Journal of Blood Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

A Clinical Investigation of Hypoxic Red Blood Cell Administration in Patients with Transfusion-Dependent Hematological Malignancies and Burns

Håkon Reikvam[1,2], Turid Helen Felli Lunde[3,4], Einar Klæboe Kristoffersen[2,3], Laurel Omert[5], Jill Bagdasarian[5], Stian K Almeland[6,7]

[1]Department of Clinical Science, University of Bergen, Bergen, Norway; [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway; [3]Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway; [4]Mohn Medical Imaging and Visualization Centre at Department of Radiology, Haukeland University Hospital, Bergen, Norway; [5]Hemanext Inc., Lexington, MA, 02421, USA; [6]Department of Clinical Medicine, University of Bergen, Bergen, Norway; [7]Department of Plastic, Hand, and Reconstructive Surgery, Haukeland University Hospital, Bergen, Norway

Correspondence: Stian K Almeland, Department of Clinical Medicine, University of Bergen, P.O. Box 7804, Bergen, 5020, Norway, Email stian.almeland@gmail.com

Purpose: Red blood cell (RBC) transfusion is frequently given for patients with chronic anemias or acute bleeding after injury or surgery. A CE mark-certified and Food and Drug Administration authorized storage system (Hemanext ONE®; Hemanext Inc. Lexington, MA, United States) has been developed to process and store leukocytes-reduced, O_2/CO_2 reduced RBCs under hypoxic conditions to improve RBC quality for transfusion. This prospective, open-label, single-center pilot safety study investigated the safety of hypoxic RBCs in 2 patient groups: hematological malignancies and acute burns.

Patients and Methods: The primary outcome was the number of patients who experienced an adverse event (AE) within 24 hours of transfusion and overall up to 7 days (±1 day) post-transfusion. Secondary outcomes included changes in hemoglobin (Hb) levels post-transfusion.

Results: Twenty patients (10 with hematological malignancies, 10 with surgical bleeding during burn excision) aged 27–96 years were included (17 males; 8 with hematological malignancies, 9 with burns and 3 females; 2 with hematological malignancies, 1 with burns). All patients in the hematological malignancies group received 2 units of hypoxic RBCs. Patients in the burn group received a mean ±standard deviation (SD) of 1.8 ±0.4 units of hypoxic RBCs. No AEs related to hypoxic RBC transfusion were reported. The mean ±SD changes in Hb from baseline to 15–60 minutes post-transfusion were 1.2 ±0.5 g/dL (hematological malignancies group) and 0.3 ±1.0 g/dL (burn group).

Conclusion: This cohort analysis showed that transfusion with hypoxic RBCs processed with the Hemanext ONE storage system was safe and well tolerated in both cohorts.

Keywords: blood transfusion, hypoxic storage, hematological malignancies, transfusion dependent, burns

Introduction

Red blood cell (RBC) transfusion is a frequently given procedure for many patients. For both malignant (eg. myelodysplastic syndrome, MDS) and non-malignant (eg. aplastic anemia and hemoglobinopathies) hematological diseases, chronic RBC transfusions are needed. Among hematological malignancies, myelodysplastic syndromes (MDS), are a heterogenous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myeloid leukemia.[1–3] RBC transfusions also play an essential role in the surgical management of major burns,[4,5] as tangential excision may lead to major blood loss and anemia.[5] Severe burns create a complex clinical challenge often requiring surgery and prolonged critical care. A major consequence of burn trauma is anemia, driven by blood loss from the injury and surgical

https://doi.org/10.2147/JBM.S573232
Received: 1 November 2025
Accepted: 7 May 2026
Published: 12 June 2026

excision, hemodilution from resuscitation, inflammation-related suppression of red cell production, and increased red cell destruction in extensive burns.[6,7] As a result, patients with major burns frequently need substantial transfusion support, with packed RBCs used to restore hemoglobin levels and ensure adequate tissue oxygenation.[6] However, RBC transfusion can be associated with adverse events including transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), and iron overload in the context of long-term chronic use.[3,8] As such, current principals of patient blood management emphasize the need for restrictive use of RBCs.[9]

Since RBCs are used sparingly, the quality/viability of the RBCs is essential and certain quality parameters can predict the efficacy and safety of a transfusion.[10] Prior to transfusion, RBCs can be stored for up to 35 days in Europe,[11] and up to 42 days in the United States.[12] During storage, RBCs undergo a series of biochemical, metabolic, and structural changes collectively known as the storage lesion.[10,13,14] These changes include not only the accumulation of cytokines and metabolic by-products, but also progressive membrane alterations, loss of deformability and increased hemolysis, the latter being an important quality indicator routinely assessed at the end of storage.[10,15]

Oxygen is the essential substrate for hemoglobin (Hb) oxidation that drives the multitude of physiological and biochemical events underlying the storage lesion, leading to a decrease in the quality of the RBC. In hypoxic storage, the oxygen content of RBC units is reduced to low levels (less than 20% sO_2 prior to refrigeration and maintained throughout storage), which may slow the oxidative pathways that promote these storage-related changes.[16] Hypoxic processing and storage may improve the safety and efficacy of transfusion therapy by potentially reducing oxidative stress and limiting the accumulation of storage-related cytokines and metabolic by-products that have been associated with inflammatory and endothelial activation during transfusion.[10,17] It has been shown to improve the energy and redox metabolism of RBCs in comparison to conventional storage methods,[16] and preserve RBC deformability.[18] In animal models, RBCs stored for 3 weeks under hypoxic conditions improved outcomes during resuscitation from hemorrhagic shock compared with conventionally stored RBCs of the same age.[19] Animals resuscitated with hypoxic RBCs required significantly less transfused volume, were resuscitated faster and demonstrated a lower incidence of ischemic organ injury upon necropsy.[19]

Hemanext Inc. (Lexington, MA, United States) has developed a CE mark and Food and Drug Administration (FDA) authorized device to process and store leukocytes-reduced (LR), O_2/CO_2 reduced RBCs under hypoxic conditions (Hemanext ONE®), to improve RBC quality for transfusion. As yet, there are limited data on the implementation of hypoxic RBCs in different clinical areas. Clinical areas that may benefit from RBCs with improved viability include those where chronic transfusion is indicated (eg., hematological malignancies) and acute intervention contexts where tissue oxygenation is particularly important (eg., acute burns). A safety analysis of the first 5 patients revealed that transfusion with hypoxic RBCs processed with the Hemanext ONE device was safe and well tolerated in patients with hematological malignancies.[20] This safety analysis describes the administration of hypoxic RBCs to patients with hematological malignancies and acute burns (total body surface area (TBSA) burn ≥10% and ≤50%) as part of a pilot post-marketing surveillance study.

Materials and Methods

Study Design

This was a prospective, open-label, single-center, non-comparative exploratory pilot study to evaluate the safety of blood transfusion with hypoxic RBCs manufactured with the Hemanext ONE device.

The study was conducted at Haukeland University Hospital, Norway, between August 2022 and May 2024. The study was carried out according to the clinical investigation plan and principles of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the International Council for Harmonisation Guidelines of Good Clinical Practice, as applicable, and local regulatory authority requirements. The study was also registered on ClinicalTrials.gov (Identifier: NCT05549232). The study protocol was approved by the Regional Ethics Committee (REK), Southeastern Norway. Written informed consent was provided by each patient prior to investigational procedures, and potential study patients were provided with a patient information sheet prior to the screening visit. The study design is detailed in Figure 1.

