Heart rate changes in chronically red cell transfusion-dependent patients-A dose-dependent effect of red cell transfusion: a randomized cross-over trial, interim analysis

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TRANSFUSION

ORIGINAL RESEARCH

Transfusion Practice

Heart rate changes in chronically red cell transfusion-dependent patients—A dose-dependent effect of red cell transfusion: A randomized cross-over trial, interim analysis

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Abstract

Background: Restrictive red blood cell transfusion strategies are widely recommended for acute anemia but may not adequately address the needs of chronically anemic patients with transfusion-dependent myelodysplastic syndromes or myeloproliferative neoplasms. For these patients with chronic anemia, alleviating symptoms and improving quality of life are key objectives. This study evaluates the impact of additional red blood cell (RBC) transfusions administered alongside standard-of-care transfusions on heart rate, physical activity, quality of life, and cognitive function.

Study Design and Methods: This interim analysis of a randomized, multicenter, within-subject, cross-over trial evaluated 12 transfusion-dependent patients receiving three transfusion regimens: standard-of-care, standard-of-care + 1 additional unit, and standard-of-care + 2 additional units. The primary outcome was heart rate, and secondary outcomes were physical activity, quality of life, and cognitive performance. Heart rate and activity were continuously monitored, while questionnaires and cognitive tasks assessed outcomes at predefined visits.

Results: Greater hemoglobin augmentation was associated with significant reductions in heart rate, with the largest decrease in patients receiving the

Abbreviations: Hb, hemoglobin; HRQoL, health-related quality of life; IQR, interquartile range; MDS, myelodysplastic syndromes; MFI, Multivariate Fatigue Index; MPN, myeloproliferative neoplasms; QUALMS, Quality of Life in Myelodysplasia Scale; RBC, red blood cell; SoC, standard of care.

standard-of-care + 2 regimen. Quality of life and fatigue measures showed transient improvements with more red blood cells transfused, though these changes were not statistically significant. Cognitive performance trends suggested possible benefits, but findings were inconsistent. Physical activity, as measured by daily step count, was unaffected by transfusions.

Conclusions: This interim analysis suggests that higher post-transfusion hemoglobin is associated with lower heart rate, reflecting enhanced oxygen delivery. Wearable monitoring was sensitive to these changes. Nonsignificant, hypothesis-generating trends toward improved QoL, fatigue, and cognition were observed.

KEYWORDS

biosensor, chronic anaemia, personalizing transfusion, quality of life, transfusion strategy

1 | BACKGROUND

Restrictive red blood cell (RBC) transfusion strategies in hemato-oncologic patients lead to reduced transfusion-associated costs, transfusion reactions[1–3] and iron overload,[4,5] and importantly are not offset by an increase in morbidity or mortality.[6–8] While this approach is hence considered the default for patients with acute and reversible anemia, its applicability to individuals with chronic transfusion dependence, such as those with myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), remains debatable. For these patients, the deep anemic trigger for their restrictive transfusions might likely and chronically impair physical well-being and quality of life (QoL). Typically, a transfusion threshold of around 8.0 g/dL is used in the Netherlands[9] and elsewhere,[10,11] which may come at a cost of increased anemia-related symptoms.

Despite the well-documented impact of anemia on functional and cognitive decline,[12] mobility,[13] and overall physical performance,[14,15] especially in elderly populations, a causality behind these associations is not proven; possibly, lower hemoglobin concentrations may simply indicate a more advanced disease, with consequently poorer QoL scores independent of the anemia. Moreover, there is limited evidence on whether RBC transfusions can improve these outcomes in patients with transfusion-dependent MDS or MPN[16–20] and which functional tests are most appropriate to evaluate this.

Apart from a feasibility study and a pilot trial suggesting an improvement in QoL in the liberal arm compared to a restrictive transfusion strategy,[19,20] no completed trials have directly compared restrictive versus liberal transfusion strategies in chronic transfusion-dependent patients. Optimizing transfusion practices in this usually outpatient population requires a comprehensive understanding of both risks and benefits, as well as the identification of clinically relevant and objective measures of well-being.

The goals of transfusion in this population diverge from those in critically ill or surgical patients, where (non-inferior) survival and vital support are the primary objectives. Instead, transfusion strategies for patients with transfusion-dependent MDS and MPN should at least acknowledge alleviation of anemia-related symptoms, improving functional capacity and QoL. Advances in wearable technology now provide opportunities to objectively measure patient-specific outcomes, including physical activity and heart rate. Preliminary pilot data suggest that RBC transfusions induce favorable hemodynamic changes, such as transient reductions in heart rate, which may correlate with improved physical activity and QoL, reduced fatigue and possibly even improved cognition.[21]

As life expectancy continues to increase, the prevalence of MDS and MPN—conditions that frequently result in transfusion dependence[22,23]—also rises, underscoring the growing relevance of our research questions.

