

# Changes in Cerebral Oxygenation during Transfusion Therapy

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**Abstract:** This study assesses the effects of transfusion of autologous or allogeneic blood on cerebral and tissue oxygenation during spinal surgery. Packed red blood cell transfusions are indicated to improve oxygen delivery to tissues. There are limited data demonstrating changes in tissue oxygenation with blood administration. Tissue (deltoid) and cerebral oxygenation were monitored using near-infrared spectroscopy during spinal surgery in patients. As indicated, cell saver or allogeneic blood was administered. Tissue and cerebral oxygenation were recorded before and after transfusion. The study enrolled 50 patients, 33 of whom (17 males and 16 females) received allogeneic blood ( $n = 8$ ) or autologous blood ( $n = 25$ ). Patients ranged in age from 9 to 19 years ( $14.0 \pm 2.3$  years) and in weight from 16.8 to 122.7 kg ( $54.6 \pm 25.7$  kg). Tissue oxygenation increased from  $83 \pm 9$  (pretransfusion) to  $86 \pm 7$  at the end of transfusion

( $p = .002$ ) and remained at the same level ( $86 \pm 7$ ) in the post-transfusion period. Cerebral oxygenation increased from  $76 \pm 8$  (pretransfusion) to  $84 \pm 8$  at the end of transfusion ( $p < .001$ ) and remained at  $84 \pm 8$  in the post-transfusion period. Changes in tissue and cerebral oxygenation were similar between cell saver and allogeneic blood and between starting hemoglobin value  $< 8$  gm/dL and starting hemoglobin  $\geq 8$  gm/dL. In conclusion, although both cerebral and tissue oxygenation increased during the administration of either allogeneic or autologous blood, the clinical impact was likely limited given the high initial tissue and cerebral oxygenation values. No differences were noted between autologous (cell saver) and allogeneic blood or based on the starting hemoglobin value. **Keywords:** cerebral oxygenation, near-infrared spectroscopy, cell saver, blood avoidance, blood transfusion. *J Extra Corpor Technol. 2016;48:173–8*

Red blood transfusions (autologous and allogeneic) are indicated to restore blood loss from surgery or hemorrhage, improve oxygen delivery to the tissues, and replete intravascular volume. Despite the benefits of transfusion therapy, significant acute and long-term effects may be seen with the administration of allogeneic blood (1–3). As such, there remains significant interest in limiting perioperative transfusion therapy with the use of restrictive transfusion guidelines as well as adjunctive therapies and practices (4).

During major surgical procedures, when large amounts of blood loss are anticipated, intraoperative cell salvage is frequently used. This technique has been shown to limit the need for allogeneic blood products (5,6). Although generally safe and effective, adverse effects may occur with the washing and reinfusion of autologous blood collected during

intraoperative cell salvage. Although guidelines have been proposed to guide transfusion decisions regarding allogeneic blood, there are limited data on which to base the clinical decisions regarding when to reinfuse blood obtained from intraoperative cell salvage. This study assesses the effects of the reinfusion of autologous blood obtained from intraoperative cell salvage on cerebral and tissue oxygenation during spinal surgery. These changes are compared to those seen with the administration of allogeneic blood products.

## MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Nationwide Children's Hospital. As this study did not alter clinical care, the need for written consent was waived. Verbal consent was obtained from a parent or guardian. The study was registered at ClinicalTrials.Gov (NCT 02,607,150). This was a prospective, observational study including patients presenting for spinal surgery in which intraoperative cell salvage was planned.

Anesthetic management included premedication with oral or intravenous midazolam. Routine American Society

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of Anesthesiologists' monitors were placed. Anesthetic induction included the inhalation of increasing concentrations of sevoflurane in 50–70% nitrous oxide in oxygen or intravenous induction with propofol (2–3 mg/kg), if intravenous access was present. Fentanyl (2–3 µg/kg) and rocuronium (.3 mg/kg) were administered following the induction of anesthesia. A second peripheral intravenous cannula and an arterial cannula were then placed. After baseline somatosensory (SSEP) and motor evoked potentials (MEP) were obtained, additional doses of rocuronium (.2 mg/kg) were administered as needed during dissection of the paraspinal muscles. Maintenance anesthesia consisted of inhaled desflurane in 30–40% oxygen and air with a synthetic opioid infusion (remifentanyl or sufentanil infusion). The inspired desflurane concentration was adjusted to maintain the bispectral index at 40–60 to ensure amnesia and the ability to achieve effect MEP and SSEP monitoring (7). Ventilation was controlled to maintain normocarbica (end-tidal and arterial PaCO<sub>2</sub> at 35–40 mmHg). Controlled hypotension was achieved with a mean arterial pressure (MAP) of 55–65 mmHg. Intermittent doses of labetalol were administered as needed to maintain the MAP at the desired level while maintaining the remifentanyl or sufentanil infusion at ≤.3 µg/kg/min. Normothermia (36–37°C) was maintained with forced air warming.

