Curr Anesthesiol Rep (2015) 5:24–32
DOI 10.1007/s40140-014-0085-2

PERIOPERATIVE DELIRIUM (JM LEUNG, SECTION EDITOR)

Blood Transfusion and Postoperative Delirium

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Published online: 26 October 2014

Abstract Postoperative delirium (POD) is a common complication of surgery associated with significant morbidity and mortality. Transfusion of packed red blood cells has been reproducibly associated with POD in many retrospective and prospective cohort studies. We review the biological evidence for a potential causal pathway between transfusion and delirium via oxidative stress and neuroinflammation, and summarize the clinical literature on delirium and transfusion to date.

Keywords Delirium · Transfusion · Anemia · Perioperative complications · Inflammation · Oxidative stress · Red blood cells · Storage lesion

Introduction

For patients admitted to hospital, postoperative delirium (POD) is a common and increasingly recognized complication, associated with significant short- and long-term morbidity and mortality. As the elderly represent a growing proportion of patients presenting for surgical procedures, the incidence of POD is expected to increase in the future. Efforts to address a potential epidemic of POD include a better understanding of the pathophysiology of POD, improving our knowledge of risk factors for POD to identify patients at risk, and recognizing precipitating factors that are potentially avoidable. Intra- and postoperative red blood cell (RBC) transfusion is potentially a precipitating factor as many clinical studies demonstrated a strong and reproducible association between transfusions and the development of POD and plausible pathophysiologic mechanisms to explain this association. This review summarizes our knowledge on the effects of RBC transfusion on the development of POD.

This article is part of the Topical Collection on *Perioperative Delirium*.

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Delirium: Definition, Incidence, Association with Adverse Outcomes, and Risk Factors

Delirium is an acute and fluctuating syndrome of impaired attention and cognition, and often an altered level of consciousness, due to systemic illness. It is common in hospitalized patients, with rates of 10–46 % in nonintensive care unit (ICU) patients, approaching 90 % in the ICU. POD occurs in 9–87 % of patients, depending on patient and surgical risk factors. POD has implications for short- and long-term morbidity and mortality. Over 40 % of in-hospital postoperative falls are attributed to POD [1]. Patients admitted from home who become delirious in hospital are more likely to be discharged to a nursing home [2, 3] and less likely to retain ability to complete basic self-care tasks [3, 4]. Furthermore, a diagnosis of delirium doubles the risk of mortality, even after extensive adjustment for comorbidities and illness severity [2].

Many patient-related and perioperative risk factors for POD have been identified, and were recently reviewed by Marcantonio [5]. Briefly, age, cognitive impairment, and vascular risk factors—including coronary artery disease, diabetes mellitus, and cerebrovascular disease—are