Using wearable technology, this study aims to assess the impact of varying RBC transfusion regimens on heart rate as the primary outcome. Secondary outcomes include QoL, physical activity, and cognitive function. By addressing these knowledge gaps, this research seeks to inform evidence-based strategies that enhance patient-centered outcomes in chronic transfusion care.

Enrollment proceeded substantially more slowly than anticipated. We therefore conducted an interim analysis with two aims: first, to provide early insights that could inform the design and expectations of future trials; and second, to permit early termination for futility if no clinically meaningful effect was apparent. With this approach, we aim to minimize unnecessary patient burden and resource use while preserving the scientific integrity of the study.

2 | STUDY DESIGN AND METHODS

This multicenter, randomized, within-subject, cross-over trial evaluated the effects of RBC transfusion regimens on heart rate in transfusion-dependent patients with WHO-defined MDS, MPN, or MDS/MPN overlap syndromes. Secondary objectives included potential effects on physical activity, QoL, and cognitive function. Eligible participants were adults aged ≥18 years with ongoing RBC transfusion dependency, a life expectancy ≥6 months, and stable treatment regimens. Key exclusions included severe pulmonary or cardiac comorbidities, poor functional status (ECOG ≥3), and significant renal impairment (eGFR <30 mL/min). Data were collected at participating centres affiliated with the Leiden University Medical Centre, in the Netherlands after informed consent was obtained. Ethical approval was granted by the medical ethics committee Leiden-Den Haag-Delft. The trial was registered at the Dutch Trial Register/LTR (ID:NL9289). The trial was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Recruitment commenced in August 2021. Due to slow enrolment, an interim analysis of the first 12 patients was conducted, with follow-up for this analysis completed in March 2024.

2.1 | Intervention

The standard-of-care (SoC) transfusion regimen, determined by the treating physician (e.g., 2 RBC units every 3 weeks), was used as a baseline. Participants subsequently received one SoC transfusion and two additional transfusion regimens—SoC + 1 and SoC + 2, corresponding to one and two additional RBC units, respectively—administered per the protocol outlined in Figure 1. Blinding was not feasible due to observable differences in transfusion amount. We used a cross-over design to increase precision by within-subject comparison, thereby reducing between-subject variability and required sample size. Between study transfusions, a washout transfusion was carried out to minimize potential carryover. Patients were randomized in a 1:1:1 ratio (allocation concealed) to three groups using Castor randomization software. This randomization accounted for potential temporal effects—like gradual patient deterioration—on outcomes, ensuring balanced evaluation of interventions across study participants.

2.2 | Outcomes

Heart rate and physical activity were continuously monitored by a biosensor—the Withings Steel HR smartwatch—starting 1 week before transfusion until the subsequent transfusion. Patients also completed the Quality of Life in Myelodysplasia Scale (QUALMS) and Multivariate Fatigue Index (MFI) questionnaires. Cognitive function was assessed via CANTAB tasks (RVP, SWMS, OTS). Hemoglobin levels were assessed before and after each transfusion to determine transfusion efficacy. Measurements were aligned with each patient's transfusion schedule.

The primary and secondary outcomes were assessed at three predefined timepoints: 2 days before the intervention transfusion (V1) 7 days after transfusion (V2) and 2 days prior to the subsequent transfusion (V3), as visualized in Figure 2. An exception was made for patients that receive transfusions on a weekly basis: in those cases, V2 was 2 days post-transfusion. To attenuate day-to-day fluctuations from transient factors (e.g., exercise or acute stress) in heart rate and activity, data from the 3 days surrounding each visit were used for analysis.

2.3 | Sample size

The sample size for the complete study was calculated based on detecting a mean difference of 1 bpm in heart rate across transfusion groups, assuming a standard deviation of 1.5 bpm. Using a paired design with $\alpha = 0.05$ and $\beta = 0.20$, 18 patients were required. Accounting for a 25% dropout rate, the total target sample size was set at 24 patients.