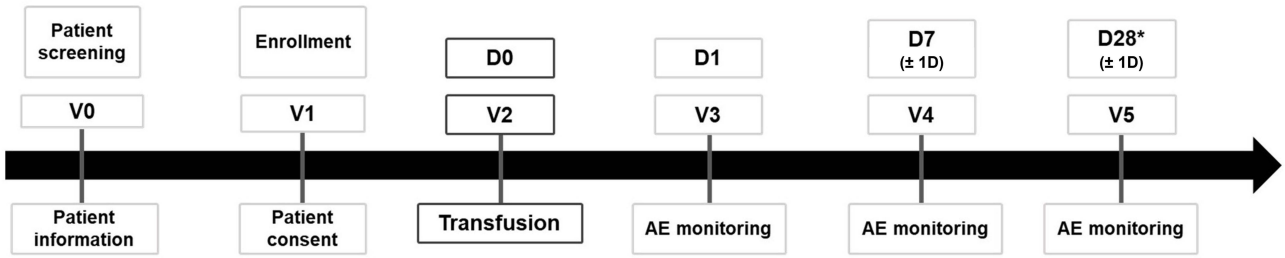

Figure 1 Study design. *Day 28 ±1 day or next transfusion episode, whichever happens first. AE = adverse event, D = day, V = visit. Figure taken from Reikvam H et al 2023 under a CC BY 4.0 license.[21]

Investigational Device

The Hemanext ONE device is a blood container set with the intended use to leukocytes-reduced (LR), O_2/CO_2 reduced RBCs under hypoxic conditions. The Hemanext ONE system is an assembly of 2 disposables: the Oxygen Reduction Bag (ORB) and the Hemanext Storage Bag (HSB) (Figure 2). In this investigation, the Hemanext ONE system was used in accordance with its intended use.[22] Units of hypoxic RBCs were manufactured at 2 regional blood banks using the Hemanext ONE system. A LR RBC unit was sterile-docked to the ORB and transferred by gravity into the device. The ORB was agitated at 72 cycles/min at 22 ± 2°C for 3 ± 0.25 hours. The deoxygenated RBCs were then transferred to the HSB for storage, and the resulting hypoxic RBCs were stored at 1−6°C for up to 35 days.[23]

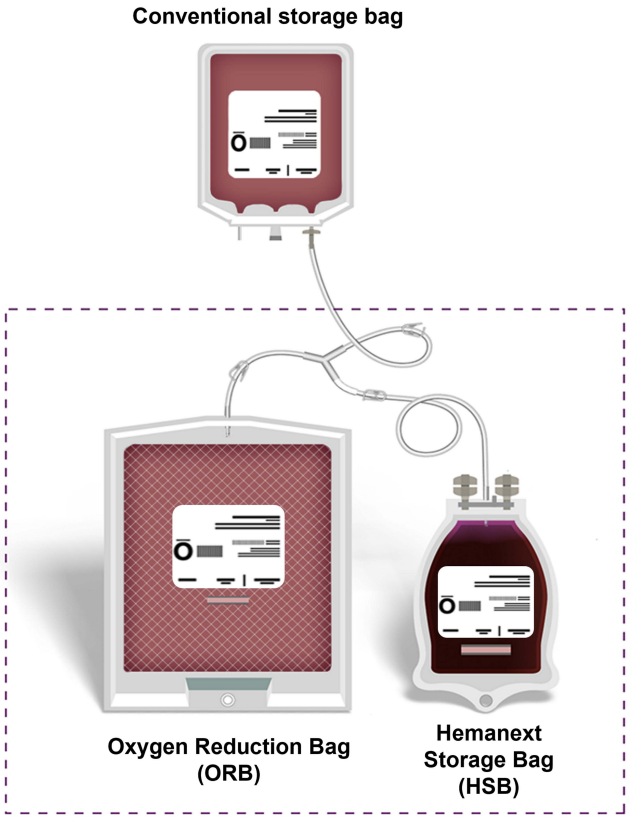

Figure 2 Hemanext ONE system.

https://doi.org/10.2147/JBM.S573232

Study Population

The study population consisted of patients with hematological malignancies who required transfusions due to ineffective erythropoiesis and burn patients requiring transfusion due to surgical bleeding. The target number for enrolment was 20 patients, comprising equal numbers of burn patients and patients with hematological malignancies. These numbers were considered sufficient to assess preliminary safety of O_2/CO_2 reduced RBCs. No formal power calculations were employed in the decision to target twenty patients for enrolment.

Patients with hematologic malignancies were specifically those with stable, non-acute diagnoses requiring chronic or repetitive RBC transfusions over several weeks, without any acute transfusion indications such as infection or bleeding, thereby distinguishing this cohort from the burn patients who required transfusion in an acute setting. Patients were included in the hematological malignancies group if they were aged ≥18 years with a diagnosis of hematological malignancy requiring chronic transfusions and had a Hb level ≤9 g/dL requiring ≥2 units of RBCs in a single transfusion event. Patients were included in the burns group if they were aged ≥18 years, with a TBSA% burn ≥10% and ≤50% requiring ≥2 units of RBCs in a single transfusion event, and the capacity to consent to participate in the clinical investigation. Patients were excluded if they had any positive antibody screening test, a known hemolytic anemia, known or suspected pregnancy, or had a history of major transfusion reactions. Specific to the burns group, patients were excluded if they had TBSA% more than 50%, or other acutely bleeding traumatic injuries.

Study Assessments

Demographic and clinical characteristics were recorded for each patient at enrolment. All patients were scheduled to receive 1 transfusion of 2 units of hypoxic RBCs produced at 2 regional blood banks using the Hemanext ONE system. Participants who would normally have received a transfusion of 2 units of conventional RBCs were instead given a transfusion of 2 units of hypoxic RBCs. Burn patients who needed additional transfusions beyond the 2 study units of hypoxic RBCs were given conventional RBCs for continuation. All transfusions were performed according to the site's standard operating procedures. For burn patients, RBC transfusions were initiated early during surgical procedures when large volume peri-operative blood loss was expected or ongoing, rather than at a specific Hb threshold. Vital signs were measured every 15 minutes during the transfusion and until 15 minutes post-transfusion. Patients were provided with a diary for collection of concomitant medications and changes in health status from enrollment to 28 days post-transfusion. Enrolled patients received standard of care for their condition as prescribed by the investigators, with the exception of receiving up to 2 units of hypoxic RBCs rather than conventional RBCs at their transfusion visit (Day 1). Follow-up was performed on Day 2 (Visit 3), Day 7 (Visit 4), and Day 28 or at the time of their subsequent transfusion, whichever came first (Visit 5). Measurements of Hb levels were carried out at enrollment (Day 0); on Day 1, before and after the transfusion; and after 28 days or at the time of the subsequent transfusion, whichever came first. Blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation were measured on Day 1, before, during, and after the transfusion. Routine laboratory analyses, including blood gases, were carried out as applicable.