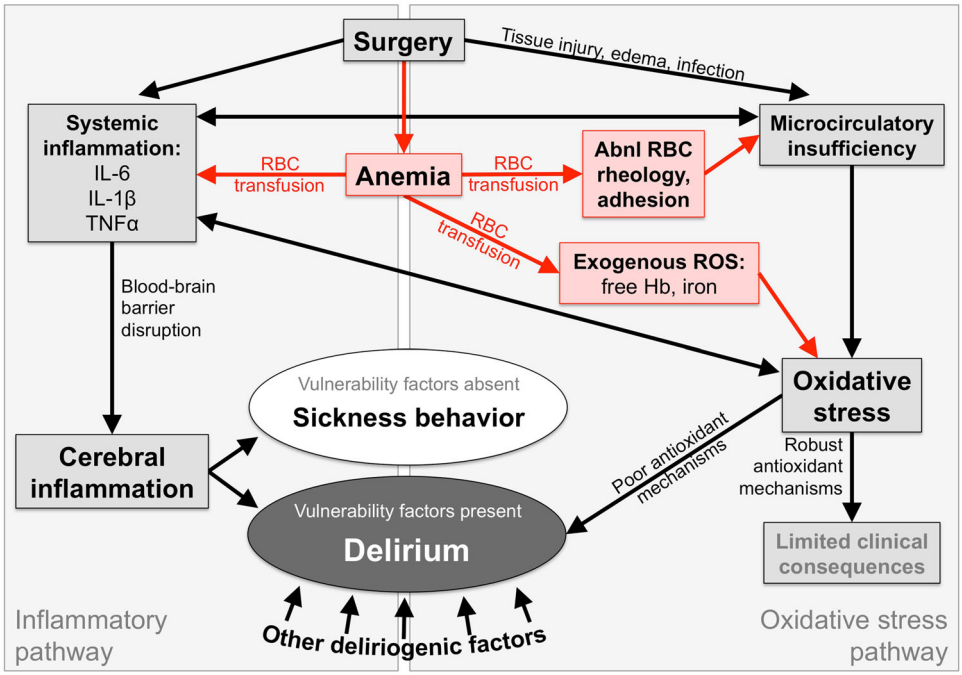

Fig. 1 Schematic demonstrating the relationships between surgery, neuroinflammation, and oxidative stress, and the impact of surgical anemia (via transfusion) on those relationships. *Double-headed arrows* represent bidirectional relationships. *Abnl* abnormal, *Hb* hemoglobin, *RBC* red blood cell, *ROS* reactive oxygen species

reproducibly associated with higher delirium risk. Of modifiable risk factors, exposure to anticholinergics, benzodiazepines, increasing invasiveness of surgery, and intraoperative blood loss and/or transfusion are also commonly identified.

Transfusion: Associated Morbidity and Physiologic Consequences

Untreated anemia can lead to life-threatening consequences, and transfusion of allogeneic packed RBCs is the mainstay of treatment to avoid the physiologic consequences of reduced oxygen delivery to tissue beds. There is uncertainty regarding appropriate transfusion thresholds at moderately low levels of hemoglobin (e.g. 8–10 g/dL). Part of this uncertainty is due to the known risks of transfusion, including viral and bacterial transmission, acute lung injury, circulatory overload, and other costs.

There is also more subtle morbidity associated with RBC transfusion that has gained attention over the last two decades. RBC transfusion is reproducibly associated with wound and systemic infection, acute respiratory distress syndrome and ventilator dependence, renal failure, myocardial infarction, stroke, and delirium [6]. These complications are attributed to the inflammatory, immunosuppressive, and/or mechanical properties of transfused RBCs.

Pathophysiologic Links Between Delirium and Transfusion

No single pathophysiologic mechanism links all of the known precipitants of POD to its fundamental abnormally, dysregulated neuronal activity in the setting of systemic illness. A recent review implicated seven pathophysiologic domains in its pathogenesis: neuroinflammation, neuronal aging, oxidative stress, neurotransmitter dysregulation, neuroendocrine abnormalities, diurnal dysregulation, and network disconnectivity [7•]. These domains are highly interconnected and interdependent. Here, we will focus on the neuroinflammatory and oxidative stress pathways, which provide the most direct correlates with physiologic changes that occur after transfusion (Fig. 1).

Neuroinflammation

The neuroinflammatory pathway is attributed to aberrant stress responses, and incorporates aspects of neurotransmitter and neuroendocrine abnormalities. Major surgery provokes a robust inflammatory response; in vulnerable patients, this may precipitate POD. Patients with delirium have elevated serum interleukin(IL)-6, IL-1β, and tumor necrosis factor alpha (TNFα) levels after coronary artery bypass grafting and hip fracture surgery [8–11], suggesting a systemic inflammatory response. Infusion of stored RBCs, in the absence of surgery, induces expression of IL-6, IL-1β, and TNFα, and provokes T cell proliferation [12]. Patients who received RBCs during cardiac surgery had even higher levels of inflammatory markers, including IL-6, than patients who received surgery without transfusion [13]. Thus, transfusion of stored RBCs, and particularly surgery with transfusion, appears to induce a peripheral inflammatory cytokine profile similar to that seen in POD.