2.4 | Statistical methods

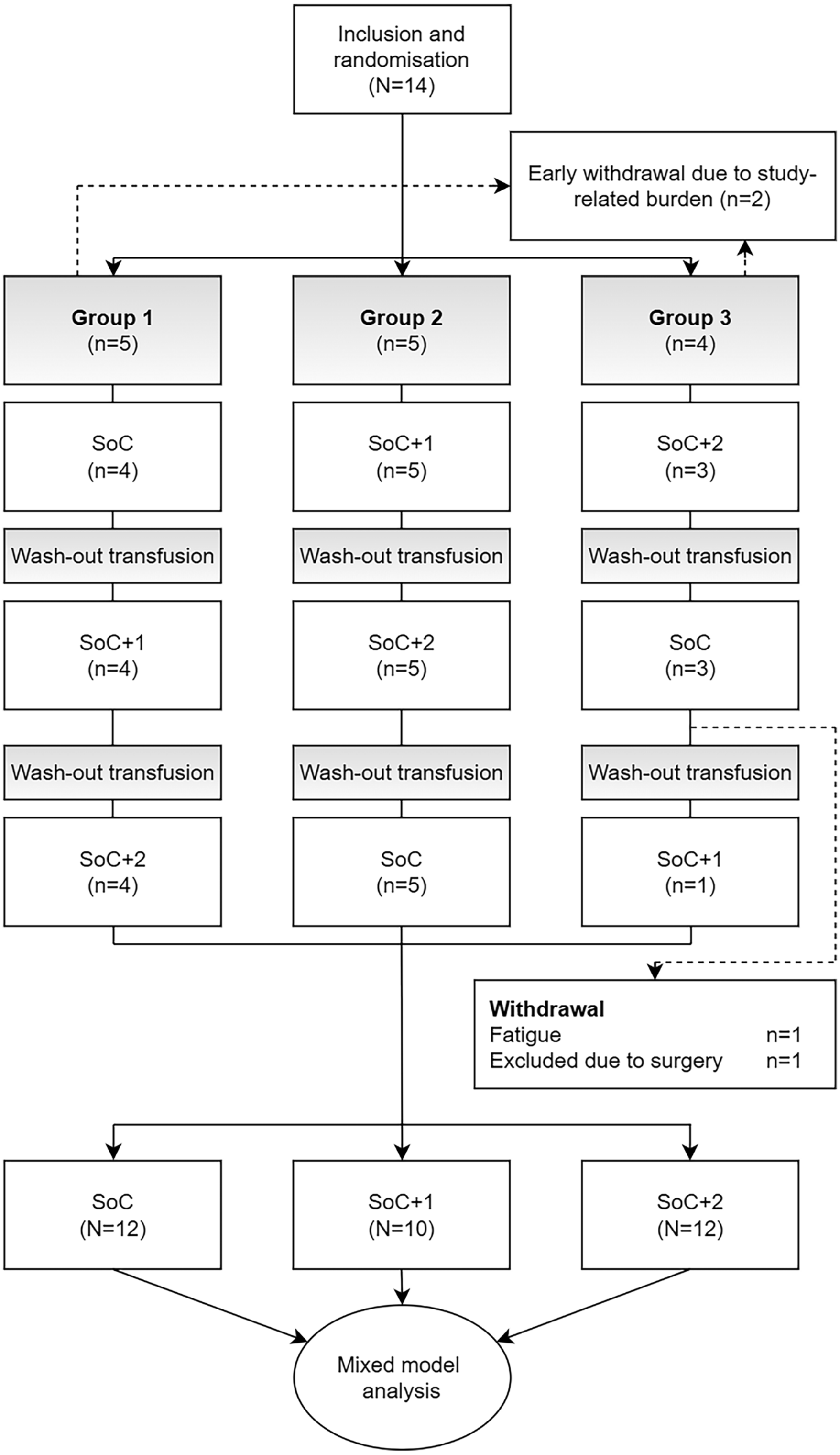
Continuous data were summarized as medians with interquartile range (IQR) and categorical data as frequencies and percentages. Primary and secondary outcomes were analyzed leveraging a linear mixed-effects model with a random intercept for patients to account for repeated measurements within participants. To compare visits and differences between transfusion regimens data were corrected for predefined confounders: age, sex, and use of β-blocker. Heart rate data were stratified for daytime and nighttime to correct for possible activity-related confounding. We applied the Benjamini-Hochberg procedure to control for the increased risk of type I error due to multiple testing. Since interim analyses introduce additional multiplicity by involving comparisons across time points, we adopted a more stringent false discovery rate of 0.025 rather than the conventional 0.05 (Supporting information 1).

3 | RESULTS

3.1 | Baseline data

Between September 2021 and December 2023, 14 patients were enrolled across four centers. Two

FIGURE 1 Flowchart of patient inclusion and randomization.



participants withdrew early citing study-related burden. The remaining 12 participants were randomized into three treatment sequences (Figure 1). Two patients withdrew before the last study transfusion—one due to fatigue and one because of surgery, which was expected to substantially influence study outcomes. All randomized patients were included in the analysis of the primary outcome adhering to an intention-to-treat approach. Baseline characteristics are presented in Table 1. Hemoglobin levels at V1 were comparable across the intervention groups (Supporting information 2). No transfusion reactions or other adverse events due to transfusions or use of study materials was observed. We performed a Benjamini-Hochberg

