Effects of Freshly Irradiated vs Irradiated and Stored Red Blood Cell Transfusion on Cerebral Oxygenation in Preterm Infants: A Randomized Clinical Trial

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**IMPORTANCE** Gamma irradiation of leukoreduced red blood cells (RBCs) prevents transfusion-associated graft-vs-host disease but also exacerbates storage lesion formation in RBCs. It is unknown whether freshly irradiated RBCs are more efficacious than irradiated and stored RBCs in preterm infants with high transfusion requirements.

**OBJECTIVE** To examine whether transfusion of freshly irradiated vs irradiated and stored RBC components improves cerebral oxygen delivery in preterm infants with anemia.

**DESIGN, SETTING, AND PARTICIPANTS** This single-center, double-blinded, proof-of-concept randomized clinical trial was conducted at the neonatal intensive care unit of Wellington Regional Hospital in Wellington, New Zealand, between December 1, 2017, and November 30, 2018. Participants were preterm infants (<34 weeks' gestation at birth) who were at least 14 days of age and had anemia. Participants underwent nonurgent transfusions, and these episodes were randomized to the intervention group (in which the infants received a transfusion of RBCs that were freshly irradiated on the day of transfusion) or control group (in which the infants received a transfusion of RBCs that were irradiated and stored for up to 14 days). Data were analyzed using the evaluable population approach.

**INTERVENTION** Transfusion of freshly irradiated RBCs.

**MAIN OUTCOMES AND MEASURES** The prespecified primary outcome was the change in cerebral regional oxygen saturation (crSO₂) from baseline (immediately before) to immediately after the transfusion. The prespecified secondary outcomes were the change in cerebral fractional tissue oxygen extraction (cFTOE) at different time points (immediately after, 24 hours after, and 120 hours or 5 days after transfusion). Outcomes were measured by blinded clinicians using near-infrared spectroscopy. A covariate-adjusted linear mixed model was used to quantify mean treatment effects and account for multiple transfusions in some infants.

**RESULTS** A total of 42 infants (mean [SD] gestational age, 26 [10] weeks and 3 days; 29 [69%] boys) were enrolled in the trial and underwent 64 transfusion episodes, which were randomized to the intervention (n = 31) or control (n = 33) group. Compared with infants in the control group, those in the intervention group showed a covariate-adjusted mean increase in crSO₂ (2.0 percentage points; 95% CI, 1.2-2.8 percentage points) and a mean decrease in cFTOE (0.02; 95% CI, 0.01-0.04) immediately after transfusion. These differences were sustained up to 120 hours or 5 days after transfusion. There were negligible mean changes in crSO₂ or cFTOE in infants in the control group at any of the follow-up time points.

**CONCLUSIONS AND RELEVANCE** Results of this trial showed that transfusion of freshly irradiated RBCs conferred a small advantage in cerebral oxygenation for at least 5 days after transfusion compared with transfusion of irradiated and stored RBC components. On-demand irradiation of RBC components may be considered to optimize oxygen delivery in the recipient, but this physiological finding requires further research.

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Preterm infants in neonatal intensive care units (NICUs), particularly those with extremely low birth weight (<1000 g), almost invariably require multiple transfusions of red blood cells (RBCs) before their estimated term birth date.1,3 Most blood transfusions are provided to medically stable infants with chronic anemia (anemia of prematurity), with the aim of increasing oxygen delivery to the metabolically active organs during the critical phase of growth and neurodevelopment. Some infants in NICUs may receive up to 200% cumulative replacement of their total circulating volume at birth by means of transfusion.4 Therefore, ensuring both the safety and efficacy of this common clinical intervention is of utmost importance.