Patients were monitored for AEs and adverse device defects throughout the entirety of their participation in the clinical investigation. AEs were collected from the Screening visit through either discharge for burn patients, the subsequent transfusion for hematological malignancy patients, or Day 28, whichever came first. AEs are coded according to MedDRA, version 25.1. Investigators monitored patients directly for AEs during their transfusion visit. Outpatients were contacted by telephone after 24 hours and then 7 days (±1 day) after their transfusion visit or monitored directly if they remained as in-patients to record any AEs experienced since their transfusion visit (Figure 1). Hematological malignancy patients returned to the clinic for a final visit at 28 days (±1 day) or just prior to their subsequent transfusion; burn patients returned to the clinic for a post-operative visit if they resided locally. AEs recorded by the investigators included any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) even if not related to the medical device. AEs were classified by type and severity according to the Association for the Advancement of Blood and Biotherapies Technical Manual (20th edition),[24] the Biomedical Excellence for Safer Transfusion Collaborative review,[25] the local adverse events reference database, and the definitions outlined in ISO 14155:2020.[26]

Blood samples were obtained at a maximum of 4 hours and a minimum of 15 minutes pre-transfusion (baseline), 15–60 minutes post-transfusion, as well as at the final visit. Standard hematology and blood chemistry tests were performed to assess Hb and otherwise monitor for AEs; no calculation of summary data of parameters beyond Hb was therefore planned.

Study Outcomes

The primary outcome of the study was the number of participants who experienced an AE (all types/grades) within a time frame of up to 24 hours following the transfusion initiation and up to 7 days (±1 day) after the transfusion.

Secondary outcomes for both patient groups were: assessment of Hb levels pre- and post-transfusion and before the subsequent transfusion, if applicable; frequency of all AEs, including transfusion-related AEs up to 7 days (±1 day) post-transfusion; AEs up to 28 days post-transfusion or until the subsequent transfusion, whichever occurred first; AEs reported in patient diaries from enrollment up to 28 days post-transfusion or until the subsequent transfusion, whichever occurred first; evaluation of vital signs during the transfusion and up to 15 minutes post-transfusion; and for acute burns patients only, assessment of arterial blood gases (pre-operative, intra-operative, and post-operative). Revised Baux (r-Baux) scores were also calculated for burn patients. Site standard practice was followed for all secondary outcomes related to Hb and vital sign measurements. For all secondary outcomes related to AE occurrence, the above procedure was followed. In addition, the patient's chart was also checked for any AE occurrences.

Estimation of Body Surface Area and Blood Volume

The patient's weight and height were used to calculate body surface area (BSA) using the Du Bois and Du Bois formula:[27] BSA (m^2) = weight $(kg)^{0.425}$ × height $(cm)^{0.725}$ × 0.007184. The patient's blood volume (BV) was calculated as follows: men = BV (l) = BSA × 3.29–1.229; women = BSA × 3.47–1.954.[28,29]

r-Baux Scores

The Baux score is a numerical index that predicts the risk of mortality and prognosis for burn patients. It was originally calculated using a simple formula that considered 2 factors: patient's age and TBSA%. However, advances in burn care led to the development of a r-Baux score in 2010, taking into consideration whether the patient suffered an inhalation injury:[30] r-Baux = TBSA + age + [17 × R], where R = 1 if the patient has an inhalation injury and R = 0 if not.

Statistical Analysis

Continuous data were summarized using descriptive statistics, and categorical data were presented using absolute frequency and percentage. The safety analysis was conducted by calculating the incidences of AEs. The All Patients Set was defined as all enrolled patients, including those patients who withdrew or dropped out of the study up to and including their last visit. The Safety Analysis Set was defined as all patients who received the transfusion. All patients in the Safety Analysis Set attended study Visits 1 to 4. Any missing data were classified as a protocol deviation. Procedures for handling the missing data included documenting what was missing, identifying why it was missing, and reporting in the data analysis per instructions outlined in the Statistical Analysis Plan. Data integrity was ensured through site staff training, routine monitoring, and standardized data management procedures. The study monitor conducted regular site contacts and source data verification to confirm protocol compliance and data accuracy. Data quality controls included automated edit checks, logical reviews, and audit-trailed corrections in accordance with the Data Management Plan.

Results

Patients

Between 30 August 2022 and 16 May 2024, 10 patients with hematological malignancies and 13 patients with acute burn injury were screened for inclusion in this safety cohort analysis. Of these 23 patients, 22 were enrolled and 19 completed the study, with 3 patients prematurely withdrawing from the study, reasons for premature withdrawal are shown in Figure 3. All enrolled patients were included in the All Patients Set, even if not transfused (N=22). All patients who

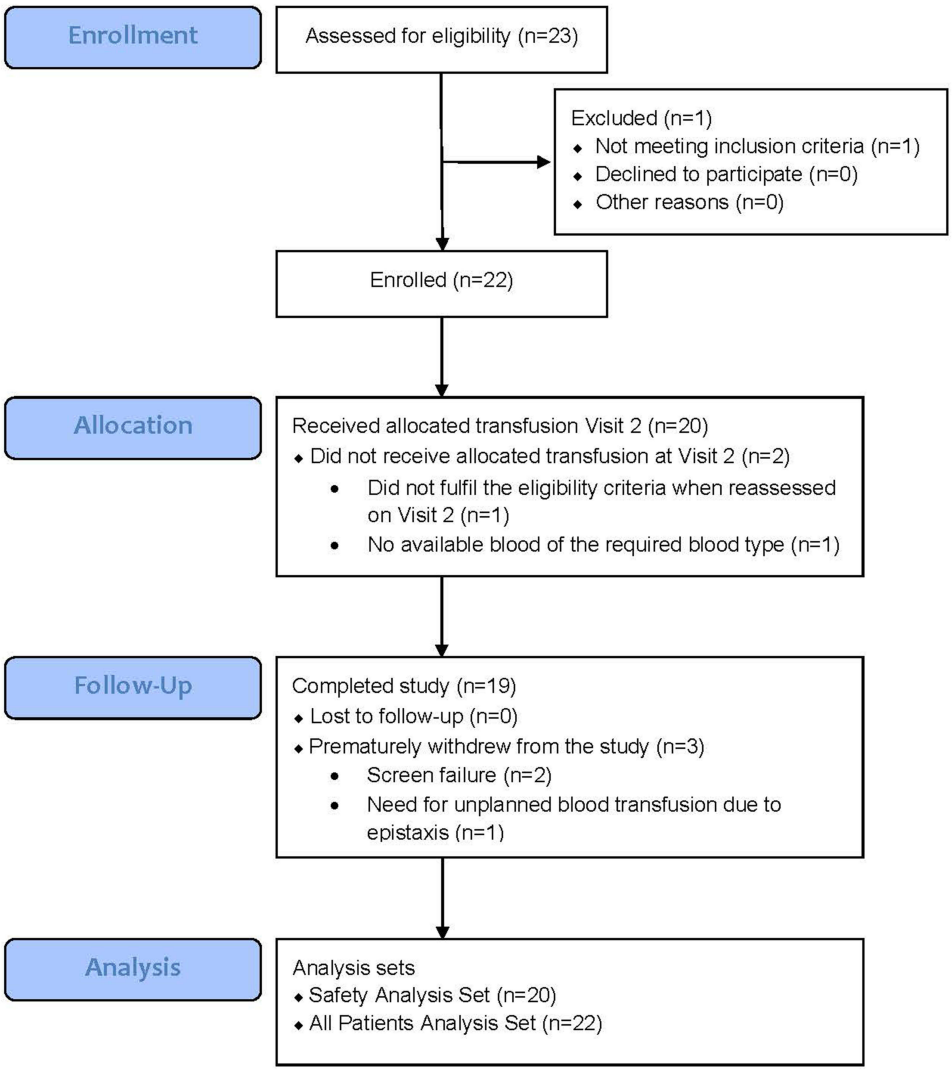

Figure 3 Disposition of patients.