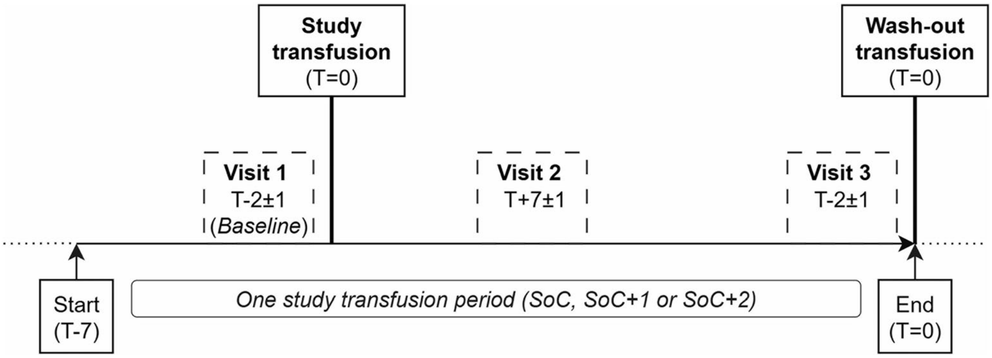


FIGURE 2 Visualization of one study transfusion period. The duration is according to the patient's standard transfusion regimen. For our included population this varied from 1 to 6 weeks.

TABLE 1 Patient baseline characteristics.

Median age years (range)	74 (64–89)
Hematological disorder	
MDS, *n* (%)	8/12 (67%)
MPN, *n* (%)	2/12 (17%)
CMML, *n* (%)	1/12 (8%)
Undefined, *n* (%)[a]	1/12 (8%)
SoC RBCs per transfusion, mean RBCs (range)	
SoC	1.8 units (1–2)
SoC + 1	2.8 units (2–3)
SoC + 2	3.8 units (3–4)
SoC transfusion interval, mean (range)	2.7 weeks (1–6)
Uses a B-blocker, *n* (%)	1/12 (8%)
Sex, Women (%)	5/12 (42%)
Pretransfusion, Hb (range)	
SoC	8.2 g/dL (6.6–9.2)
SoC + 1	7.9 g/dL (5.8–8.4)
SoC + 2	7.7 g/dL (5.5–9.0)
Post-transfusion, Hb (range)	
SoC	9.5 g/dL (7.7–11.1)
SoC + 1	9.8 g/dL (7.1–11.4)
SoC + 2	10.5 g/dL (8.1–11.8)
Pre-consecutive transfusion, Hb (range)	
SoC	8.1 g/dL (7.3–9.4)
SoC + 1	8.4 g/dL (7.6–9.8)
SoC + 2	8.9 g/dL (7.6–12.6)

Abbreviations: CMML, chronic myelomonocytic leukemia; Hb, hemoglobin; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasmata; RBCs, red blood cells; SoC, standard-of-care.

[a] Undefined: One patient was considered to have MDS and had been relatively stable on transfusion for some years making it an excellent subject for this study. However, the patient had refused bone marrow aspiration for a certain diagnosis.

procedure to correct for multiple testing with a false discovery rate of .025 which yielded a threshold for significance of $p = .0047$.

3.2 | Heart rate

Following a SoC transfusion, the median heart rate demonstrated a nonsignificant reduction of 1.1 bpm at V2 compared to V1. Following one extra RBC: SoC + 1 heart rate at V2 decreased by 4.2 bpm compared to V1 ($p = .008$; nonsignificant). Similarly, in the SoC + 2 group, heart rate at V2 was 5.6 bpm lower than at V1 ($p < .001$). Stratifying the heart rate for daytime and nighttime measurements yielded significant changes both in the SoC + 1 and SoC + 2 groups for both daytime and nighttime measurements. Detailed summary statistics are presented in Table 2 and Figure 3. Mixed-model results with effect sizes are presented in Supporting information 3.

Between-group comparisons at V2 indicated that SoC + 1 (mean absolute difference − 0.8 bpm, estimated marginal mean: −2.5 bpm) and SoC + 2 (−3.5 bpm; EMM: −3.1 bpm) were not significantly different from those in the SoC group, although the point estimates were compatible with a dose-dependent trend.

When analyzing the normalized change in heart rate (Δheart rate) relative to the mean at V1, the dose-dependent effect of RBC transfusion became more pronounced (Supporting information 4). Figure 3 illustrates the distribution of Δheart rate data. These figures underscore the dose-dependent reduction in heart rate observed at V2 and suggest a sustained effect at V3.

A return to baseline heart rate a few days before the subsequent transfusion (V1 ≈ V3) would typically be anticipated following a SoC transfusion. However, heart rate at V3 following SoC transfusion was higher than at V1, albeit without reaching statistical significance. This unexpected finding may reflect adjustments in transfusion volumes implemented to prevent volume overload. Specifically, patients who routinely received three RBC units as SoC were administered two, three, and four RBC units during the study instead of three, four, and five RBC units, to mitigate the risk of complications associated with transfusing 5 RBC units.

TABLE 2 Outcomes per visit from Withings HR smartwatch, CANTAB, and health-related quality of life (HRQoL) questionnaires.