In modern transfusion practice, donors and their donated blood products undergo stringent screening and processing to ensure a high standard of safety for recipients. One common processing method is gamma irradiation of leukoreduced RBCs, which prevents the proliferation of viable donor leukocytes and thus eliminates the risk of transfusion-associated graft-vs-host disease (TA-GVHD) in the recipient.5 Transfusion-associated graft-vs-host disease is a rare but life-threatening complication of RBC transfusion that affects individuals with established immunodeficiency. A systematic review of case reports has suggested that preterm infants with immature immunity may be at risk for TA-GVHD.6 In these infants, it remains uncertain whether modern prestorage leukoreduction alone is sufficient in preventing TA-GVHD. A number of institutions worldwide have adopted a universal irradiation policy because of the potential risk of TA-GVHD in those with previously undiagnosed immune dysfunction.7 Similarly, irradiation of RBCs given to neonates is routine practice in many NICU settings.

Recommended dosimetry and shelf life of irradiated RBCs differ between countries and continents. In Europe and Australasia, it is safe to store irradiated RBCs for up to 14 days (and for up to 28 days in the United States).8-10 Although these recommendations are primarily based on the acceptable levels of hemolysis and extracellular potassium concentrations in stored units, there is a paucity of studies on the oxygen delivery capacity of irradiated and stored RBCs. Limited in vivo evidence to date has highlighted the potentially detrimental effect of storage after irradiation on the ability of RBCs to increase vital organ oxygenation.11 This finding, in conjunction with in vitro evidence of accelerated storage lesion formation in irradiated and stored RBCs,12-18 raises a clinically relevant question: does storage after irradiation compromise the primary function of transfused RBCs to improve oxygen delivery in the recipient?

The aim of this trial is to examine whether transfusion of freshly irradiated, compared with irradiated and stored (according to the Australian and New Zealand Society of Blood Transfusion [ANZSBT] Guidelines19), RBC components improves cerebral oxygen delivery in preterm infants with anemia. We hypothesized that infants who received freshly irradiated RBC components would have increased cerebral regional oxygen saturation (crSO2) and cerebral fractional tissue oxygen extraction (cFTOE) compared with infants who received irradiated and stored RBC components.

## Keywords

**Question** Is a transfusion of freshly irradiated red blood cells (RBCs) more efficacious in improving oxygen delivery capacity than a transfusion of irradiated and stored RBCs?

**Findings** In this randomized clinical trial involving 40 preterm infants with chronic anemia, transfusion of freshly irradiated RBCs resulted in favorable cerebral oxygenation kinetics, with improvement maintained for up to 5 days after transfusion, compared with transfusion of irradiated and stored RBCs.

**Meaning** The findings from this trial suggest that on-demand RBC irradiation may be considered at institutions to optimize oxygen delivery for the transfusion recipient.

## Methods

**Study Design and Population**

The Near Infrared Spectroscopy for Monitoring Brain Oxygenation: Randomized Controlled Trial of Freshly Irradiation vs Standard Red Cell Transfusion for Anemia of Prematurity (NIMO-Rad) trial was a single-center, double-blinded, proof-of-concept RCT conducted at the NICU of Wellington Regional Hospital in Wellington, New Zealand, between December 1, 2017, and November 30, 2018. Written informed consent was obtained prospectively from the legal guardians of participating infants. Approval for the trial was granted by the Human Disability and Ethics Committee of New Zealand, and the trial protocol is provided in Supplement 1. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Preterm infants (<34 weeks’ gestation at birth) who were at least 14 days of age in the Wellington NICU were considered for inclusion. Eligible infants were enrolled if their legal guardian provided written informed consent, after which the attending clinician made a decision to give nonurgent RBC transfusion for anemia of prematurity. This decision was made solely by the attending clinical team using the high transfusion thresholds adopted from the PINT (Premature Infants in Need of Transfusion) trial.19 Infants who were on invasive respiratory support, were undergoing treatment for systemic infections, or had a hemodynamically significant ductus arteriosus or edema (from potential interference with signal acquisition) were excluded. If the enrolled infants received multiple RBC transfusions during the trial period, each transfusion episode was randomized independently on the condition that the infants continued to meet the inclusion criteria, the infants met no exclusion criterion, and the full 5-day follow-up data collection from the previous transfusion was complete. Reasons for exclusion of eligible infants are listed in Figure 1. No participant received an additional transfusion during the 5-day follow up period.