received the transfusion with hypoxic RBCs (N=20) were included in the Safety Analysis Set. Ten patients (100%) from the hematological malignancies group and 10 patients (83%) from the burn group were included in the Safety Analysis Set (Figure 3). The baseline characteristics (All Patients Set) of patients are shown in Table 1. The patients enrolled in the hematological malignancies group were older overall than those in the burn group (mean ±SD age 72 ±16.4 years vs 50 ±19.6 years, respectively). The hematological malignancies patients had a lower mean ±SD body weight than the burn patients, 75.8 ±16.0 kg vs 84.6 ±25.4 kg, respectively, and a lower body mass index (BMI) (mean 24.7 kg/m^2, median 23.5 kg/m^2 vs mean 28.0 kg/m^2 and median 26.4 kg/m^2, respectively). Patient diagnoses in the hematological cohort included hematological malignancy (n=2, 20%), myelodysplastic syndrome (n=2, 20%), primary myelofibrosis (n=2, 20%), acute myeloid leukemia (n=1, 10%), benign monoclonal hypergammaglobulinemia (n=1, 10%), myelofibrosis (n=1, 10%), and sideroblastic anemia (n=1, 10%).

A total of 20 patients received transfusions with hypoxic RBCs. Eighteen patients received the stipulated 2 units of hypoxic RBCs. All patients in the hematological malignancies group received 2 units of hypoxic RBCs. Burn patients were transfused during surgical excision of the burn wound to address hemodynamic instability and improve oxygen delivery when ongoing bleeding from the excised wound bed occurred. Patients in the burn group received a mean ±SD of 1.8 ±0.4 units of hypoxic RBCs. Two patients in the burn group received only 1 unit of hypoxic blood each per investigator decision, as additional blood units were not needed. The median r-Baux score calculated for 10 patients in

Table 1 Demographics and Baseline Characteristics (All Patients Set)

	Acute Burn (N=12)	Hematological Malignancies (N=10)	Total (N=22)
Age, years			
n/n_{miss}	12/0	10/0	22/0
Mean (SD)	49.6 (19.5)	72.0 (16.4)	59.8 (21.1)
Median	44.0	76.0	61.5
Q1, Q3	35.5, 61.5	72.0, 80.0	43.0, 77.0
Sex			
Male	10 (83.3%)	8 (80.0%)	18 (81.8%)
Female	2 (16.7%)	2 (20.0%)	4 (18.2%)
Height (cm)			
n/n_{miss}	11/1	10/0	21/1
Mean (SD)	173.4 (6.1)	174.6 (7.6)	174.0 (6.7)
Median	175.0	176.0	175.0
Q1, Q3	170.0, 176.0	173.0, 179.0	172.0, 178.0
Body Weight (kg)			
n/n_{miss}	11/1	10/0	21/1
Mean (SD)	84.6 (25.4)	75.8 (15.9)	80.4 (21.4)
Median	78.0	74.5	75.0
Q1, Q3	65.0, 97.0	67.0, 85.0	67.0, 88.0
BMI (kg/m^2)			
n/n_{miss}	11/1	10/0	21/1
Mean (SD)	28.0 (7.8)	24.7 (3.8)	26.4 (6.3)
Median	26.4	23.5	24.2
Q1, Q3	21.9, 31.7	22.2, 28.4	22.2, 28.4
Hemoglobin			
n/n_{miss}	10/0	10/0	20/0
Mean (SD)	10.6 (2.2)	8.0 (0.7)	9.3 (2.1)
Median	10.0	8.3	8.6
Q1, Q3	9.2, 11.6	7.5, 8.4	8.2, 10.0
r-Baux score[a]			
n/n_{miss}	10/2	–	–
Mean (SD)	67.2 (19.7)	–	–
Median	59.5	–	–
Q1, Q3	52.8, 82.3	–	–
Hematological malignancy diagnosis, n (%)			
Hematological malignancy	–	2 (20.0%)	–
Myelodysplastic syndrome	–	2 (20.0%)	–
Primary myelofibrosis	–	2 (20.0%)	–
Acute myeloid leukemia	–	1 (10.0%)	–
Hypergammaglobulinemia benign monoclonal	–	1 (10.0%)	–
Myelofibrosis	–	1 (10.0%)	–
Sideroblastic anemia	–	1 (10.0%)	–

Notes: [a]r-Baux scores only calculated for patients with burns. Percentages are based on the number of patients included within each patient group.

Abbreviations: n/n_{miss}, number of subjects with evaluable/missing data; Q1, first quartile; Q3, third quartile; SD, standard deviation.

the burn group was 59.5 (interquartile range 52.8 to 82.3). The mean ±SD duration of the transfusion was 2 hours 24 ±56 minutes in the hematological malignancies group (range 1 hour 30 minutes to 4 hours 30 minutes) and 45 ±18 minutes in the burn group (range 15 minutes to 1 hour 10 minutes).

Safety

An overview of AEs are shown in Table 2. Overall, 11 patients (55%) experienced an AE (9 AEs in 4 patients [40%] in the hematological malignancies group and 17 AEs in 7 patients [70%] in the burn group). Overall, the most commonly reported AE was pyrexia (1 patient [10%] in the hematological malignancies group and 3 patients [30%] in the burn group). All other AEs were reported by 1 or 2 patients each. One patient in the burn group experienced 2 serious, ongoing AEs (oliguria and wound infection) on Day 6 and 7 after transfusion, respectively; both were deemed unrelated to the treatment. In the first 24 hours following the transfusion (primary outcome), a total of 5 AEs were reported in 5 patients (2 AEs in 2 patients [20%] in the hematological malignancies group and 3 AEs in 3 patients [30%] in the burn group). Each AE was a single occurrence and belonged to a different System Organ Class (SOC) (Table 3).

In the first 7 days (±1 day) following the transfusion with hypoxic RBCs (primary outcome), 21 AEs were reported in 11 patients (55%). Fourteen events occurred in 7 patients (70%) in the burn group, and 7 events occurred in 4 patients (40%) in the hematological malignancies group (Table 4). The most frequently reported AEs during this period were pyrexia (4 events in 4 patients [20%] overall; 3 patients [30%] in the burn group and 1 patient [10%] in the hematological malignancies group), pruritus (2 events in 2 patients [20%] in the burn group), headache (2 events in 2 patients in the hematological malignancies group), and atrial fibrillation (2 events in 1 patient in the hematological malignancies group). In total, the hematological malignancies group experienced 9 AEs across 4 patients while the burn group reported 13 AEs

Table 2 Overview of Adverse Events (Safety Analysis Set)

	Acute Burn (N=10)		Hematologic Malignancies (N=10)		Total (N=20)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any AE 24 hrs following the transfusion	3 (30)	4	2 (20)	2	5 (25)	6
Any AE up to 7 days (±1 day) following the transfusion	7 (70)	15	4 (40)	7	11 (55)	22
Any AE from enrollment up to 7 days (±1 day) following the transfusion	7 (70)	15	4 (40)	7	11 (55)	22
Any AE overall	7 (70)	18	4 (40)	9	11 (55)	27
Any serious AE	1 (10)	2	0	0	1 (5)	2
Any AE leading to withdrawal of the study treatment	0	0	0	0	0	0
Any medication or treatment given because of the AE	6 (60)	13	2 (20)	2	8 (40)	15
AEs by severity						
Negligible	6 (60)	9	3 (30)	6	9 (45)	15
Minor	4 (40)	7	2 (20)	3	6 (30)	10
Serious	1 (10)	2	0	0	1 (5)	2
Critical	0	0	0	0	0	0
Catastrophic	0	0	0	0	0	0
AEs by relationship to Hemanext ONE system						
Not related	7 (70)	18	4 (40)	9	11 (55)	27
Possible	0	0	0	0	0	0
Probable	0	0	0	0	0	0
Causal relationship	0	0	0	0	0	0
AEs by causality to study procedure						
Not related	7 (70)	18	4 (40)	9	11 (55)	27
Possible	0	0	0	0	0	0
Probable	0	0	0	0	0	0
Causal relationship	0	0	0	0	0	0

Notes: Percentages are based on the number of patients included within each patient group.
Abbreviations: AE, adverse event; n, number of subjects.