There was no change in the anesthetic care except for the additional use of near infrared spectroscopy (NIRS) to monitor tissue oxygenation (INVOS™, Medtronic, Minneapolis, MN). In accordance with our clinical practice, intraoperative cell salvage was used. Following the induction of general anesthesia, tissue and cerebral oxygenation were monitored using NIRS. The sensors were applied non-invasively to the deltoid muscle to measure tissue oxygenation and the forehead to measure cerebral oxygenation.

NIRS is a non-invasive device that uses infrared light, a technique similar to pulse oximetry, to penetrate living tissue and estimate brain tissue oxygenation by measuring the differential absorption of infrared light as it passes through the tissue (8,9). To measure cerebral oxygenation, infrared light is directed into the cranium from a light source and two sensors placed at fixed distances from the light source (3 and 4 cm in the system used for the current) measure the light after it has passed through extracranial tissue (proximal sensor) or both extracranial and intracranial tissue (distal sensor). Tissue or cerebral oxygenation is determined from the ratio of the absorption of the two wavelengths of infrared light from the probe which reflect the concentration of deoxygenated (absorption at 730 nm) and the concentration of the sum of deoxygenated and oxygenated hemoglobin (absorption at 805 nm). The INVOS cerebral oximeter displays a numerical value (rSO<sub>2</sub>), which is the ratio of oxyhemoglobin to total hemoglobin detected by the infrared sensor light path. The rSO<sub>2</sub> is reported as a percentage on a

scale that ranges from 15% to 95%. The INVOS cerebral oxygenation monitor uses two sensors to receive the infrared light after it has penetrated the cranium in an effort to eliminate artifact from extracranial blood flow and thereby provide a more accurate estimate of cerebral oxygenation. To ensure the appropriate depth of penetration of the infrared light, there are different sized sensors including one for neonates based on the patient's weight.

As clinically indicated, cell saver blood (autologous) or allogeneic blood was administered. Tissue and cerebral oxygenation were recorded at 2-minute intervals for 10 minutes before the transfusion, at the completion of the transfusion, and at 2-minute intervals for 10 minutes after the transfusion. The pretransfusion and post-transfusion values (six values obtained at 2-minute intervals over 10 minutes) were averaged to obtain pretransfusion and posttransfusion values, respectively. Ventilation (PaCO<sub>2</sub> and end-tidal CO<sub>2</sub>) and inspired oxygen concentration were kept constant during this time. Hemodynamic data including heart rate, blood pressure, and oxygen saturation were collected at 2-minute intervals along with the tissue and cerebral oxygenation values.

Continuous variables are presented as means with standard deviations, whereas categorical variables are presented as counts and percentages. Between-group comparisons were performed using independent *t* tests for continuous measures and Fisher's exact tests for categorical measures. As some patients received multiple transfusions during surgery, tissue oxygenation and hemoglobin were analyzed for the first allogeneic transfusion among patients who received at least one allogeneic transfusion. Autologous transfusions were analyzed in patients who did not receive an allogeneic transfusion, with no patient in this group receiving multiple transfusions of cell saver blood.

Changes in tissue oxygenation (pre-transfusion; at the end of transfusion; and posttransfusion) and changes in hemoglobin (measured before and 30–60 minutes after the transfusion) were analyzed using paired *t* tests. Repeated measures analysis of variance (ANOVA) was used to compare changes in tissue oxygenation and changes in hemoglobin by transfusion type (autologous vs. allogeneic), and to compare changes in tissue oxygenation based on the pretransfusion hemoglobin (<8 gm/dL vs. ≥8 gm/dL). All analyses were performed using Stata/IC 13.0 (StataCorp LP, College Station, TX). *p* Values <.05 were considered statistically significant.