Ethnicity of the infants was reported by their legal guardians and was coded according to the New Zealand Ministry of Health Level I ethnic codes. The ethnic categories were Asian, European, Māori, Middle Eastern, and Pacific.
Randomization and Blinding

Transfusion episodes were randomized either to the intervention group (in which infants received a transfusion with RBCs that were freshly irradiated or irradiated on the day of the transfusion) or the control group (in which infants received a transfusion with RBCs that were irradiated and stored for up to 14 days per the ANZSBT Guidelines). One of us (G.A., a biostatistician) generated a randomization sequence with no restriction using a computerized random sequence generator (Sealed Envelope). The randomization sequence was concealed in a brown envelope and given to the New Zealand Blood Service hospital blood bank before enrollment. After the attending clinician prescribed RBC transfusion for an enrolled infant, a transfusion notification was sent to the hospital blood bank, and the RBC component was issued according to the randomization sequence. There was a 3-hour interval between the transfusion notification and the issuance of the RBC component. For the intervention group, this interval allowed sufficient time for on-demand gamma irradiation to be performed. For the control group, the interval served to maintain blinding of the clinical team.

Because on-demand RBC irradiation was not a standard practice at Wellington Regional Hospital, trial-related transfusion was performed only on Mondays to Saturdays, excluding New Zealand public holidays. For infants who were eligible for multiple transfusions, each transfusion episode was randomized chronologically and independently to the intervention or control group in accordance with the pregenerated randomization sequence. Receipt of more than 1 transfusion was taken into account in the linear mixed model to account for pseudoreplication (eAppendix in Supplement 2).

The RBC components were issued by unblinded blood bank personnel who were not members of the clinical or RCT team. The expiration date and irradiation date of the RBC components were checked by the acting charge nurse managers at the NICU as part of routine transfusion safety protocols and were then masked to maintain blinding of the attending clinicians, bedside nurses, investigators, and parents or legal guardians.

RBC Components for Transfusion

The RBCs used for transfusion were produced from whole blood from known donors with negative cytomegalovirus antibody results and collected in citrate-phosphate dextrose anticoagulant. Plasma was removed, either with or without removal of the buffy coat, and the RBCs were resuspended in an additive solution of saline, adenine, glucose, and mannitol followed by the removal of leucocytes to a maximum residual white cell content of $5 \times 10^6$ per unit. The unit was subsequently divided into 4 satellite packs (pedipacks) using a closed system, and the RBC components were stored between 2 and 6 °C.

Irradiation was performed in accordance with ANZSBT Guidelines. Briefly, RBC components that were less than 14 days old (since donation) were subjected to irradiation with a minimum dose achieved in the irradiation field of 25 Gy; no part received greater than 50-Gy irradiation.

All enrolled infants received a transfusion of 15 mL/kg of the neonatal RBC component over 3 hours. To account for the potentially confounding effects of time since donation and donor characteristics, 4 pedipacks from each adult donor were divided equally between the intervention and control groups (2 pedipacks each).

Outcomes and Sample Size Estimation

In this proof-of-concept RCT, the prespecified primary outcome was the change in $crSO_2$ from baseline (immediately before transfusion) to immediately after transfusion. The prespecified secondary outcomes were the change in cFTOE immediately after transfusion and in the $crSO_2$ and cFTOE at 24 hours and 120 hours (5 days) after transfusion.

To obtain the physiological outcome measures, we used spatially resolved near-infrared spectroscopy (SenSmart Model X-100; Nonin) to determine $crSO_2$ at a sampling rate of 0.25 Hz for 3 hours at the following time points of the transfusion: immediately before, immediately after, 24 hours after, and 120 hours (5 days) after. In all cases, a neonatal sensor with a light penetration depth of 25 mm (EQUANOX Advance Model 8004CB-NA; Nonin) was placed on the left forehead, avoiding the hair and the midline. Peripheral arterial oxygen saturation ($SpO_2$) was recorded concurrently for the calculation of cFTOE, which used this formula: $(SpO_2 - crSO_2) / SpO_2$.