Table 3 Adverse Events 24 Hours Following the Transfusion (Safety Analysis Set)

System Organ Class/Preferred Term	Acute Burn (N=10)		Hematologic Malignancies (N=10)		Total (N=20)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse event	3 (30.0%)	3	2 (20.0%)	2	5 (25.0%)	5
Cardiac disorders	0	0	1 (10.0%)	1	1 (5.0%)	1
Atrial fibrillation	0	0	1 (10.0%)	1	1 (5.0%)	1
General disorders and administration site conditions	1 (10.0%)	1	0	0	1 (5.0%)	1
Pyrexia	1 (10.0%)	1	0	0	1 (5.0%)	1
Metabolism and nutrition disorders	1 (10.0%)	1	0	0	1 (5.0%)	1
Hypocalcemia	1 (10.0%)	1	0	0	1 (5.0%)	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (10.0%)	1	1 (5.0%)	1
Epistaxis	0	0	1 (10.0%)	1	1 (5.0%)	1
Skin and subcutaneous tissue disorders	1 (10.0%)	1	0	0	1 (5.0%)	1
Pain of skin	1 (10.0%)	1	0	0	1 (5.0%)	1

Notes: Adverse events are coded according to MedDRA, MedDRA version 25.1. Percentages are based on the number of patients included within each patient group.
Abbreviations: n, number of subjects; m, number of events.

Table 4 Adverse Events Up to 7 Days (±1 Day) Following the Transfusion (Safety Analysis Set)

System Organ Class/Preferred Term	Acute Burn (N=10)		Hematologic Malignancies (N=10)		Total (N=20)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse event	7 (70.0%)	14	4 (40.0%)	7	11 (55.0%)	21
General disorders and administration site conditions	3 (30.0%)	3	1 (10.0%)	1	4 (20.0%)	4
Pyrexia	3 (30.0%)	3	1 (10.0%)	1	4 (20.0%)	4
Skin and subcutaneous tissue disorders	3 (30.0%)	4	0	0	3 (15.0%)	4
Pruritus	2 (20.0%)	2	0	0	2 (10.0%)	2
Pain of skin	1 (10.0%)	1	0	0	1 (5.0%)	1
Rash	1 (10.0%)	1	0	0	1 (5.0%)	1
Infections and infestations	1 (10.0%)	1	1 (10.0%)	1	2 (10.0%)	2
Nasopharyngitis	0	0	1 (10.0%)	1	1 (5.0%)	1
Wound infection	1 (10.0%)	1	0	0	1 (5.0%)	1
Metabolism and nutrition disorders	2 (20.0%)	2	0	0	2 (10.0%)	2
Electrolyte imbalance	1 (10.0%)	1	0	0	1 (5.0%)	1
Hypocalcemia	1 (10.0%)	1	0	0	1 (5.0%)	1
Nervous system disorders	0	0	2 (20.0%)	2	2 (10.0%)	2
Headache	0	0	2 (20.0%)	2	2 (10.0%)	2
Respiratory, thoracic and mediastinal disorders	1 (10.0%)	1	1 (10.0%)	1	2 (10.0%)	2
Cough	1 (10.0%)	1	0	0	1 (5.0%)	1
Epistaxis	0	0	1 (10.0%)	1	1 (5.0%)	1
Cardiac disorders	0	0	1 (10.0%)	2	1 (5.0%)	2
Atrial fibrillation	0	0	1 (10.0%)	2	1 (5.0%)	2

(*Continued*)

https://doi.org/10.2147/JBM.S573232

Table 4 (Continued).

System Organ Class/Preferred Term	Acute Burn (N=10)		Hematologic Malignancies (N=10)		Total (N=20)	
	n (%)	m	n (%)	m	n (%)	m
Gastrointestinal disorders	1 (10.0%)	1	0	0	1 (5.0%)	1
Nausea	1 (10.0%)	1	0	0	1 (5.0%)	1
Psychiatric disorders	1 (10.0%)	1	0	0	1 (5.0%)	1
Sleep disorder	1 (10.0%)	1	0	0	1 (5.0%)	1
Renal and urinary disorders	1 (10.0%)	1	0	0	1 (5.0%)	1
Oliguria	1 (10.0%)	1	0	0	1 (5.0%)	1

Notes: Adverse events are coded according to MedDRA, MedDRA version 25.1. Percentages are based on the number of patients included within each patient group.
Abbreviations: n, number of subjects; m, number of events.

in 6 patients. One burn patient experienced 2 SAEs (wound infection and oliguria). None of the AEs were deemed related to the blood product or the Hemanext ONE system.

Hb Levels

Mean Hb levels are shown in Figure 4, with changes in Hb levels at each visit shown in Table 5. Hb levels were measured at Visit 2 (transfusion day) before and 15–60 minutes post-transfusion and subsequently at Visit 5 (Day 28 ±1 day). Before the transfusion with hypoxic RBCs, the hematological malignancies group (mean ±SD 8.0 g/dL ±0.7, range 6.9 to 9.0 g/dL) had slightly lower values than the burn group (mean ±SD 10.6 g/dL ±2.3; range 8.1 to 15.1 g/dL).

In the hematological malignancies group, Hb levels increased from baseline to post-transfusion with a mean ±SD change of 1.2 ±0.5 g/dL and were similar when compared with baseline levels at Visit 5, with a mean ±SD change of 0.2 ±1.2 g/dL. In the burn group, Hb levels remained largely unchanged from baseline to post-transfusion with a mean ±SD change of 0.3 ±1.0 g/dL and a mean ±SD change at Visit 5 of 0.8 ±2.1 g/dL.

At Visit 5, patients in the hematological malignancies group had a mean ±SD Hb level of 8.3 ±1.5 g/dL. At Visit 5, patients in the burn group had mean ±SD Hb levels of 11.4 ±1.2 g/dL. One patient was withdrawn prior to Visit 5 due to requiring a transfusion, resulting in their having missing Hb data for Visit 5 (Table 5).