In a mouse model of orthopedic surgery, increased TNFα disrupts the blood–brain barrier (BBB) [14], allowing proinflammatory cytokines to access regions of the

brain that highly express inflammatory cytokine receptors like the hippocampus. Furthermore, in a rat model of sepsis—also a potent precipitant of human delirium—the hippocampus and hypothalamus also produce markedly increased levels of IL-6 and IL-1β mRNA [15]. Nonsurgical patients with delirium display abnormal cerebral inflammatory markers: in a small post-mortem study, brain tissue from elderly patients who died with delirium had higher levels of IL-6 compared with age-matched controls [16], While no comparable study has been done to evaluate cerebral inflammatory markers following surgery or RBC transfusion, the BBB disruption seen with systemic inflammation precipitated by surgery suggests that neuroinflammation is likely an unintended consequence of perioperative transfusion.

The phenotypic correlate of systemic inflammation has been termed "sickness behavior", incorporating fatigue, reduced activity, anorexia, and anhedonia [17]. Delirium is notably absent from this definition. It is hypothesized [18] that neuroinflammation causes "sickness behavior" in patients without preexisting vulnerability, but in combination with deficits in another domain—e.g., dementia, oxidative stress, neuronal aging—even mild neuroinflammation can precipitate delirium. While the systemic inflammation from RBC transfusion is not clinically significant in most patients, in patients with reduced cognitive reserve [19] the neuroinflammation hypothesis provides a plausible link between perioperative transfusion and POD.

Oxidative Stress

Endogenous reactive oxygen species (ROS) and reactive nitrogen species are generated during normal metabolism, but production increases during times of hypoxia or ischemia, tissue injury, infection, and inflammation. The delicate balance between pro-oxidant compounds (which, for simplicity, we will refer to as ROS) and antioxidant capacity can be easily upset by surgery and/or by the exogenous administration of ROS (reviewed by Rosenfeldt and colleagues [20]).

Leukocyte adhesion and degranulation, prompted by tissue injury, inflammation, or infection, releases ROS and other mediators. Endothelial cell junctions fail and perivascular edema accumulates, disrupting oxygen delivery to tissues. This causes or exacerbates existing microcirculatory insufficiency, and further ROS are generated, perpetuating the inflammatory cycle. Preoperative microcirculatory insufficiency, reflected by low preoperative cerebral oxygen saturation, is independently associated with development of POD after abdominal or cardiac surgery [21, 22], potentially reflective of greater intraoperative cerebral oxidative stress.

Although the goal of transfusion is to increase tissue oxygen delivery, at least transient microcirculatory insufficiency occurs in peripheral tissues with RBC transfusion. Many animal and human studies have shown that, for the first 24 h, allogeneic RBC transfusion fails to improve and may decrease tissue oxygenation [23–27]. This is attributed in part to the rheological and adhesive properties of stored RBCs. After 14 days of storage, the percentage of undeformable RBCs is significantly higher than in fresh blood, and continues to increase throughout the storage duration until 12 % are undeformable at 28 days [28]. Furthermore, storage continuously increases RBC adherence to vascular endothelium [28]. As the estimated mean duration of storage of a unit of transfused RBCs in the United States in 2011 was 17.9 days [29], and in a Dutch study 37 % of transfusions were of blood stored for greater than 21 days [30], these alterations in the mechanical properties of stored RBCs have the potential to cause clinically significant derangements in tissue oxygenation and precipitate oxidative stress. An association between the duration of blood storage and POD was recently demonstrated: Each additional day of average storage beyond 21 days was associated with a 1.02- to 1.23-fold increase in the odds of POD [31].

Decreased ability to nullify ROS likely plays a role in POD as well. Patients with low preoperative catalase, an enzyme that acts as a "sink" for exogenous ROS [32], had increased rates of POD after cardiac surgery; postoperatively, in patients without delirium, catalase levels increased but in delirious patients levels declined even further [33]. Several mechanisms, including declining levels of the antioxidant reduced glutathione and increasing amounts of free iron and hemoglobin, progressively increase the free radical load posed by a unit of transfused blood (recently reviewed by Flatt and colleagues) [34]. RBC transfusion provides, in effect, a bolus of ROS; in vulnerable patients, failure of endogenous mechanisms to respond to oxidative stress may be manifested as delirium.