		V1 (T = −2 ± 1 days)	V2 (T= 7 ± 1 days)	V3 (T2 = -2 ± 1 days)
Heart rate median BPM (IQR)				
Total	SoC	77.1 (72.7–80.8)	76.0 (70.0–78.2)	79.4 (75.7–83.0)
	SoC + 1	79.8 (72.7–85.5)	75.6 (69.2–82.2)	76.5 (71.5–84.0)
	SoC + 2	77.6 (72.3–83.3)	72.0 (65.5–75.6)**	75.3 (71.2–81.2)
Daytime	SoC	78.3 (74.1–81.8)	77.6 (71.9–80.5)	79.9 (75.5–85.1)
	SoC + 1	81.5 (74.0–88.2)	74.8 (71.1–83.8)**	78.3 (73.2–85.6)
	SoC + 2	77.7 (74.3–85.5)	72.6 (67.1–77.0)**	76.0 (73.5–83.9)
Nighttime	SoC	72.2 (67.0–76.7)	70.8 (65.8–74.7)	76.1 (72.4–80.8)
	SoC + 1	75.4 (69.4–82.1)	72.1 (64.3–77.6)*	71.3 (66.5–80.0)
	SoC + 2	76.4 (66.2–79.9)	67.2 (59.8–72.6)**	72.8 (66.1–78.7)
Activity steps (IQR)				
	SoC	3972 (2162–6565)	5860 (2263–9506)	5508 (2903–7833)
	SoC + 1	6043 (2478–11808)	5580 (2581–15451)	5726 (3174–11912)
	SoC + 2	4500 (2532–10920)	5520 (2166–13840)	5936 (2376–12354)
CANTAB score (IQR)				
OTSPSFC higher is better	SoC	11.0 (9.5–12.5)	11 (10.3— 12.8)	10.0 (8.5–12.5)
	SoC + 1	9.5 (8.3–12.3)	11.5 (7.5–13.5)	11.5 (7.5–13.5)
	SoC + 2	11.0 (4.0–13.0)	10.0 (8.0–13.0)	12.5 (9.0–13.8)
SWMS lower is better	SoC	1.0 (0.0–18.0)	6.5 (0.3–20.0)	2.0 (0.5–11.5)
	SoC + 1	12.5 (3.3–20.3)	15.0 (0.0–18.5)	15.0 (0.0–18.5)
	SoC + 2	7.0 (0.0–19.0)	3.0 (1.0–18.0)	12.0 (6.3–18.0)
RVPA higher is better	SoC	0.91 (0.88–0.95)	0.94 (0.91–0.98)	0.94 (0.91–0.99)
	SoC + 1	0.9 (0.87–0.98)	0.94 (0.86–0.99)	0.94 (0.86–0.99)
	SoC + 2	0.96 (0.87–0.99)	0.97 (0.88–0.99)	0.97 (0.88–0.99)
QUALMS score (IQR) higher is better				
QUALMS	SoC	62 (59–75)	64 (56–79)	64 (61–67)
	SoC + 1	62 (58–67)	70 (62–73)	63 (58–67)
	SoC + 2	64 (62–77)	69 (60–75)	70 (60–75)
Physical burden	SoC	59 (48–82)	60 (48–82)	55 (50–70)
	SoC + 1	55 (46–63)	68 (55–70)	61 (48–68)
	SoC + 2	65 (50–72)	66 (52–78)	72 (58–79)
Benefit finding	SoC	58 (33–75	58 (33–73	50 (42–75
	SoC + 1	50 (42–75	50 (33–71	58 (42–67
	SoC + 2	58 (40–77	58 (42–73	63 (40–75
Emotional burden	SoC	66 (59–75)	66 (60–75)	68 (64–75)
	SoC + 1	64 (61–73)	70 (65–74)	68 (59–73)
	SoC + 2	69 (60–77)	66 (62–73)	69 (52–74)
MFI score (IQR) lower is better				
General fatigue	SoC	13 (9–16)	12 (8–16)	13 (10–16)
	SoC + 1	15 (12–16)	8 (6–12)	11 (8–15)
	SoC + 2	12 (10–16)	10 (6–18)	10 (8–14)

(Continues)

TABLE 2 (Continued)

		V1 (T = −2 ± 1 days)	V2 (T= 7 ± 1 days)	V3 (T2 = -2 ± 1 days)
Physical fatigue	SoC	13 (8–19)	12 (9–17)	14 (10–18)
	SoC + 1	16 (12–17)	10 (7–17)	13 (9–17)
	SoC + 2	13 (10–18)	9 (6–19)	12 (10–16)
Decreased activity	SoC	13 (7–18)	13 (10–15)	14 (11–18)
	SoC + 1	16 (12–17)	12 (9–17)	12 (10–17)
	SoC + 2	12 (12–15)	10 (8–18)	12 (9–15)
Decreased motivation	SoC	12 (11–14)	12 (9–14)	13 (9–14)
	SoC + 1	12 (12–14)	11 (7–13)	13 (9–15)
	SoC + 2	11 (10–15)	11 (9–12)	12 (9–12)
Mental fatigue	SoC	7 (5–10)	8 (4–13)	7 (4–12)
	SoC + 1	10 (7–12)	7 (5–11)	10 (4–12)
	SoC + 2	12 (6–12)	8 (4–11)	8 (5–11)

Note: Leveraging mixed models for absolute heart rate data, corrected for multiple testing with the Benjamini-Hochberg procedure (see Supporting information 4 for mixed-model outcomes for the Δheart rate analysis).