## RESULTS

The study cohort included 50 patients, 33 of whom (17 males and 16 females) received either allogeneic blood (*n* = 8) or autologous blood (*n* = 25) (Table 1). Patients ranged in age from 9 to 19 years (14.0 ± 2.3 years) and in

**Table 1.** Demographic, oxygenation, and transfusion data.

Variable	N (%)	Overall Mean (SD)	Autologous Mean (SD)	Allogeneic Mean (SD)	p Value*
Age (years)	–	14.0 (2.3)	13.9 (2.0)	14.1 (3.2)	.830
Male	17 (52)	–	–	–	–
Weight (kg)	–	54.6 (25.7)	61.3 (25.4)	33.8 (13.0)	.007
Number of transfusions†	–	1.3 (0.6)	1.0 (0)	2.3 (0.7)	<.001
Allogeneic transfusion	8 (24)	–	–	–	–
Pre-transfusion oxygenation (average of 6 measurements at 2-minute intervals)	–	–	–	–	–
Deltoid‡§	–	83 (9)	84 (8)	79 (10)	.136
Cerebral‡	–	76 (8)	76 (8)	76 (9)	.996
Average of deltoid and cerebral measurements‡	–	79 (6)	80 (6)	77 (8)	.334
End-of-transfusion oxygenation	–	–	–	–	–
Deltoid§	–	86 (7)¶	87 (7)¶	84 (8)	.353
Cerebral	–	84 (8)¶	84 (7)¶	84 (9)¶	.996
Average of deltoid and cerebral measurements	–	85 (6)¶	86 (5)¶	84 (8)¶	.529
Post-transfusion oxygenation (average of five measurements at 2-minute intervals)	–	–	–	–	–
Deltoid§	–	86 (7)	87 (7)	84 (7)	.387
Cerebral	–	83 (8)	84 (7)	84 (9)	.948
Average of deltoid and cerebral measurements	–	85 (6)**	85 (5)	84 (8)	.591
Pre-transfusion hemoglobin (gm/dL)	–	8.9 (1.7)	9.0 (1.7)	8.4 (1.7)	.377
Post-transfusion hemoglobin (gm/dL)‡¶	–	9.5 (1.8)¶	9.5 (2.0)¶	9.6 (0.9)	.924

\*p value by two-tailed independent t test comparing allogeneic and autologous transfusions.

†Tissue oxygenation values are reported for the first allogeneic transfusion, if the patient received an allogeneic transfusion. Tissue oxygenation values are reported for the first autologous transfusion, if the patient received no allogeneic transfusions.

‡Data missing for one allogeneic transfusion.

§Data missing for one autologous transfusion.

¶Data missing for three autologous transfusions.

||Statistically significant (p < .05) change from pre-transfusion mean.

\*\*Statistically significant (p < .05) change from end-of-transfusion mean.

weight from 16.8 to 122.7 kg (54.6 ± 25.7 kg). There were no statistically significant differences in age (p = .830) or the proportion of male patients between the autologous and allogeneic groups (56% and 38%, respectively; p = .438), although patients receiving allogeneic transfusions weighed less than those receiving autologous transfusions (33.8 ± 13.0 vs. 61.3 ± 25.4 kg; p = .007).

Tissue oxygenation measured from the deltoid increased from 83 ± 9 in the pretransfusion period to 86 ± 7 at the end of transfusion (p = .002), and remained at approximately the same level (86 ± 7) in the posttransfusion period. Cerebral oxygenation increased from 76 ± 8 in the pretransfusion period to 84 ± 8 at the end of transfusion (p < .001) and remained at 84 ± 8 in the posttransfusion period. Hemoglobin increased from 8.9 ± 1.7 gm/dL pretransfusion to 9.5 ± 1.8 gm/dL posttransfusion (p = .006).

No statistically significant differences in tissue or cerebral oxygenation were detected at any site or time point between patients receiving autologous and allogeneic transfusions, either before, at the completion of, or after the transfusion. Patients receiving autologous and allogeneic transfusions experienced similar increases in tissue oxygenation and hemoglobin. In autologous transfusions, tissue oxygenation measured at the deltoid increased from 84 ± 8 in the pretransfusion period to 87 ± 7 at the end of transfusion (p = .011), cerebral oxygenation increased

from 76 ± 8 to 84 ± 7 (p < .001), and hemoglobin increased from 9.0 ± 1.7 to 9.5 ± 1.8 (p = .030). In allogeneic transfusions, tissue oxygenation measured at the deltoid increased from 79 ± 10 to 84 ± 8 (p = .099) and the hemoglobin increased from 8.4 ± 1.7 to 9.6 ± .9 gm/dL (p = .109). Neither of these reached statistical significance. However, in allogeneic transfusions, a statistically significant increase was noted in cerebral oxygenation from 76 ± 9 to 84 ± 9 (p = .026). Using repeated measures ANOVA, interactions between transfusion type and time point determined that there were no statistically significant differences in the magnitude of change in tissue oxygenation at the deltoid (p = .451), cerebral oxygenation (p = .245), or hemoglobin (p = .301) associated with receiving an autologous vs. an allogeneic transfusion.