In summary, RBC transfusion has been shown to be a potent inflammatory stimulus and a contributor to local (cerebral and peripheral) tissue hypoxia and oxidative stress via multiple complementary and interacting mechanisms. These derangements are frequently implicated in the pathogenesis of delirium (Fig. 1).

Clinical Investigations: Transfusion and POD

Data from Observational Studies

Several retrospective as well as prospective cohort studies link blood transfusions to POD (Tables 1 and 2). The first study to describe the effect of blood transfusion on the incidence of POD was published in 1998 [35]. In a study of

Table 1 Cohort studies of postoperative delirium following transfusion in patients undergoing cardiac and/or vascular surgery

Author	Type of surgery	No. of patients	Type of study	Timing of transfusions	Diagnosis of POD	Incidence of POD	Reported effect of transfusion on POD	Reported effect of anemia on POD
Sasajima et al. [44]	Vascular surgery	110	Prospective observational cohort study	Intraoperative transfusion	CAM, at least once-daily assessment by nursing staff.	42.3 %	No association	No association
Schneider et al. [43]	Vascular surgery	47	Prospective observational cohort study	Postoperative transfusion, intraoperative autotransfusion	DSM-IV criteria, daily assessments by psychiatrists	36 %	Postop transfusions IP for incidence, severity and duration of POD	Pre- and postop anemia IP for POD severity, preop anemia IP for POD duration
Bucerius et al. [36]	Cardiac surgery	16,184	Retrospective cohort study	Not specified	According to APA guidelines. By physicians involved in the daily clinical care	8.4 %	Transfusion of >2,000 mL IP for POD OR 3.15 [2.71–3.65]	Not reported
Norkiene et al. [37]	Cardiac surgery (CABG)	1,367	Prospective and retrospective cohort study	Postoperative transfusion	DSM-IV criteria; assessments by ICU clinicians taking part in daily patient care	3.07 %	Transfusion IP for POD OR 4.59 [2.10–10.1]	No association
Chang et al. [38]	Cardiac surgery	288	Retrospective chart review	Intra- and postoperative transfusion	DSM-IV criteria; assessment by psychiatrists	41.7 %	Intra- and postop transfusion associated with POD (univariate)	Postop anemia (Hct <30 %) IP for POD
Katznelson et al. [39]	Cardiac surgery	1,059	Prospective observational cohort study	Intraoperative transfusion	CAM-ICU every 12 h in ICU, assessment by ICU nurses	11.5 %	Transfusion of >5 units IP for POD OR 3.29 [2.09–5.19]	Preop Hb <12 g/dL associated with POD (univariate)
Kazmierski et al. [63]	Cardiac surgery	563	Prospective observational cohort study	Postoperative transfusion	DSM-IV criteria psychiatrist assessment	16.3 %	RBC transfusion >4 units associated with POD (univariate)	Preop anemia (Hb threshold not defined) is IP OR 4.77 [1.35–16.8]
Stransky et al. [40]	Cardiac surgery	506	Prospective cohort study	Postoperative transfusion	ICDSC daily 1–3 days after surgery	11.6 % (9 % hypoactive delirium)	Transfusion IP for hypoactive delirium OR 1.18 [1.05–1.34]	Preop Hb IP against hypoactive delirium OR 0.73 [0.60–0.91] per g/dL
Arenson et al. [42]	Cardiac surgery	1,010	Retrospective observational cohort study	Postoperative transfusion	CAM and CAM-ICU every 8 h	14.7 % (21.4 % in patients >65 years)	Transfusion IP for POD	Pre- and intraop anemia were associated with POD (univariate)
Whitlock et al. [41]	Cardiothoracic surgery	310	Secondary analysis of a randomized controlled trial	Intraoperative transfusion	CAM-ICU by ICU nurse twice daily for up to 10 days	23.5 %	Transfusion IP for POD OR 1.26 (per 1 unit) [1.10–1.43]	Preop Hb was lower in patients with POD (univariate) (unpublished data)