Informed by data from a previous observational study, we estimated a priori that a total of 60 transfusion episodes were required to detect a 5% difference in $crSO_2$ response between the intervention and control groups, with a 2-tailed, unpaired statistical test; 96% power; and $P = .05$ (using G*Power, version 3.1; Heinrich-Heine-Universität Düsseldorf). We based this estimation on an unpaired test between the study groups in the absence of information about how many infants would
ultimately receive more than 1 transfusion. We estimated that the presence of paired (within-participants) cases would ultimately increase rather than decrease the statistical power when modeled appropriately.

Statistical Analysis

Data were analyzed with the evaluable population approach using SPSS, version 24 (IBM SPSS). A linear mixed model was formulated to quantify mean treatment effects with their associated 95% CIs (eAppendix in Supplement 2). Normal distribution of model residuals was confirmed with a histogram.

Results

A total of 61 infants met the inclusion criteria and were considered for nonurgent RBC transfusion by the attending clinical team. Of these infants, 42 (69%) were enrolled in the RCT, of whom 29 were boys (69%) and 11 were girls (26%), with a mean (SD) gestational age of 26 (10) weeks and 3 days. The enrolled infants underwent a total of 64 transfusion episodes, which were randomized to the intervention (n = 31) or control (n = 33) group. No infant received more than 3 trial transfusions. Two infants with 4 transfusion episodes (6%) were lost to follow-up (Figure 1) and were excluded from the final analysis. The most common reason for loss to follow-up was the development of signs of sepsis that needed broad spectrum antibiotics during the 5-day follow-up (n = 3). No infants had a sepsis diagnosis that was confirmed by a positive blood culture result. The clinicians did not believe that such presumed sepsis was associated with the transfusion of RBC components.

Characteristics of the enrolled infants are shown in the Table. Mean baseline values of gestational age, postnatal age, birth weight, weight at the time of the transfusion, hemoglobin count, hematocrit ratio, baseline oxygenation kinetics, and age of RBC components since donation were similar between the 2 groups (Table). The mean (SD) age of RBC components since irradiation in the control group was 9 (3) days. The mean (SD) age of RBC components since donation was shorter for the intervention vs control group (10 [4] days vs 13 [5] days; P = .08).

The main effect of treatment on crSO₂ across all follow-up time points was 2.1 (95% CI, 1.6-2.7) percentage points; P < .001. The treatment and follow-up time interaction was not statistically significant, indicating relatively consistent mean treatment effects at each follow-up time point. Compared with infants in the control group, those in the intervention group showed a higher covariate-adjusted mean crSO₂ of 2.0 (95% CI, 1.2-2.8) percentage points immediately after transfusion (Figure 2). Compared with the control group, the intervention group sustained a posttransfusion increase in covariate-adjusted mean crSO₂, at 24 hours (2.4 percentage points; 95% CI, 1.8-3.1 percentage points) and 120 hours (2.0 percentage points; 95% CI, 0.8-3.2 percentage points). However, there remained negligible changes in crSO₂ in infants in the control group over the follow-up points (Figure 2). Mean treatment effects at each follow-up point were similar in magnitude in the unadjusted models, and mean treatment effects at each follow-up time point were statistically significant (Figure 2; eAppendix in Supplement 2).

Table. Infant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) Intervention group (n = 29)</th>
<th>Control group (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), wk + d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational</td>
<td>26 + 3 (24 + 0-31 + 5)</td>
<td>26 + 3 (24 + 0-31 + 5)</td>
</tr>
<tr>
<td>Corrected postnatal</td>
<td>32 + 4 (28 + 0-38 + 2)</td>
<td>32 + 4 (28 + 0-38 + 2)</td>
</tr>
<tr>
<td>Weight, g</td>
<td>875 (237)</td>
<td>923 (269)</td>
</tr>
<tr>
<td>Birth</td>
<td>1572 (319)</td>
<td>1602 (351)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>European</td>
<td>18 (62)</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Māori</td>
<td>5 (17)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pacific</td>
<td>2 (7)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Hematological parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>86 (9)</td>
<td>84 (8)</td>
</tr>
<tr>
<td>Hematocrit, ratio</td>
<td>0.26 (0.03)</td>
<td>0.26 (0.03)</td>
</tr>
<tr>
<td>Oxygenation kinetics, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>crSO₂</td>
<td>77 (3)</td>
<td>78 (3)</td>
</tr>
<tr>
<td>SpO₂</td>
<td>91 (3)</td>
<td>92 (3)</td>
</tr>
<tr>
<td>cFTOE, ratio</td>
<td>0.15 (0.04)</td>
<td>0.15 (0.03)</td>
</tr>
<tr>
<td>Age of RBC components, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Since donation</td>
<td>10 (4)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Since irradiation</td>
<td>0 (3)</td>
<td>9 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: cFTOE, cerebral fractional tissue oxygen extraction; crSO₂, cerebral regional oxygen saturation; RBC, red blood cell; SpO₂, peripheral arterial oxygen saturation.