Abbreviations: bpm, beats per minute; IQR, interquartile range; MFI, Multivariate Fatigue Index; OTSPSFC, One Touch Stockings task: problem solved on first choice, a measure of executive functions including reasoning and problem solving; QUALMS, Quality of Life in Myelodysplasia Scale; SoC, standard-of-care; RVPA, rapid visual processing – A; SWM, Spatial Working Memory task.

*$p < .0047$ compared to V1 (same intervention); **$p < .001$.

3.3 | Activity

Median cumulative steps showed variability across visits and transfusion groups. The SoC group had a slight, nonsignificant increase from V1 to V2, followed by a small decrease at V3. The SoC + 1 and SoC + 2 groups exhibited inconsistent patterns with no clear trend across visits.

3.4 | Cognition

Three of the 12 included patients did not complete the CANTAB cognitive assessments because they did not have a computer at home ($n = 2$) or did not want to participate in the cognitive testing ($n = 1$). Mixed-model analyses of the remaining nine patients revealed no statistically significant effects of RBC transfusions on cognitive performance across the study visits. However, as visualized in Figure 4 and detailed in Table 2, there were some trends observed across the different subdomains.

In the One Touch Stocking task, SoC + 1 demonstrated a slight improvement at V2. The SoC + 2 group exhibited an increase from V1 to V3, suggesting a trend toward sustained improvement.

For the Spatial Working Memory Strategy task, SoC + 2 showed a trend toward reversibly improved performance. In contrast, SoC and SoC + 1 showed greater variability, with no consistent improvement in performance across visits.

In the Rapid Visual Processing task, SoC + 2 demonstrated the highest median scores at all visits, with a slight increase from V1 to V3. Both SoC and SoC + 1 groups showed minimal changes across visits.

3.5 | Patient-reported quality of life

Mixed-model analyses revealed no statistically significant effects of RBC transfusions on overall QUALMS scores or its subdomains (physical burden, benefit finding, and emotional burden) or on fatigue levels as measured by the Multidimensional Fatigue Inventory and its subdomains (General Fatigue, Physical Fatigue, Decreased Activity, Decreased Motivation, and Mental Fatigue) across the study visits. However, descriptive trends indicated potential improvements with the SoC + 1 and SoC + 2 regimens.

Specifically, for QUALMS, the physical burden subdomain showed higher median scores at V2 for both SoC + 1 and SoC + 2 compared to the SoC regimen. Notably, the improvements in physical burden with SoC + 2 persisted into V3, whereas SoC + 1 returned to baseline levels by this time point.

In terms of fatigue, General Fatigue scores decreased from V1 to V2 with SoC + 1 and SoC + 2. Similar