APA American Psychiatric Association, *CAM* Confusion Assessment Method, *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *Hb* hemoglobin, *IP* independent predictor, as assessed by multivariable logistic regression, *ICDSC* Intensive Care Delirium Screening Checklist, *intraop* intraoperative, *postop* postoperative, *POD* postoperative delirium, *preop* preoperative, *RBC* red blood cells

Table 2 Cohort studies and randomized controlled trials of postoperative delirium following transfusion in patients undergoing noncardiac surgery

Author	Type of surgery	No. of patients	Type of study	Timing of transfusions	Diagnosis of POD	Incidence of POD	Reported effect of transfusion on POD	Reported effect of anemia on POD
Marcantonio [35]	Major noncardiac surgery	1,341	Prospective observational cohort study	Postoperative transfusion	Daily CAM by study personnel	9 %	Transfusions associated with POD (univariate)	Postop anemia is IP for POD
Behrends et al. [51]	Major noncardiac surgery	472	Secondary analysis of RCT data	Intraoperative transfusion	CAM by study assistants on day 1 and 2	29 %	Transfusion of >1,000 mL RBC strongest IP for POD on day 1	Preop Hb <13 g/dL associated with POD (univariate)
Ozyurtkan et al. [64]	Noncardiac thoracic surgery	100	Prospective observational cohort study	Postoperative transfusion	DSM-IV criteria Daily assessments by psychiatrists	18 % postop psychiatric disorders, 44 % of those POD	Transfusions associated with POD (univariate), no multivariable analysis performed	Pre- and postop anemia not associated with POD
Kawaguchi et al. [45]	Spine surgery	341	Retrospective observational cohort study	Intraoperative transfusion	CAM by study personnel, review of medical and nursing records	3.8 % (12.5 % in patients >70 years)	No association	Postop anemia on day 1 associated with POD (univariate)
Gao et al. [46]	Spine surgery	549	Retrospective observational cohort study	Intraoperative transfusion	Nurse screening, diagnosis by physicians using DSM-IV criteria	3.3 %	Transfusion >800 mL is IP for POD	Postop Hb <10 g/dL is IP for POD
Lee and Park [47]	Spine surgery	81	Prospective observational cohort study	Intraoperative transfusion	DSM-IV criteria and CAM	13.6 %	No association	Postop anemia associated with POD (univariate)
Vochteloo et al. [50]	Surgery for hip fracture	1,262	Observational cohort study	Mostly (97.9 %) postoperative transfusion	DSM-IV criteria as documented in medical and nursing staff records	30.3 % (anemic patients) 21.3 % (nonanemic patients)	Transfusion IP for POD OR: 1.67[1.28–2.20]	Preop anemia associated with POD (univariate)
Gruber-Baldini et al. [52••]	Surgery for hip fracture	139	Randomized controlled trial	Postoperative transfusion	Memorial delirium assessment scale (MDAS), CAM, administered by trained research assistants	Postop day 1: 31 % in liberal vs. 40 % in restrictive transfusion group (n.s.)	Postoperative blood transfusions to maintain Hb >10 g/dL not associated with a difference in the severity or frequency of delirium when compared to a transfusion threshold of 8 g/dL Patients in the restrictive transfusion group received fewer blood transfusions	
Fan et al. [54]	Hip arthroplasty	186	Randomized controlled trial	Perioperative transfusion	CAM-ICU by attending anesthesiologist preoperatively, and 1, 2, 3 days after surgery	21.3 % (restrictive transfusion group), 23.9 % (liberal transfusion group)	Transfusion to maintain Hb >10 g/dL resulted in a similar incidence of POD compared with a restrictive (Hb >8 g/dL) transfusion protocol Patients in the restrictive transfusion group received fewer blood transfusions	