Changes in tissue and cerebral oxygenation were also compared between patients with a pre-transfusion hemoglobin <8 gm/dL (n = 11) and patients with pretransfusion hemoglobin ≥8 gm/dL (n = 22) (Table 2). Four patients in each group received an allogeneic transfusion (36% and 18%, respectively; p = .391). In the low-hemoglobin group, tissue oxygenation at the deltoid increased non-significantly from 85 ± 8 to 88 ± 8 (p = .087) while cerebral oxygenation exhibited a statistically significant increase from 74 ± 7 to 84 ± 7 at the end of a transfusion (p = .001). A similar increase in cerebral oxygenation from 77 ± 8 to

**Table 2.** Data based on hemoglobin value before transfusion.

Variable	Hemoglobin <8 gm/dL Mean (SD)	Hemoglobin ≥8 gm/dL Mean (SD)	<i>p</i> Value*
Pretransfusion oxygenation (average of six measurements at 2-minute intervals)			
Deltoid	85 (8)	82 (9)	.431
Cerebral	74 (6)	77 (8)	.266
Average of deltoid and cerebral measurements	79 (7)	80 (6)	.791
End-of-transfusion oxygenation			
Deltoid	88 (8)	86 (7)†	.508
Cerebral	84 (8)†	85 (8)†	.711
Average of deltoid and cerebral measurements	86 (7)†	85 (5)†	.782
Post-transfusion oxygenation (average of five measurements at 2-minutes intervals)			
Deltoid	88 (7)	85 (7)‡	.336
Cerebral	82 (8)‡	85 (7)	.289
Average of deltoid and cerebral measurements	85 (6)	85 (5)	.954

\**p* value by two-tailed independent *t* test comparing mean values by initial hemoglobin level.

†Statistically significant (*p* < .05) change from pre-transfusion mean.

‡Statistically significant (*p* < .05) change from end-of-transfusion mean.

85 ± 8 (*p* < .001) was observed in the high-hemoglobin group. In the latter group, there was also a statistically significant increase in tissue oxygenation measured at the deltoid from 82 ± 9 to 85 ± 8 (*p* = .010). Repeated measures ANOVA confirmed no statistically significant differences in the magnitude of increase in tissue oxygenation at the deltoid (*p* = .551) or cerebral oxygenation (*p* = .667) between the two groups defined by initial hemoglobin.

## DISCUSSION

The general goals of the perioperative administration of packed red blood cells are to restore intravascular volume and increase oxygen delivery to the tissues. Given the recent recognition of the potential adverse effects of the administration of allogeneic blood products, numerous studies have attempted to identify the lowest acceptable transfusion trigger and evaluate other adjunctive therapies to limit the need for allogeneic blood transfusions (10). One such therapy that may limit the need for perioperative allogeneic transfusions is intraoperative cell salvage (11,12). Although generally safe and effective as well as devoid of many of the concerns associated with the administration of allogeneic blood products, significant adverse effects may occur related to the reinfusion of fragmented cells, residual anticoagulant, free hemoglobin, and other factors. As such, it is imperative to identify the beneficial effects of such therapy to develop guidelines for its use and the subsequent administration of salvaged blood. Although strict hemoglobin criteria have been developed for the use of allogeneic blood, clinical practice demonstrates that such criteria are generally not used for the return of intraoperative salvaged blood. In many circumstances, the blood may be reinfused merely because it is

thought to be beneficial, is available, and generally thought to be devoid of risk.

The current study sought to evaluate changes in both cerebral and tissue oxygenation with the administration of either allogeneic or autologous blood during spinal surgery. Although both cerebral and tissue oxygenation increased during the administration of both allogeneic and autologous blood, the increase was limited and perhaps of limited clinical significance given that the initial tissue and cerebral oxygenation level was well within or above the normal range.