* Ethnicity of the infants was reported by the legal guardians and was identified for each transfusion episode as some infants received multiple transfusions and were in both intervention and control groups.
The main effect of treatment on cFTOE across all follow-up points was statistically significant and amounted to a reduction of 0.02 (95% CI, 0.02-0.04; P < .001). The treatment and follow-up time interaction was not statistically significant, indicating relatively consistent mean treatment effects at each follow-up point. Compared with the control transfusion, the intervention showed a statistically significant covariate-adjusted mean reduction in cFTOE immediately after transfusion (0.02; 95% CI, 0.01-0.04) and at 120 hours (0.03; 95% CI, 0.01-0.04). In infants in the intervention group, we found negligible differences in cFTOE at these time points (Figure 2).

Discussion

To our knowledge, the NIMO-Rad trial was the first to quantify the mean treatment effects of storage on the oxygen delivery capacity of gamma-irradiated, transfused RBCs. The findings indicated that storage of irradiated RBCs within the ANZSBT Guidelines-recommended time frame (<14 days) significantly reduced the oxygen delivery capacity of transfused RBCs. Furthermore, the observed difference in oxygen kinetics was maintained for up to 5 days (120 hours) after transfusion, indicating that, contrary to previous suggestions, the function of transfused RBCs does not recover in vivo.24,25

To date, clinical trials of the efficacy and safety of RBC storage have focused almost exclusively on time since donation.26,27 However, it is plausible that this time frame is not the best indicator of structural, biochemical, and functional degradation of stored RBCs.28 Gamma irradiation is associated with an exponential acceleration in RBC hemolysis, which has been associated with increased extracellular potassium and free iron, reduced bioactivity of nitric oxide, rheological changes that alter the ability of RBCs to pass through the microvasculature, decreased 2,3-diphosphoglyceric acid, lower adenine triphosphate concentrations, reduced pH level, and microparticle and microvesicle formation (jointly referred to as storage lesion formation).16-18,29-31 Preclinical studies have demonstrated that, unlike other medical interventions, transfused RBCs are not a functionally homogeneous entity, yet there is a paucity of published data on the effect of processing and subsequent storage of RBC components on their in vivo function. This effect must be urgently addressed.

Preterm infants in the NICU represent a unique cohort of medically stable patients with chronic anemia. The causes for anemia of prematurity are multifactorial and include a breakdown of fetal hemoglobin after exposure to ex utero oxygen-rich environment, immature hemopoietic system in the context of rapid postnatal growth, iatrogenic blood loss, nutritional deficiencies, and chronic inflammation.32,33 Although optimal transfusion thresholds for anemia of prematurity are currently under review, it is generally accepted that the so-called top-up transfusion is required for this patient population for stable oxygen delivery to vital organs during crucial phases of growth and neurodevelopment.34,35 Although commonly adopted transfusion-related trial outcome measures capture important variables, such as all-cause mortality and multiorgan dysfunction,36,37 they are less informative about the physiological efficacy of RBC transfusion. We suggest that a more direct measure of in vivo oxygen kinetics using noninvasive cerebral regional oximetry may provide a valuable insight into the function and efficacy of transfused RBCs.