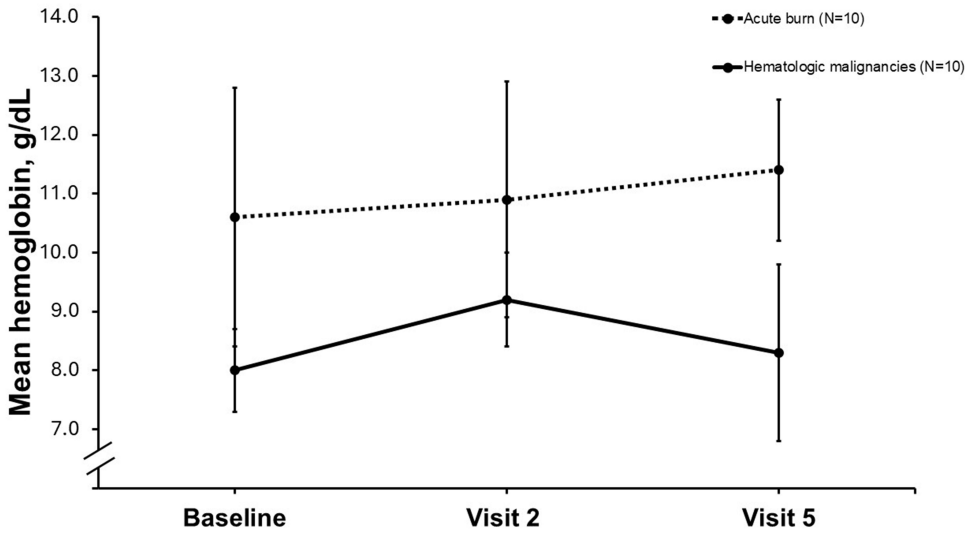

Figure 4 Mean hemoglobin levels at baseline, Visit 2, and Visit 5 (Safety Analysis Set). Error bars represent standard deviation. Baseline was defined as the last valid evaluation prior to the first dose of study medication. Visit 2 was defined as post-transfusion. Visit 5 was defined as the first visit after 28 days/before the following transfusion.

Table 5 Hemoglobin Levels 15–60 Minutes Post-Transfusion, and at Study Exit (Day 28)

Hemoglobin g/dL	Acute Burn (N=10)	Hematologic Malignancies (N=10)	Total (N=20)
Visit 2			
n/n_{miss}	10/0	10/0	20/0
Mean (SD)	10.9 (2.0)	9.2 (0.8)	10.1 (1.7)
Median	11.0	9.1	9.8
Q1, Q3	9.7, 12.3	8.8, 9.9	8.8, 11.0
Change from baseline to Visit 2			
n/n_{miss}	10/0	10/0	20/0
Mean (SD)	0.3 (1.0)	1.2 (0.5)	0.7 (0.9)
Median	0.5	1.1	1.0
Q1, Q3	−0.3, 1.0	0.9, 1.4	0.5, 1.2
Visit 5			
n/n_{miss}	9/1	9/1	18/2
Mean (SD)	11.4 (1.2)	8.3 (1.5)	9.9 (2.0)
Median	12.0	8.0	9.9
Q1, Q3	10.1, 12.3	7.4, 8.8	8.0, 12.0
Change from baseline to Visit 5			
n/n_{miss}	9/1	9/1	18/2
Mean (SD)	0.8 (2.1)	0.2 (1.2)	0.5 (1.7)
Median	0.9	0.1	0.2
Q1, Q3	0.2, 1.8	−0.6, 0.2	−0.6, 0.9

Notes: Baseline was defined as the last valid evaluation prior to the first dose of study medication. Visit 2 was defined as post-transfusion. Visit 5 was defined as the first visit after 28 days/before the following transfusion.
Abbreviations: n/n_{miss}, number of subjects with evaluable/missing data; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Laboratory Findings and Vital Signs

Vital signs at group level were generally stable over the course of the transfusion in both groups. Individual variations were seen, particularly in blood pressure. No AEs relating to vital signs were reported.

Discussion

The Hemanext ONE system is a blood container set used to process and store hypoxic RBCs for any patient requiring a blood transfusion. A clinical investigation demonstrated that the Hemanext ONE system exceeded United States regulatory requirements for post-transfusion in vivo recovery (PTR) by a significant margin, and that hypoxic storage yields more viable RBCs than conventionally stored RBCs.[16]

The safety and tolerability of blood prepared using the Hemanext ONE system was evaluated in this study by monitoring for AEs for 28 days (±1 day) following transfusion of hypoxic RBCs, as well as by standard laboratory assessments, vital sign measurements, and physical examinations. This safety analysis in 20 patients with either hematological malignancies or acute burn injury demonstrated that transfusion with hypoxic RBCs processed with the Hemanext ONE system was safe and well tolerated. AEs observed up to 28 days after transfusion were not evaluated as being related to the transfusion of hypoxic RBC units and there were no changes in vital signs. Hb levels followed the expected pattern for each patient group. Patients in the hematological malignancies group (with chronic anemia) had a mean ±SD increase in Hb levels directly post-transfusion of 1.2 ±0.5 g/dL, followed by a reduction to around baseline levels at the time of the next transfusion. Patients in the burn group (who were transfused to replace lost blood) overall maintained baseline Hb levels after transfusion. Although the hematological malignancy cohort included patients with differing underlying diagnoses and likely varying degrees of thrombocytopenia and minor bleeding risk, their Hb values remained relatively stable over time, with consistently similar post-transfusion increments. In contrast, the burn cohort

showed greater variability in Hb levels as follow-up progressed, reflecting the evolving impact of ongoing blood loss and fluid shifts during acute burn care.

Hematological malignancies, such as MDS, myelofibrosis and leukemia, are increasing in prevalence worldwide as the population average age continues to increase.[31,32] MDS are a heterogenous group of myeloid disorders characterized by peripheral blood cytopenias due to ineffective hematopoiesis.[33] Anemia can result from the ineffective production of normal blood cells, leading to inadequate oxygen delivery. To alleviate the symptoms of anemia, which include fatigue and weakness, RBC transfusion is required and forms an essential component of supportive care for patients with MDS.[34] Patients with transfusion-dependent MDS require frequent use of hospital outpatient services to receive RBC transfusions,[35] which may be given at weekly intervals, in intensive treatment.[36] Frequent transfusions are associated with a large burden on patients, as they can experience transfusion reactions,[3] reductions in quality of life (QoL),[37] and iron overload.[3,38] Larger volume and/or repetitive use of hypoxic RBCs for blood transfusion may result in improved outcomes, both in acute and chronic transfusion settings. A 2-arm cross-sectional study with blood donated by 12 healthy volunteers compared the PTR of conventionally and hypoxically stored RBCs after 24 days of storage.[16] It was found that the PTR values were greater in hypoxically stored RBCs than in conventionally stored RBCs (90.2% vs 87.3%; $p<0.05$).[16] To reduce the burden for those who require frequent RBC transfusions, the larger number of viable RBCs in hypoxically stored blood may be beneficial through increasing time between transfusions. The effects of iron overload may also be reduced, as the use of hypoxic RBCs over standard RBCs may reduce the release of free iron into the circulation.

Major burn trauma triggers an inflammatory cascade of events, leading to oxidative stress and tissue damage, ultimately leading to the development of multiple organ dysfunction.[39] This was reflected in the reported AEs in the first week after peri-operative transfusion in the burn population in this study, all of which represented the expected trajectory of events in this complex heterogeneous patient group. Early excision and grafting are essential for survival but often involve substantial blood loss,[40] consistent with the shorter transfusion durations seen in the burn cohort. Burn patients in this study had a median r-Baux score of 59.5 (interquartile range 52.8 to 82.3), indicating a substantial baseline mortality risk, particularly when inhalational injury is present. The r-Baux score has shown to be a reliable predictor of mortality across diverse patient populations, with higher scores indicating a higher risk of mortality.[41] A large retrospective study using the Baux score to predict mortality, reported a 50% mortality rate in patients with a score of 110, and a 100% mortality rate when the score exceeds 160.[42] The r-Baux score, which incorporates the presence of inhalational injury, increases the total score by 17 points, thus increasing the mortality risk.[30] Although not demonstrable in this dataset, hypoxic RBCs may offer physiological advantages in acute burn resuscitation by reducing oxidative stress, improving oxygen delivery, and potentially decreasing transfusion requirements and organ dysfunction, as suggested by preclinical models. Given the high transfusion demands during extensive burn surgery, this population warrants further investigation into the potential benefits of hypoxic RBCs in large-volume acute transfusion settings.