Both allogeneic and autologous transfusions led to a similar increase in tissue oxygenation and hemoglobin demonstrating the comparable benefit of salvaged autologous blood to allogeneic blood. Likewise, the increase in tissue oxygenation was the same for patients with a hemoglobin <8 gm/dL vs. those with a hemoglobin >8 gm/dL in the pre-transfusion period. Given these findings, from the current data, it is difficult to identify specific criteria for the administration of cell saver blood. Although the current transfusion trigger for allogeneic blood is generally considered to be in the 7–8 gm/dL range, we identified no difference in the baseline oxygenation levels (tissue and cerebral) or the increase following transfusion in those patients with a starting hemoglobin >8 gm/dL and those with a starting hemoglobin that was <8 gm/dL.

In many cases, the salvaged blood is administered to increase the hemoglobin concentration in an attempt to avoid transfusions during the subsequent perioperative course as ongoing bleeding from the surgical site may result in a subsequent decrease in the hemoglobin by an additional 1–2 gm/dL during the postoperative period. As none of the patients in the cohort received a transfusion during their postoperative course, we cannot comment on the utility of the reinfusion of the salvaged blood on preventing the need for postoperative transfusion therapy.



Although our study is the first to evaluate the effects on tissue and cerebral oxygenation of salvaged blood and to compare it to allogeneic blood, other investigators have attempted to evaluate changes in tissue or cerebral oxygenation following the administration of allogeneic blood (13–19). In these studies, tissue and cerebral oxygenation have been measured using various devices including NIRS, transcutaneous oxygen tension, jugular blood venous oxygen saturation, and direct tissue oxygenation with an implanted Clark electrode. Regardless of the technique used to assess tissue oxygenation, these studies have uniformly demonstrated increases in tissue oxygenation with the administration of allogeneic blood. Despite such changes, a clinical impact on outcome has been difficult if not impossible to demonstrate.

However, despite such findings, several factors may occur during the collection and storage of allogeneic blood that impacts the effect on tissue oxygenation. After 4 days of storage, allogeneic blood is devoid of 2,3-diphosphoglycerate, resulting in the decreased offloading of oxygen at the tissue level due to the increased binding of oxygen to hemoglobin with a left-ward shift of the oxyhemoglobin dissociation curve (<http://www.ventworld.com/resources/oxydisso/dissoc.html>). This defect requires up to 24 hours or more after transfusion to correct (20). As all of the allogeneic blood that was transfused to the patients in the current study was <7 days old, the findings may be impacted when the duration of storage is longer.

Limitations of the current study include the variability in patient comorbid conditions as well as the indications for the surgical procedure. Although all patients were undergoing posterior spinal fusion, the etiology of the scoliosis included both neuromuscular and idiopathic scoliosis. Likewise, there was variability in associated comorbid conditions, age, age of allogeneic blood administered, and gender. Other variabilities that were not rigorously controlled included fluid management. However, this variability was limited by the fact that our intraoperative anesthetic care including fluid management and the use of controlled hypotension for such patients is protocolized and provided by a limited number of anesthesia faculty. Factors which might impact tissue and cerebral oxygenation including oxygen saturation, inspired oxygen concentration, PaCO<sub>2</sub>, body temperature, and MAP were controlled throughout intraoperative care and during data collection. Each patient served as their own control as the tissue and cerebral oxygenation following transfusion were compared to the baseline values obtained prior to transfusion. However, as tissue and cerebral oxygenation were not obtained before anesthetic induction, we cannot comment on these parameters during the awake state without the effects of general anesthesia. Such data would have been helpful in determining the impact of transfusion. Furthermore, during such cases, a key component is spi-

nal cord oxygenation. Although tissue oxygenation was measured, a more specific means of monitoring spinal cord blood flow and oxygenation would be key in the care of such patients. Future studies regarding this and the development of non-invasive means of monitoring spinal cord oxygenation would be a significant advance in scoliosis surgery.

