality are accentuated by commonly utilized therapies that limit cardiovascular responses (β-blockade).[13-15] As such, these data support the conclusion that perioperative anemia is unsafe.

Evidence maintains that management of these patients with iron and limited treatment with erythropoiesis-stimulating agent (ESA) can increase the hemoglobin (Hb) level preoperatively and reduce transfusion.[16,17] Most trials have utilized allogeneic red blood cell (RBC) transfusion and ESAs as the main modalities of treatment. However, both of these therapies have been associated with increased morbidity, including an increased incidence of thrombosis and cancer progression, infection, length of stay, and mortality.[3,18,19] Thus, in some respects, both anemia and some of its treatments can be viewed as being unsafe. More data are required to determine which therapies can improve outcomes, including event-free survival in specific patient populations.

What is the mechanism of anemia-induced mortality?

As with many disease processes, developing effective treatments for anemia-induced morbidity and mortality requires specific knowledge of the pathophysiology; however, we do not yet have a clear understanding of theses mechanisms. It has been assumed that severe anemia leads

to inadequate tissue oxygen delivery, resulting in tissue hypoxia, organ failure, and death (Fig. 1). This is supported by the observation that acute anemia results in an increase in mortality that is proportional to the reduction in Hb.[20] Consistent with this observation, the mean lethal Hb level has been estimated to be near 25 $g{\cdot}L^{-1}$ in humans and animals.[3,21] In less severe chronic anemia, however, some authors have proposed that anemia may be adaptive.[22] In addition to these opposing views, it is also possible that anemia may be merely associated with, rather than causative of, multisystem organ failure and death (Fig. 1). Thus, a more complete understanding of the mechanisms and effects of anemia is required to inform clinical practice effectively.

As defined by studies in animals and humans, acute reduction in Hb is sensed at the cellular level and leads to adaptive cardiovascular responses to optimize tissue oxygen delivery.[3,23,24] These responses include 1) a characteristic increase in cardiac output (CO) that is proportional to the degree of anemia; 2) a reduction in systemic vascular resistance with organ-specific vasodilation to facilitate preferential perfusion of vital organs, including the heart and brain; and 3) an increase in tissue oxygen extraction. In addition, anemia results in the activation of hypoxic cellular mechanisms, including neuronal nitric oxide synthase (nNOS) and hypoxia inducible factor (HIF), with the purpose of maintaining oxygen homeostasis and sustaining organism survival.[21,25] These mechanisms are thought to be adaptive because the genetic deletion of nNOS results in severe attenuation of the HIF response and increased mortality in acutely anemic mice. Specifically, anemic mice deficient in nNOS, an enzyme that produces nitric oxide, cannot generate the expected increase in CO and have a profoundly attenuated HIF response to anemia. These deficiencies contribute to increased mortality in these mice, which die earlier and at a higher Hb concentration in a model of acute anemia.[21] The physiologic mechanisms by which nNOS-derived nitric oxide signalling supports survival during acute anemia include 1) regulation of the increase in CO required to maintain global tissue oxygen delivery during anemia; and 2) priming or amplifying the hypoxia inducible factor-1α (HIF-1α), a transcription factor regarded as the master regulator of adaptive hypoxic cellular responses.[26] Thus, nNOS regulates both the acute cardiovascular responses that optimize oxygen delivery to vital organs and the ability of each cell to adapt to reduced levels of oxygen. Together, these mechanisms support the maintenance of oxygen homeostasis during acute anemia. In the absence of these responses, healthy young mice experience a shift in their mean lethal Hb concentration from 25 $g{\cdot}L^{-1}$ to a higher value near 35 $g{\cdot}L^{-1}$.[21] Experimental models have shown that these hypoxic cellular responses are also upregulated during chronic anemia[27] and in older hypertensive rodents,[28] suggesting that they may have relevance to both the pediatric and the older adult patient populations that undergo anesthesia for surgical treatment. The overall conclusion from current experimental models strongly suggests that impaired oxygen delivery and tissue hypoxia contribute to increased mortality during acute anemia.

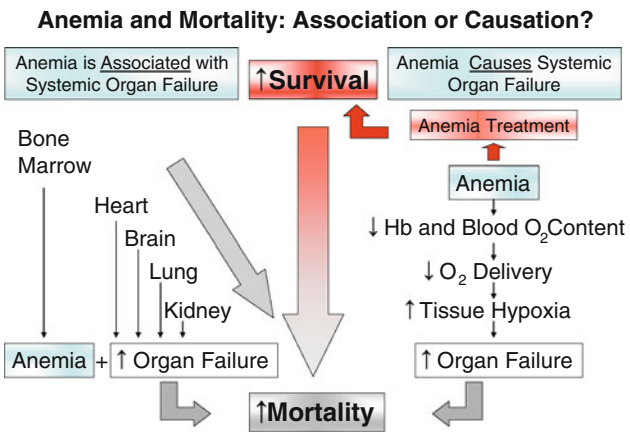

Fig. 1 Potential pathways by which treatment of anemia may affect survival

Why have current treatments of anemia not improved patient outcomes and safety?