APA American Psychiatric Association, *CAM* Confusion Assessment Method, *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *Hb* hemoglobin, *IP* independent predictor, as assessed by multivariable logistic regression, *ICDSC* Intensive Care Delirium Screening Checklist, intraop intraoperative, *postop* postoperative, *POD* postoperative delirium, *preop* preoperative, *RBC* red blood cells

1,341 patients, Marcantonio and colleagues demonstrated that intraoperative blood loss, number of units of RBCs transfused postoperatively, and lowest postoperative hematocrit all had a strong univariate association with POD, and an adjusted analysis identified low postoperative hematocrit as an independent risk factor for POD [35]. The study concluded that postoperative hematocrit should be kept at 30 % to prevent POD, assuming that delirium may be the consequence of a central nervous system insult caused by the low hematocrit (i.e. decreased oxygen delivery).

Subsequent studies confirmed associations between POD and increased RBC transfusions, as well as preoperative and postoperative anemia, further highlighting the difficulty of differentiating between the effects of intraoperative blood loss and anemia and of resulting blood transfusions. Furthermore, intraoperative blood loss may be a surrogate for surgical complexity, duration, and/or complications that may themselves increase the risk of POD. For this reason, this review emphasizes those studies that established transfusion or anemia as independent predictors, adjusting the risks for POD by applying multivariable logistic regression.

Six out of eight investigations in cardiac surgery patients identified intra- or postoperative RBC transfusions as an independent predictor for POD (Table 1) [36–42]. Three of these articles also identified preoperative anemia as an independent predictor of POD, and one study identified postoperative anemia as a predictor for POD [39]. A study in patients undergoing noncardiac thoracic surgery (Table 2) also demonstrated an association of postoperative transfusions with POD, but the authors failed to perform a multivariable analysis to assess independent predictors. Of two studies in vascular surgery patients (Table 1), one investigation identified postoperative transfusions as an independent predictor for POD [43, 44].

In three investigations conducted in patients undergoing spine surgery (Table 2), only one study was able to identify postoperative anemia as well as intraoperative transfusion as an independent predictor of POD [45–47]. However, interpretation of the other two studies may be affected by the small number of patients with POD: the total numbers of patients diagnosed with POD in those two studies were 13 [45] and 11 [47] patients.

Further support for the association between intra- or postoperative transfusions and POD comes from observational studies in liver transplantation [48], gynecologic tumor surgery [49], hip replacement surgery [50], and a recently published outcome study in patients undergoing major noncardiac surgery (Table 2) [51]. Three of these studies identified transfusions as independent predictors of POD [48, 50, 51].

Data from Randomized Controlled Trials

There is clearly a reproducible association between RBC transfusions and/or indications for transfusion (i.e., preoperative or postoperative anemia) and the development of POD. However, the observational nature of most of these studies makes determining the directionality of the relationship difficult: did intra- or postoperative anemia and resultant cerebral hypoxia cause delirium and patients were then appropriately transfused, or did POD develop following RBC transfusion? Furthermore, in an observational study it is difficult to correct for the possibility that more severe surgical trauma or surgical complications, resulting in increased blood loss or postoperative anemia, may be a more powerful precipitating factor for the development of POD.

Two recent trials have tried to address these issues by randomizing patients to a restrictive or liberal blood transfusion protocol (Table 2). In 2013, Gruber-Baldini and colleagues published an ancillary study to the Functional Outcomes in Cardiovascular Patients undergoing Surgical Hip Fracture Repair (FOCUS) study [52••, 53]. One hundred thirty-nine patients with cardiovascular disease that had undergone surgery for hip fracture and had a hemoglobin concentration of less than 10 g/dL were subsequently randomized to a liberal transfusion group (with goal hemoglobin greater than 10 g/dL) or a restrictive transfusion group (RBCs were transfused when hemoglobin concentration fell below 8 g/dL or patients developed symptoms of anemia). Despite a higher rate of transfusions in the liberal transfusion group, the incidence of POD was not different between treatment groups. On the other hand, the lower postoperative hemoglobin concentrations in the restrictive transfusion group were also not associated with an increase in POD.