In summary, there was an increase in the tissue and cerebral oxygenation levels following transfusion of either autologous or allogeneic blood. Although the clinical impact on tissue and cerebral oxygenation was limited, the reinfusion of salvaged blood may impact the postoperative hemoglobin value and hence the need for subsequent transfusion. During general anesthesia that decreases tissue and cerebral oxygen consumption, intraoperative tissue and cerebral oxygen levels can be expected to be higher than those seen during the postoperative period. Once the effects of general anesthesia on metabolism and tissue oxygen needs have dissipated, the impact of blood transfusion and the higher hematocrit may be different. Prolonged, postoperative monitoring of tissue and cerebral oxygenation may provide additional data to the benefit of intraoperative transfusion of autologous (cell saver) blood. In addition to these findings, there was no difference in the increase in tissue and cerebral oxygenation when comparing the administration of allogeneic blood with salvaged and washed autologous blood demonstrating the efficacy of intraoperative cell salvage as a means of increasing tissue and cerebral oxygenation while avoiding the potential deleterious physiologic effects of allogeneic transfusion.

## REFERENCES

1. Istaphanous GK, Wheeler DS, Lisco SJ, Shander A. Red blood cell transfusion in critically ill children: A narrative review. *Pediatr Crit Care Med*. 2011;12:174–83.
2. Barcelona SL, Thompson AA, Coté CJ. Intraoperative pediatric blood transfusion therapy: A review of common issues. Part I: Hematologic and physiologic differences from adults; metabolic and infectious risks. *Paediatr Anaesth*. 2005;15:716–26.
3. Barcelona SL, Thompson AA, Coté CJ. Intraoperative pediatric blood transfusion therapy: A review of common issues. Part II: Transfusion therapy, special considerations, and reduction of allogeneic blood transfusions. *Paediatr Anaesth*. 2005;15:814–30.
4. Apfelbaum JL, Nuttall GA, Connis RT. Practice guidelines for perioperative blood management: An updated report by the American society of anesthesiologists task force on perioperative blood management. *Anesthesiology*. 2015;122:1–35.
5. Ashworth A, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth*. 2010;105:401–6.
6. Esper SA, Waters JH. Intra-operative cell salvage: A fresh look at the indications and contraindications. *Blood Transfus*. 2011;9:139–47.
7. Martin DP, Bhalla T, Thung A, et al. A preliminary study of volatile agents or total intravenous anesthesia for neurophysiological monitoring during posterior spinal fusion in adolescents with idiopathic scoliosis. *Spine*. 2014;39:E1318–24.
8. Stephen J, Hogue CW Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol*. 2014;28:429–39.
9. Tobias JD. Cerebral oxygenation monitoring: Near infrared spectroscopy. *Expert Rev Med Devices*. 2006;3:235–43.

10. Meier J, Müller MM, Lauscher P, Sireis W, Seifried E, Zacharowski K. Perioperative red blood cell transfusion: Harmful or beneficial to the patient? *Transfus Med Hemother*. 2012;39:98–103.
11. Williamson KR, Taswell TF. Intraoperative blood salvage: A review. *Transfusion*. 1991;31:662–75.
12. Hodge A, Preston T, Fitch J, et al. Quality improvement methodologies increase autologous blood product administration. *J Extra Corpor Technol*. 2014;46:45–52.
13. Schlager O, Gschwandtner ME, Willfort-Ehringer A, et al. Transcutaneous oxygen tension monitoring in critically ill patients receiving packed red blood cells. *J Crit Care*. 2014;29:1057–62.
14. Nielsen K, Dahl B, Johansson PI, Henneberg SW, Rasmussen LS. Intraoperative transfusion threshold and tissue oxygenation: A randomised trial. *Transfus Med*. 2012;22:418–25.
15. Yuruk K, Bartels SA, Milstein DM, Bezemer R, Biemond BJ, Ince C. Red blood cell transfusions and tissue oxygenation in anemic hematology outpatients. *Transfusion*. 2012;52:641–6.
16. Yamal JM, Rubin ML, Benoit JS, et al. Effect of hemoglobin transfusion threshold on cerebral hemodynamics and oxygenation. *J Neurotrauma*. 2015;32:1239–45.
17. Kurtz P, Helbok R, Claassen J, et al. The effect of packed red blood cell transfusion on cerebral oxygenation and metabolism after subarachnoid hemorrhage. *Neurocrit Care*. 2016;24:118–21.
18. Memtsoudis SG, Danninger T, Stundner O, et al. Blood transfusions may have limited effect on muscle oxygenation after total knee arthroplasty. *HSS J*. 2015;11:136–42.
19. Fiser RT, Irby K, Ward RM, et al. RBC transfusion in pediatric patients supported with extracorporeal membrane oxygenation: Is there an impact on tissue oxygenation? *Pediatr Crit Care Med*. 2014;15:806–13.
20. Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. *Proc Natl Acad Sci USA*. 2007;104:17063–8.