The introduction of additive solutions allows RBCs to be stored before transfusion for up to 35 days in Europe[11] and up to 42 days in the United States,[12] although extended storage durations are associated with several disadvantages.[43] Evidence from some studies suggests that patients who receive RBCs at the upper limit of this time frame may have an increased risk of morbidity and mortality due to a high storage lesion burden.[44,45] However, findings across the literature are not fully consistent, and the clinical relevance of these changes remains an area of ongoing investigation.[10,43,44] There are also significant changes in the plasma levels of hemolytic markers, oxidized purines, plasticizers, and oxidized lipids[13] and, over time, the deformability of RBCs also diminishes, which affects perfusion in the microcirculation.[46]

Within the national guidelines for transfusion service at this center, RBCs range from 1–35 days old. Hypoxic storage confers biochemical advantages that may translate into clinical benefits. Hypoxic processing of RBCs reduces oxidative stress and has been shown to counteract some metabolic impairments that occur during refrigerated storage.[47,48] Hypoxic storage has also been shown to improve post-transfusion recovery over conventionally stored RBCs, and the use of hypoxically stored blood improves oxygen delivery.[49–51] Additionally, hypoxically stored blood may decrease the required number of RBC transfusions. Therefore, this reduction in blood requirements may lead to lower transfusion dose density and decreased risk of iron overload[47,52] in patients with hematological malignancies.

This study has several limitations that are inherent to a pilot post-marketing study. The small sample size reduces statistical precision and limits the generalizability of the findings. The absence of a control arm prevents direct comparison with standard care or alternative interventions, making it difficult to attribute observed effects solely to the study treatment. In addition, the monocentric design may introduce center-specific biases and further constrain external validity. Finally, the study was not powered to detect infrequent or rare AEs. There is a need for larger, controlled studies to better characterize transfusion-induced changes and the potential clinical benefits of hypoxic RBCs.

This full cohort safety analysis has demonstrated that hypoxic RBCs were well tolerated in patients with hematological malignancies and acute burn injury. Further studies investigating the efficacy of hypoxic RBC administration have been initiated. The overall clinical program will elucidate any potential benefits of transfusion with hypoxic RBCs, including impacts on transfusion interval, patient QoL, and ferritin levels over time in patients who require chronic RBC transfusion compared with conventional RBCs.

Conclusion

This pilot study found no safety concerns associated with transfusion of hypoxic RBCs manufactured and stored with the Hemanext ONE system. Moreover, hemoglobin levels were within the target range at follow-up, which indicates that hypoxic RBCs functioned as intended. As efficacy cannot be evaluated from this dataset, further clinical studies are needed to evaluate the advantages of using hypoxic RBCs compared with conventional RBCs in patients needing acute or chronic transfusions.

Abbreviations

BMI, body mass index; BSA, body surface area; BV, blood volume; AE, adverse event; Hb, hemoglobin; MDS, myelodysplastic syndromes; n/n_{miss}, number of subjects with evaluable/missing data; PTR, post-transfusion in vivo recovery; Q1, first quartile; Q3, third quartile; QoL, quality of life; RBC, red blood cell; SAE, serious adverse event; SD, standard deviation; SOC, System Organ Classes; TBSA, total body surface area; TRALI, transfusion-related lung injury; TACO, transfusion-associated circulatory overload.

Data Sharing Statement

Individual participant data are not available. The Study Protocol and Statistical Analysis Plan are available indefinitely at Clinicaltrials.gov (Identifier: NCT05549232).

Acknowledgments

The authors wish to thank the clinical staff of the Burn Unit and Hematology Department at Haukeland University Hospital, as well as the laboratory staff at the University of Oslo Blood Bank and the Haukeland University Hospital Blood Bank, for their invaluable contributions and support in making this pilot study possible. Medical Writing assistance was provided by Meridian HealthComms Ltd, Manchester, UK in accordance with Good Publication Practice (GPP 2022), funded by Hemanext, Inc.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Hemanext, Inc.

Disclosure

HR and SKA have received support for congress travel from Hemanext, Inc. LO and JB report employment with and stock in Hemanext, Inc. The authors report no other conflicts of interest in this work.

References

1. Menssen AJ, Walter MJ. Genetics of progression from MDS to secondary leukemia. *Blood*. 2020;136(1):50–60. doi:10.1182/blood.2019000942
2. Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98 (8):1307–1325. doi:10.1002/ajh.26984
3. Wood EM, McQuilten ZK. Outpatient transfusions for myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program*. 2020;2020 (1):167–174. doi:10.1182/hematology.2020000103
4. Tichil I, Rosenblum S, Paul E, Cleland H. Treatment of Anaemia in Patients with Acute Burn Injury: a Study of Blood Transfusion Practices. *J Clin Med*. 2021;10(3):476–485. doi:10.3390/jcm10030476
5. Kaserer A, Rössler J, Slankamenac K, et al. Impact of allogeneic blood transfusions on clinical outcomes in severely burned patients. *Burns*. 2020;46(5):1083–1090. doi:10.1016/j.burns.2019.11.005
6. Palmieri TL, JHt H, Arnoldo B, et al. Transfusion Requirement in Burn Care Evaluation (TRIBE): a Multicenter Randomized Prospective Trial of Blood Transfusion in Major Burn Injury. *Ann Surg*. 2017;266(4):595–602. doi:10.1097/sla.0000000000002408
7. Burgess M, Valdera F, Varon D, Kankuri E, Nuutila K. The Immune and Regenerative Response to Burn Injury. *Cells*. 2022;11(19):3073. doi:10.3390/cells11193073
8. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. *Hematology Am Soc Hematol Educ Program*. 2018;2018 (1):585–594. doi:10.1182/asheducation-2018.1.585
9. Carson JL, Stanworth SJ, Guyatt G, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. *JAMA*. 2023;330(19):1892–1902. doi:10.1001/jama.2023.12914
10. Yoshida T, Prudent M, D'Alessandro A. Red blood cell storage lesion: causes and potential clinical consequences. *Blood Transfus*. 2019;17 (1):27–52. doi:10.2450/2019.0217-18
11. European Directorate for the Quality of Medicines & HealthCare (EDQM). *Guide to the Preparation, Use and Quality Assurance of Blood Components*. 19th edn. Council of Europe; 2017.
12. U.S. Food and Drug Administration (FDA). *Dating Periods for Whole Blood and Blood Components. Code of Federal Regulations, Title 21, Part 610.53*. Washington, DC: U.S. Government Publishing Office; 2016.
13. D'Alessandro A, Reisz JA, Zhang Y, et al. Effects of aged stored autologous red blood cells on human plasma metabolome. *Blood Adv*. 2019;3 (6):884–896. doi:10.1182/bloodadvances.2018029629
14. Zimring JC. Established and theoretical factors to consider in assessing the red cell storage lesion. *Blood*. 2015;125(14):2185–2190. doi:10.1182/blood-2014-11-567750
15. European Directorate for the Quality of Medicines & HealthCare (EDQM). *Guide to the Preparation, Use and Quality Assurance of Blood Components*. 22nd edn. Council of Europe Publishing; 2025.
16. D'Alessandro A, Yoshida T, Nestheide S, et al. Hypoxic storage of red blood cells improves metabolism and post-transfusion recovery. *Transfusion*. 2020;60(4):786–798. doi:10.1111/trf.15730
17. Anastasiadi AT, Stamoulis K, Kriebardis AG, Tzounakas VL. Molecular modifications to mitigate oxidative stress and improve red blood cell storability. *Front Physiol*. 2024;15:1499308. doi:10.3389/fphys.2024.1499308
18. Karafin MS, Field JJ, Ilich A, et al. Hypoxic storage of donor red cells preserves deformability after exposure to plasma from adults with sickle cell disease. *Transfusion*. 2023;63(1):193–202. doi:10.1111/trf.17163
19. Williams AT, Jani VP, Nemkov T, et al. Transfusion of anaerobically or conventionally stored blood after hemorrhagic shock. *Shock*. 2020;53 (3):352–362. doi:10.1097/SHK.0000000000001386
20. Reikvam H, Hetland G, Ezligini F, et al. Safety of hypoxic red blood cell administration in patients with transfusion-dependent hematological malignancies: an interim analysis. *Transfus Apher Sci*. 2023;62(5):103755–103759. doi:10.1016/j.transci.2023.103755
21. Reikvam H, van de Watering L, Prowse C, Devine D, Heddle NM, Hervig T. Evaluation of noninvasive methods for the estimation of haemoglobin content in red blood cell concentrates. *Transfus Med*. 2011;21(3):145–149. doi:10.1111/j.1365-3148.2010.01059.x
22. Hemanext Inc. Lexington MA. HemanextONE Instructions for Use. 2023. Available from: https://hemanext.com/wp-content/uploads/2024/04/Hemanext-US-IFU-FF-ML.pdf. Accessed Jan 1, 2025.
23. Agostini V, Henschler R, Lunde THF, et al. A validation study of the in vitro performance of hypoxic red blood cells for transfusion across centers in Europe. *Transfusion*. 2025;65(12):2306–2315. doi:10.1111/trf.18408
24. Cohn CS, Delaney M, Johnson ST, Katz LM. *AABB Technical Manual*. 20th edn. Association for the Advancement of Blood and Biotherapies; 2020:408–409,434–444.
25. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet*. 2016;388(10061):2825–2836. doi:10.1016/s0140-6736(15)01313-6
26. International Organization for Standardization. *ISO 14155:2020. Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice*. Geneva: ISO; 2020.
27. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989;5(5):303–311.
28. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery*. 1962;51(2):224–232.
29. Wendelbo Ø, Netland Opheim E, Felli Lunde TH, Bruserud Ø, Hervig T, Reikvam H. A prospective observational study on effects of fever on red cell transfusion outcome. *Vox Sang*. 2017;112(5):484–486. doi:10.1111/vox.12526
30. Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the baux score. *J Trauma*. 2010;68(3):690–697. doi:10.1097/TA.0b013e3181c453b3
31. Cancer Registry of Norway. *Cancer in Norway 2021 - Cancer Incidence, Mortality, Survival and Prevalence in Norway*; 2022.