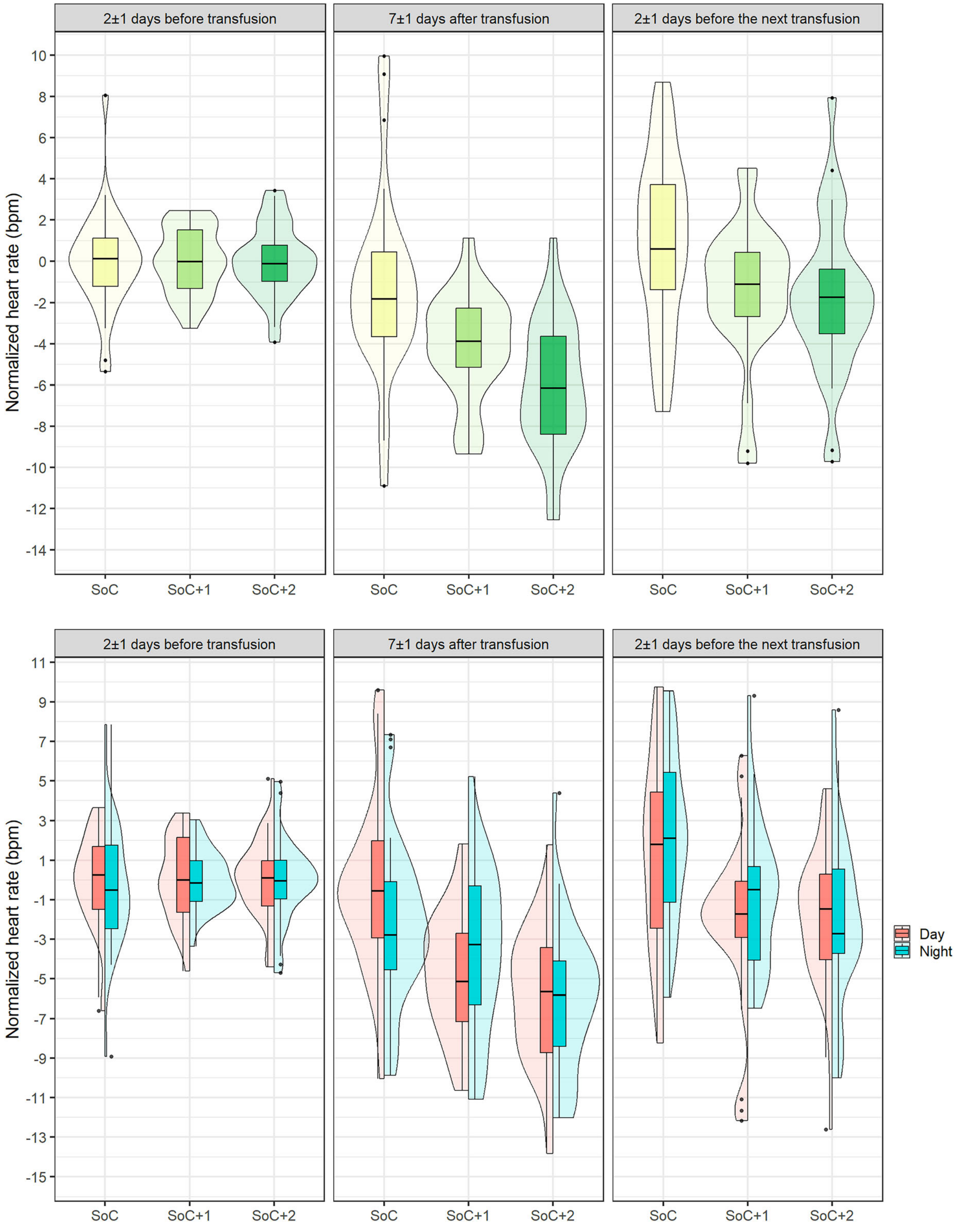


FIGURE 3 Median heart rate across study visits, normalized to the mean heart rate recorded during the first visit. This figure presents the summary of heart rate measurements at three time points: 2 days prior to transfusion, 7 days following transfusion, and 2 days prior to the subsequent transfusion. The violin plots illustrate the data distribution, while the overlaid boxplots highlight the median and interquartile ranges. Figure 3A shows the normalized median heart rate over a 24-h period. Figure 3B stratifies the normalized median heart rate into daytime (06:00–23:59) and nighttime (00:00–05:59) periods. The mean heart rate recorded during the first visit.

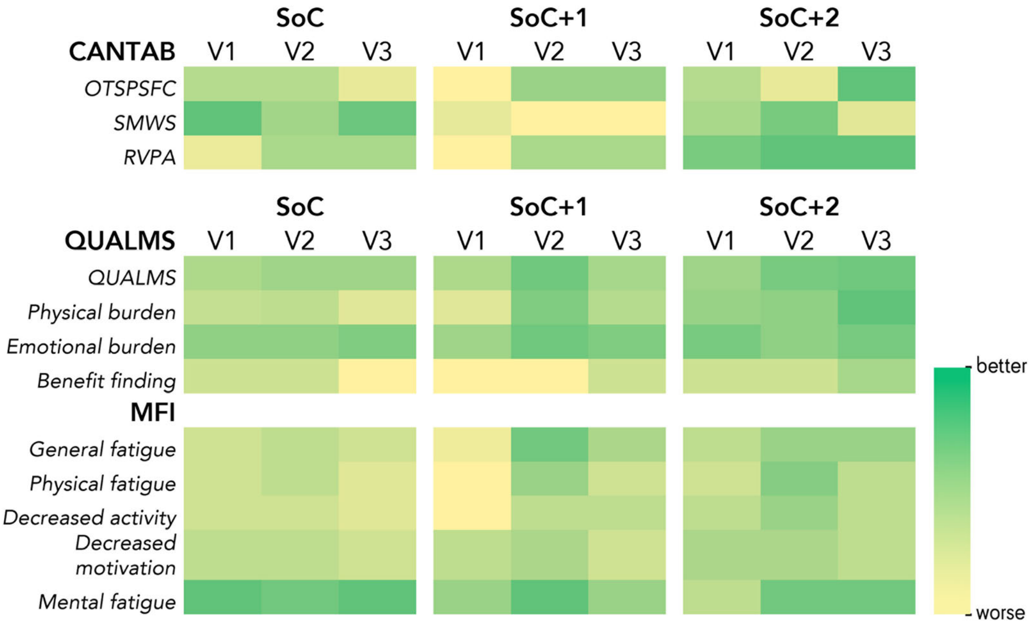


FIGURE 4 Heatmap of Quality of Life in Myelodysplasia Scale (QUALMS), Multivariate Fatigue Index (MFI) and CANTAB outcomes with green indicating better outcomes and yellow indicating worse outcomes.