If acute reductions in blood oxygen content and tissue oxygen delivery are responsible for increased mortality, then treatments that increase blood oxygen content should improve survival. To date, however, the collective evidence has failed to show that treatments of anemia can improve survival. As mentioned above, RBC transfusions, ESAs and hemoglobin-based oxygen carriers (HBOC) have all been shown to increase blood oxygen content but without an overall improvement in survival. Paradoxically, each of these treatments has been associated with increased morbidity and mortality.[3,18,19,29] Although the mechanisms are likely complex, potential factors contributing to these adverse outcomes include RBC storage lesion (RBC transfusion), upregulation of prothrombotic mechanisms (ESAs), and increased systemic nitric oxide binding (HBOCs). With respect to ESA therapy, the negative outcome data for medical patients may have unnecessarily discouraged the use of erythropoietin in some surgical patient populations. For example, more recent clinical studies have shown that long-term ESA use does not necessarily improve survival but does increase the risk of thrombotic complications and may enhance cancer progression.[18,19] On the other hand, previous systematic reviews in cardiac and non-cardiac surgery have shown

that ESA therapy can reduce RBC transfusions without a resultant increase in thrombotic complications.[16,30,31] This discrepancy may be due to the fact that these patients received short-term therapy and anticoagulation in the perioperative period. Although the use of iron and ESA has been shown to be efficacious in reducing red blood cell transfusions, it is unclear whether this effect is associated with a reduction in adverse outcomes, including mortality. Finally, differences in the etiology of anemia and variability in the optimal Hb concentration in different patient populations and in individual patients may require more tailored treatment strategies to improve the outcomes of anemic patients. Therefore, novel approaches to the treatment and management of preoperative anemia must be sought.

Can patient-specific Hb thresholds for tissue hypoxia be determined?

In surgical patients who experience acute blood loss, the decrease in Hb concentration is proportional to the increase in mortality, with an estimated mean lethal Hb value near 25 $g{\cdot}L^{-1}$;[3] however, the determinants of any one individual patient's Hb threshold for tissue hypoxia are likely to be multifactoral and highly variable. For example, one case report summarized the intact survival of a patient with an acute nadir Hb near $\sim$ 7 $g{\cdot}L^{-1}$. This demonstrates that individuals can survive at profoundly different Hb thresholds during acute anemia and provides the proof of principle that the impact of anemia is variable and patient-specific.[32] By contrast, some patients undergoing cardiac surgery have an increased risk of mortality when their preoperative Hb levels are lower than 100 $g{\cdot}L^{-1}$.[9,10] Thus, patients may be able to tolerate different levels of Hb reduction based on their genetic background, level of conditioning, and associated comorbidities. Therefore, treatments that focus on one level of Hb for a population may not be appropriate for all individuals in that population.[33]

Currently, we have no objective and reliable means of determining when an individual patient is at risk of anemia-induced tissue hypoxia, organ injury, and death.[34] We transfuse RBCs to restore adequate tissue O_2 delivery but haven't devised clinical methods to measure tissue O_2 tension accurately after transfusion. New methods for assessing the adequacy of tissue oxygen delivery after red cell transfusion include near infrared spectroscopy,[35,36] positron emission tomography,[37] functional magnetic resonance imaging, and invasive oxygen electrodes.[38,39] These measurements assess tissue O_2 tension directly or the degree of O_2 extraction and oxyhemoglobin saturation. While some studies using these approaches showed improved O_2 delivery and tissue partial pressure of O_2 with transfusion, others did not. Furthermore, these methods for assessing anemia-induced tissue hypoxia or the impact of RBC transfusion are not yet in general use.

One aspect of our research has been to identify adaptive mechanisms that help mammals survive low Hb levels. Based on this research, we have provided animal and human data that assess potential specific biomarkers of anemia-induced tissue hypoxia. These data included biomarkers of tissue hypoxia (systemic erythropoietin, cerebral near-infrared spectroscopy); microvascular oxyhemoglobin desaturation (altered plasma nitrite/nitrate ratios), and enhanced nitric oxide production and/or activation (plasma methemoglobin).[40,41] Prospective studies are currently underway to identify whether such biomarkers of anemia-induced tissue hypoxia can accurately predict adverse clinical outcomes. With these data in hand, trials can then be designed to identify patient-specific Hb thresholds for tissue hypoxia, and this approach can then be used to determine if specific treatments improve patient outcomes.