32. Zhang N, Wu J, Wang Q, et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. *Blood Cancer J*. 2023;13(1):82. doi:10.1038/s41408-023-00853-3
33. Castelli R, Schiavon R, Deliliers GL. The impact of anaemia, transfusion dependency, comorbidities and polypharmacy in elderly patients with low-risk myelodysplastic syndromes. *Med Oncol*. 2018;35(3):33. doi:10.1007/s12032-018-1094-7
34. de Swart L, Crouch S, Hoeks M, et al. Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes. *Haematologica*. 2020;105(3):632–639. doi:10.3324/haematol.2018.212217
35. Jouzier C, Cherait A, Cony-Makhoul P, et al. Red blood cell transfusion burden in myelodysplastic syndromes (MDS) with ring Sideroblasts (RS): a retrospective multicenter study by the Groupe Francophone des Myelodysplasies (GFM). *Transfusion*. 2022;62(5):961–973. doi:10.1111/trf.16884
36. Cannas G, Thomas X. Supportive care in patients with acute leukaemia: historical perspectives. *Blood Transfus*. 2015;13(2):205–220. doi:10.2450/2014.0080-14
37. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6(8):e732. doi:10.1097/HS9.0000000000000732
38. Sanz G, Nomdedeu B, Such E, et al. Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome. *Blood*. 2008;112(11):640. doi:10.1182/blood.V112.11.640.640
39. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS One*. 2011;6(7):e21245. doi:10.1371/journal.pone.0021245
40. Anyanwu JA, Cindass R. Burn Debridement, Grafting, and Reconstruction. In: *StatPearls*. StatPearls Publishing; 2024.
41. Edgar MC, Bond SM, Jiang SH, Scharf IM, Bejarano G, Vrouwe SQ. The Revised Baux Score as a Predictor of Burn Mortality: a Systematic Review and Meta-Analysis. *J Burn Care Res*. 2023;44(6):1278–1288. doi:10.1093/jbcr/irad075
42. Roberts G, Lloyd M, Parker M, et al. The Baux score is dead. Long live the Baux score: a 27-year retrospective cohort study of mortality at a regional burns service. *J Trauma Acute Care Surg*. 2012;72(1):251–256. doi:10.1097/TA.0b013e31824052bb
43. Lee JS, Kim-Shapiro DB. Stored blood: how old is too old? *J Clin Invest*. 2017;127(1):100–102. doi:10.1172/JCI91309
44. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008;358(12):1229–1239. doi:10.1056/NEJMoa070403
45. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. *Crit Care*. 2009;13(5):R151. doi:10.1186/cc8050
46. Weinberg JA, MacLennan PA, Vandromme-Cusick MJ, et al. The deleterious effect of red blood cell storage on microvascular response to transfusion. *J Trauma Acute Care Surg*. 2013;75(5):807–812. doi:10.1097/TA.0b013e3182a74a9b
47. Yoshida T, AuBuchon JP, Tryzelaar L, Foster KY, Bitensky MW. Extended storage of red blood cells under anaerobic conditions. *Vox Sang*. 2007;92(1):22–31. doi:10.1111/j.1423-0410.2006.00860.x
48. Dumont LJ, Yoshida T, AuBuchon JP. Anaerobic storage of red blood cells in a novel additive solution improves in vivo recovery. *Transfusion*. 2009;49(3):458–464. doi:10.1111/j.1537-2995.2008.02038.x
49. ClinicalTrials.gov. Clinical investigation to evaluate the Hemanext® Oxygen Reduction System - Pivotal Trial. Identifier NCT03301779. Available from: https://clinicaltrials.gov/study/NCT03301779?term=hemanext&rank=2. Accessed Sep 1 2024.
50. Muller CR, Courelli V, Govender K, Omert L, Yoshida T, Cabrales P. Hypoxically stored RBC resuscitation in a rat model of traumatic brain injury and severe hemorrhagic shock. *Life Sci*. 2024;340:122423. doi:10.1016/j.lfs.2024.122423
51. Rabcuka J, Blonski S, Meli A, et al. Metabolic reprogramming under hypoxic storage preserves faster oxygen unloading from stored red blood cells. *Blood Adv*. 2022;6(18):5415–5428. doi:10.1182/bloodadvances.2022007774
52. Zolla L, D'Alessandro A. An efficient apparatus for rapid deoxygenation of erythrocyte concentrates for alternative banking strategies. *J Blood Transfus*. 2013;2013:896537. doi:10.1155/2013/896537