A randomized controlled trial in 186 patients by Fan and colleagues (2014) used a similar protocol in patients undergoing hip arthroplasty under spinal anesthesia [54]. Patients were randomized before surgery to be in either a liberal transfusion group (hemoglobin maintained above 10 g/dL) or restrictive transfusion group (hemoglobin maintained at 8–10 g/dL). Again, the incidence of POD in both study groups was not different.

The interventional studies demonstrated that a restrictive transfusion protocol is not associated with worse outcome and that allowing postoperative hemoglobin concentrations to decrease to as low as 8 g/dL does not increase the risk for the development of POD. However, these studies failed to demonstrate that the reduced number of RBC transfusion translates to a reduction of POD. The failure to demonstrate a reduction of POD could be due to insufficient statistical power of these investigations. Another possible explanation is the fact that even in the restrictive

transfusion groups the administration of RBCs was still quite common. If transfusions per se, independent of the amount transfused, trigger POD, the impact of the restrictive transfusion protocol might have been too small. On the other hand, the number of patients who received more than 2 units of blood was low in both studies: 14/138 [52••] and 24/186 [54]. If a certain amount of blood transfused is required to trigger POD, as suggested in some of the retrospective studies [35, 46, 51], this threshold may have only been reached in a small number of patients of the two studies. However, these two prospective trials have considerable impact since they provide evidence that moderate anemia does not cause POD and demonstrate the safety of a restrictive transfusion protocol in a high-risk population.

Discussion

Unfortunately, the findings of the prospective studies may leave the clinician with the impression that there is little that can be done to minimize the risk of POD in an anemic patient. Tolerating more severe anemia to avoid transfusions completely is not an option as the benefits of transfusions in severely anemic patients are well established [55]. The most promising approach is to avoid intra- and postoperative anemia [56•]. Several modalities have been shown in the past to reduce perioperative transfusion requirements. Preoperative treatment with hematinics in patients presenting for elective surgery with preoperative anemia has been shown to reduce transfusion requirements [57, 58]. Improved point of care testing to detect intraoperative coagulopathies [59] as well as routine intraoperative use of fibrinolytics such as tranexamic acid have also proven to reduce perioperative transfusion requirements [60]. It remains to be established whether such interventions could reduce the incidence of POD.

Another factor of so far unknown relevance is the timing of the blood transfusion. Multiple simultaneous triggers of an inflammatory response may be needed to achieve a detrimental level of neuroinflammation. Intraoperative blood administration is known to amplify the inflammatory response evoked by surgery [13]. Pre- or postoperative blood administration may have a reduced impact, as the inflammatory response to surgery is transient [61]. Advanced targeted transfusions, i.e. transfusions performed 1 or 2 days before surgery in anemic patients scheduled for elective procedures have been shown to have clinical benefits presumably by reducing oxidative stress [62]. And since the physiologic derangements caused by transfusion of stored erythrocytes are mostly resolved within 24–48 h after transfusion, the detrimental effects of RBC storage would not coincide with surgery, resulting in improved oxygen delivery during surgery.

Conclusions

While the association between RBC transfusions and development of POD is well established, more interventional studies are warranted to demonstrate that decreasing the number of blood transfusions or avoiding blood transfusions can translate to a decreased incidence of POD. However, since the etiology of POD is multi-factorial, controlling for just one precipitating factor may not be enough to significantly impact the development of POD. An anesthetic plan trying to reduce the risks of POD should also aim to minimize the effects of other established precipitating factors.

Considering the potential for improved outcome in a vulnerable patient population, more effort is needed to define and then to avoid precipitating factors for the development of POD. Avoiding blood transfusions may be prudent, but is just one piece in a larger puzzle.

Acknowledgments This work was supported by departmental funds.

Compliance with Ethics Guidelines

Conflicts of Interest Elizabeth L. Whitlock and Matthias Behrends declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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