Can we define anemia treatment thresholds in specific patient populations?

Since publication of the Transfusion Requirements in Critical Care (TRICC) trial,[42] we have appreciated that some patients can tolerate a lower level of Hb. This finding has changed patient care and reduced unnecessary transfusion of RBCs. The recent transfusion guidelines from the American Association of Blood Banks provides one of the most up-to-date syntheses of the literature with recommendations for specific transfusion thresholds.[43] These guidelines provide a starting point from which to consider the treatment of the anemic patient. As acknowledged, the values of Hb triggers differ amongst different patient populations. For example, patients with acute cardiac syndromes,[44] neurotrauma,[45] or comorbidities associated with advanced age may require higher Hb levels.[46] Interestingly, this perspective may be reflected in the progressive increase in both the Hb threshold for treatment and the average Hb in the restrictive arms of subsequent transfusion trials (Hb $\sim$ 90 $g{\cdot}L^{-1}$) (Fig. 2), although much of this difference can be attributed to differences in study designs.

Based on evidence that patients with unstable coronary syndromes may require a higher "safe" Hb level, transfusion trials have been completed in patients undergoing cardiac surgery. Although designed as a non-inferiority trial, data presented in the Transfusion Requirements after Cardiac Surgery (TRACS) trial suggest that patients in the restrictive arm had a trend toward increased mortality when compared with patients in the liberal arm.[47] This finding is

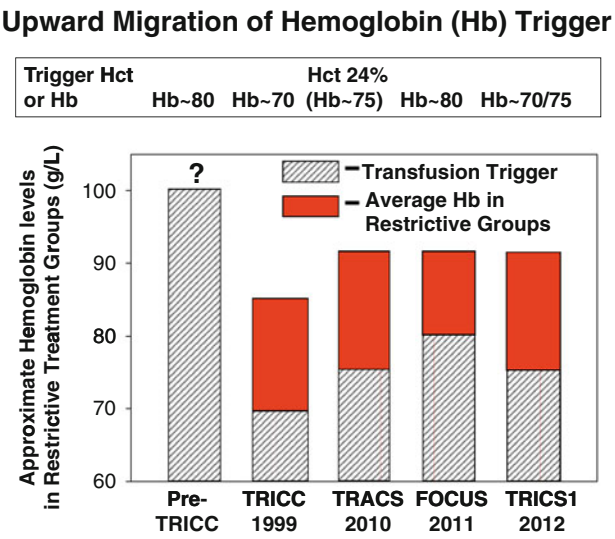

Fig. 2 Depiction of average hemoglobin levels and transfusion triggers in the restrictive arms of completed transfusion trials showing an upward trend in the average level of hemoglobin achieved in the restrictive arms of each study. The figure was derived from generalized and modified data presented in references [42,46-48]

supported by data from the Transfusion Requirements in Cardiac Surgery 1 (TRICS1) trial in which patients in the restricted arm had about twice the number of adverse events compared with patients in the liberal transfusion arm.[48] Although neither trial was powered to detect differences in clinical outcomes, they emphasize the importance of determining whether patients undergoing cardiac surgery may require a higher level of Hb. In addition, the impact of factors, such as age of blood, RBC storage lesion, increased oxygen affinity and fragility of RBC membranes, and altered nitric oxide binding capacity may also contribute to the lack of a positive impact of RBC transfusion on patient outcome. Adequately powered clinical trials are needed to determine which surgical patients would benefit, or be harmed, from a higher transfusion threshold and to determine the "safe" transfusion thresholds for specific patient populations, including patients undergoing cardiac surgery and those with neurological injury.

Can patient blood management and perioperative blood conservation improve safety?