The NIMO-Rad trial was conducted at a NICU with high transfusion thresholds, which were adopted from the PINT trial. Previous studies that used near-infrared spectroscopy demonstrated that pretransfusion hemoglobin and hematocrit counts were inversely associated with the magnitude of changes in cerebral oxygenation after RBC transfusion.38 At high transfusion thresholds in preterm infants, small or no changes in cerebral oxygenation were observed after transfusion, indicating that changes in oxygen delivery capacity may be compensated by cardiovascular adaptation at these thresholds.39 We found that the small increases in cerebral oxygenation, both in the intervention (2.0%) and control (0.2%) groups, were consistent with findings in previous studies.

![Figure 2. Effect of Freshly Irradiated Red Blood Cells (RBCs) vs Irradiated and Stored RBCs on Cerebral Regional Oxygen Saturation (crSO2) and Cerebral Fractional Tissue Oxygen Extraction (cFTOE)](https://jamanetwork.com/)

A sustained increase in crSO2 and decrease in cFTOE up to 120 hours (5 days) after transfusion were observed in infants in the intervention group. Negligible changes in crSO2 or cFTOE were observed at any of the time points in infants in the control group. Data are presented as unadjusted means (95% CIs) except for the baseline (0 time point) values, which were used as covariates in the statistical model.
We observed no substantial difference in demographic variables and hematological parameters between the 2 groups. In addition, we accounted for the potential confounder of donor characteristics by equally allocating single-donor pedipacks between the 2 groups. We also analyzed the data using a covariate-adjusted statistical model. The mean (SD) age of RBC components since donation was shorter for the intervention group, although the difference from the control group did not reach statistical significance. It is plausible that the unblinded staff of the hospital blood bank may have had a natural bias toward selecting RBC components with a shorter shelf life for the intervention group. However, given that the age of RBC components since donation had a negligible effect on oxygen kinetics or clinical outcomes, we believe this potential difference would not have altered the outcomes of this RCT. We therefore attribute the difference in oxygen kinetics after transfusions in this trial to the practice of storage after gamma irradiation.

This RCT presented new evidence that irradiated and stored RBCs function differently from freshly irradiated RBCs in vivo. Informed by these findings, we postulate that patients who are transfusion dependent for chronic anemia, including preterm infants, may benefit from freshly irradiated RBC components as this transfusion may confer superior oxygen delivery to vital organs. On-demand irradiation of RBC components before transfusion is still within the safety framework of current international guidelines and may be considered at institutions where this approach is practicable. However, the long-term clinical implications of these findings warrant further investigation.

Limitations

This RCT has several limitations. In this physiological study, the clinical significance of the small changes in cerebral oxygenation kinetics was not fully understood. Currently, there are ongoing trials to determine whether reduction in cerebral hypoxia and hyperoxia burdens could improve long-term outcomes in preterm infants. A mean increase in cerebral oxygenation over the 5 days after transfusion by about 2.0% was smaller than the anticipated change of 5.0%. It is possible that these changes may preferentially benefit critically ill infants vs those with chronic anemia. However, because of logistical challenges, on-demand irradiation may not be suitable for those who require urgent RBC transfusion. In this trial, we excluded infants who required mechanical ventilation or had substantial neonatal comorbidities, such as sepsis. In light of the TOP (Transfusion of Prematures) and ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants) trials, which favored a restrictive transfusion practice in preterm infants, a larger clinical trial is required to reexamine the effect of irradiation practice on cerebral oxygenation kinetics and clinical outcomes in this vulnerable patient group.

Conclusions

In this NIMO-Rad trial, transfusion of freshly irradiated RBCs conferred a small benefit in cerebral oxygenation that persisted for at least 5 days after transfusion compared with transfusion of irradiated and stored RBC components, which adhered to the ANZSBT Guidelines. On-demand irradiation of RBC components may be considered at institutions where this approach is practicable given that it remains within the safety framework of current international guidelines. Further research is warranted to ascertain the clinical significance of this physiological finding.
EffectsofFreshlyIrradiatedvsIrradiatedandStoredRedBloodCellTransfusiononCerebralOxygenation

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