Patient blood management can be defined as a multidisciplinary and multimodal approach to treat anemia, prevent blood loss, and minimize blood transfusion with the overall goal of improving patient outcomes.[17] The success of these programs has helped reduce the overall rate of RBC transfusion and improve clinical outcomes. The network of Ontario Transfusion Coordinators (ONTraC), a province-wide multidisciplinary blood conservation program, was established in Ontario in 2002 with the support of the Ministry of Health and Long-Term Care. The central goal of this program is to promote blood conservation and alternative treatments to transfusion of RBCs.[49] Transfusion coordinators were placed in 25 hospitals in the province, and the multidisciplinary team, which includes anesthesiologists, nurse practitioners, surgeons, perfusionists, and laboratory technologists among others, focuses primarily on increasing preoperative Hb levels by management of anemia (i.e., treatment with oral and intravenous iron and erythropoietin). This initiative requires that the diagnosis of anemia occurs at a sufficiently early time prior to surgery to enable adequate treatment. Optimally, a lead time of three to four weeks is required. The program also focuses on minimizing bleeding during surgery through use of antifibrinolytic therapy, topical hemostatic agents, meticulous attention to surgical hemostasis, and cell salvage. Repeated education about the appropriate indications for transfusion has been essential. A key task was to develop blood management champions. These champions become the leaders who promote the achievement of clinical excellence and optimal patient blood management. Through the coordinated efforts of its multidisciplinary members, ONTraC has shown an overall reduction in the incidence of blood transfusion in targeted patient populations, including patients undergoing hip and knee arthroplasty and coronary artery bypass grafting (Fig. 3). These overall reductions in transfusion rates have been associated with reduced length of hospital stay and infection rates (Table 1). The data provide evidence in support of the hypothesis that a patient

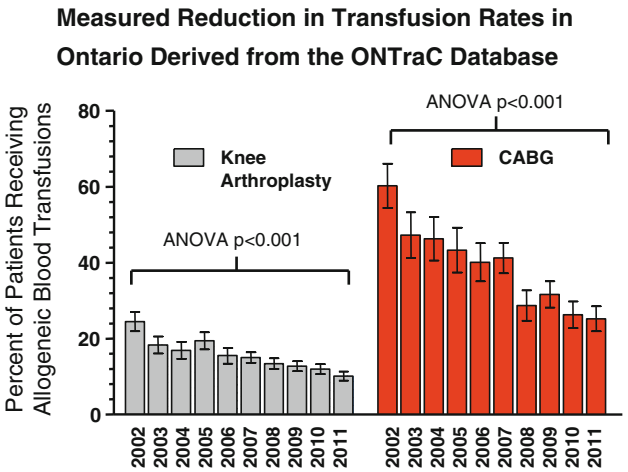

Fig. 3 Previously unpublished data from the network of Ontario Transfusion Coordinators (ONTraC) showing a reduction in red blood cell transfusion for knee arthroplasty and coronary artery bypass grafting (CABG) [mean (standard deviation)]. Transfusion rates decreased from 24.5% to 10.1% for knee surgery and from 60.2% to 25.2% for CABG surgery from 2002 to 2011 (ANOVA, $P < 0$ .0001 for both)

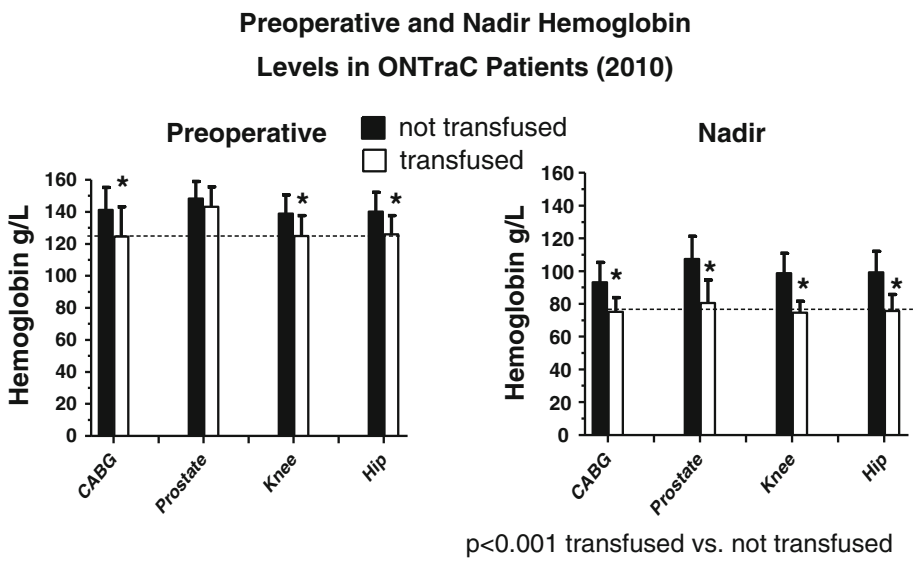

Fig. 4 Previously unpublished data from the network of Ontario Transfusion Coordinators (ONTraC) showing preoperative and postoperative nadir hemoglobin values in patients who were not transfused (black bars) and those who were transfused with red blood cells (white bars) for coronary artery bypass grafting (CABG), radical prostatectomy, and knee or hip arthroplasty surgery. The preoperative and nadir postoperative hemoglobin levels were significantly lower in patients who received a red blood cell transfusion than in those who did not receive a transfusion. The data suggest that a preoperative hemoglobin level < 130 g·L^{-1} represents a treatable target to avoid nadir hemoglobin levels requiring transfusion after surgery [mean (standard deviation) are compared by *t* test]

Table 1 Impact of transfusion on LOS and infection rate

Clinical Outcome		Transfused	Not transfused	*P* (*t* test)
LOS in days; mean (SD)	Knee	7.9 (13.3)	6.1 (16.2)	> 0.05
	Hip	7.6 (9.3)	5.8 (13.9)	0.034
	CABG	11.8 (21.6)	7.2 (11.4)	0.013
Postoperative infections	Knee	1.7%	1.1%	NA
	Hip	5.4%	1.9%	NA
	CABG	10.5%	3.4%	NA

(Infections included incision-site infections, deep surgical wound infections, septicemia, pneumonia, urinary tract infections, bone/joint infections, other. All had fever, positive cultures, and were treated with antibiotics.) LOS = length of stay; SD = standard deviation; NA = not assessed; CABG = coronary artery bypass grafting

Table 2 Effect of preoperative Hb on transfusion rates after total knee or hip arthroplasty or CABG

Preoperative Hb	Percent transfused		
	Knee	Hip	CABG
Hb < 130 g·L^{-1}	26.0%	31.5%	56.3%
Hb > 130 g·L^{-1}	6.1%	7.3%	16.5%
Hb > 140 g·L^{-1}	3.7%	3.7%	10.2%
P (ANOVA)	< 0.0001	< 0.0001	< 0.0001

Hb = hemoglobin concentration; CABG = coronary artery bypass grafting; ANOVA = analysis of variance

Table 3 Effect of having a long lead time to optimize preoperative treatment of anemia

Lead time	Percent Transfused	
	Knee	CABG
< 7 days	10.4%	41.3%
7-14 days	9.8%	31.4%
15-21 days	8.6%	25.0%
> 21 days	7.3%	22.8%
P (ANOVA)	< 0.0001	< 0.0001

CABG = coronary artery bypass grafting; ANOVA = analysis of variance

blood management program can improve patient outcome and therefore enhance safety for anemic patients undergoing surgical procedures.

The potential for improved patient safety can be shown by the prevalence of anemia in our surgical patient population. The prevalence of anemia in these patients has been

estimated to be from 20-50% for different surgical patient populations.[13,17] The finding that mild levels of anemia can increase patient mortality[5,7] has emphasized the need to assess the impact of treating these patients. In the ONTraC database, patients with a Hb level < 130 g·L^{-1} experienced an increase in transfusion rate and a lower postoperative Hb level compared with patients with a Hb level > 130 g·L^{-1} (Fig. 4, Table 2). In addition, the percentage of transfused patients decreased significantly with increasing lead time for preoperative assessment and anemia treatment (Table 3). Collectively, these data suggest that both transfusion and adverse patient outcomes should be reduced if adequate time is provided to treat anemia and increase Hb preoperatively.

Conclusions

Anemia and RBC transfusion are both associated with increased morbidity and mortality. Anemia is a prevalent problem in cardiac and non-cardiac surgical patients. A significant proportion of anemic patients may respond to available therapies to treat low Hb levels effectively. Evidence of benefit from RBC transfusion is hard to find, and most benefit from RBC transfusion is assumed and not scientifically proven. Some patients will benefit, but we need to be better able to identify who these patients are. It is not necessarily better to give more blood, and many transfusions are probably unnecessary. Multidisciplinary and multimodal patient blood management programs are able to effect treatment of anemia, reduce blood transfusions, and improve patient outcomes. Improving the management of anemic patients by 1) identifying an appropriate Hb threshold for transfusion in specific patient populations; 2) identifying patient-specific biomarkers of anemia-induced tissue hypoxia; and 3) instituting patient blood management programs, may further improve patient outcomes and the "safety" of anesthesia and surgery.

Key points

- Acute and chronic anemia are independent predictors of adverse patient outcomes, including increased mortality, and may therefore jeopardize patient safety.
- The mechanism(s) of anemia-induced morbidity and mortality are complex and include inadequate tissue oxygen delivery.
- Current therapies to treat anemia, including red blood cell transfusion, erythrocyte stimulating agents, and blood substitutes, have not been shown to improve patient outcomes.
- A blood conservation program (e.g., ONTraC) can reduce red blood cell transfusion and improve patient outcomes by reducing length of hospital stay and rates of perioperative infection.
- New multimodal approaches to the management of anemia may continue to improve perioperative patient outcomes and safety.

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Competing interests None declared.

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