reductions were observed in Physical Fatigue, with both SoC + 1 and SoC + 2 showing improvements at V2 compared to V1. These improvements were less pronounced or absent at V3, with fatigue levels in most subdomains returning closer to baseline. The exception was General Fatigue, where trends suggested sustained improvements at V3 with SoC + 1 and SoC + 2. Detailed results are presented in Table 2. A heatmap (Figure 4) illustrates the patterns of change in QUALMS and MFI scores across the different transfusion regimens and visits.

4 | DISCUSSION

The primary objective of this study is to explore the impact of varying transfusion regimens on heart rate in chronic transfusion-dependent anemic patients. Our findings suggest that transfusing more RBCs is associated with significant reductions in heart rate, with the largest decrease observed in patients with the highest hemoglobin augmentation (SoC + 2), indicating a dose-dependent effect. Moreover, at V3, heart rates in the SoC + 1 and SoC + 2 groups were lower than in the SoC group, suggesting a sustained effect of greater hemoglobin augmentation. Oxygen delivery is determined by the product of arterial oxygenation and cardiac output.[24] Thus, the observed reduction in heart rate likely reflects a decreased requirement for cardiopulmonary compensation, thereby enhancing physiological reserves.

We hypothesized that nighttime heart rate, being less affected by physical activity, would better reflect hemoglobin-related effects, while daytime rates might show greater activity-induced cardiopulmonary changes. In contrast, our mixed models showed significant heart rate changes during daytime more than during nighttime. Possibly, cardiopulmonary compensatory mechanisms induced by anemia are more pronounced during physical activity—when oxygen demand is elevated—compared to resting conditions. These findings highlight the variability of heart rate and its dependence on multiple factors, limiting its utility as a standalone marker of transfusion efficacy.

Regarding the secondary outcomes, neither this trial nor interim analysis was powered to detect changes, and no statistically significant transfusion-related effects were observed across groups. While many outcomes showed suggestive trends, daily activity levels, measured by cumulative step counts, did not. No associations were found between transfusion regimen and step count, nor did step count trends explain observed heart rate differences. This indicates that step counts were not a reliable indicator of transfusion-related effects. Variability in daily steps likely reflected individual lifestyle and scheduling differences rather than hemoglobin-driven changes. Alternative measures, such as the 6-min walk test,[25] may more effectively capture functional responses to transfusion and warrant consideration in future studies.

Trends toward improved cognitive function were also observed, particularly in SWMS and RVP performance.

Additional improvements in RVP and OTS tasks at V3 may reflect either a sustained effect of transfusion or increased task familiarity.[26] The absence of statistically significant findings may reflect the challenges of using web-based CANTAB assessments in older populations. Alternatively, hemoglobin augmentation in chronically transfusion-dependent elderly patients may not produce immediate cognitive benefits, despite associations reported in observational studies.[27,28]

QoL trends indicated a transient reduction in physical burden and fatigue, with a potential sustained improvement in physical subdomains associated with higher hemoglobin level augmentation. These findings are consistent with the hypothesis that higher hemoglobin levels may alleviate fatigue by improving oxygen delivery and reducing the compensatory demands of anemia. This finding is also in line with the completed trials comparing restrictive to liberal transfusion thresholds.[19,20] The absence of statistical significance may reflect the variability in patient responses and the study's small sample size. Furthermore, a recent systematic review questioned whether anemia treatment alone is sufficient to improve health-related quality of life (HRQoL).[29] Given the multitude of factors influencing quality of life, it remains uncertain whether existing HRQoL instruments lack sensitivity to detect changes, or whether increases in hemoglobin levels alone simply do not translate into meaningful improvements. However, we should also acknowledge that striving toward less large variations in Hb might have more impact on QoL than higher Hb peaks only.

This study has several limitations. The small sample size and substantial intra- and inter-patient variability may have limited the detection of statistically significant effects and masked underlying trends. Moreover, improvements observed in questionnaire and cognitive assessments may partly reflect practice effects. While current transfusion practice remains largely guided by hemoglobin thresholds, our findings aim to prompt a shift toward individualized, outcome-based transfusion strategies. However, this study is limited in that it compares groups rather than individuals, which constrains its ability to fully explore personalized transfusion needs. Future approaches should incorporate continuous monitoring through biosensors and patient-specific algorithms to guide transfusion decisions—balancing optimal quality of life with the need to avoid both anemia-related deterioration and unnecessary transfusions in patients who tolerate lower hemoglobin levels.

The clinical benefit of reducing heart rate in this often frail patient population remains to be established. Nevertheless, given the transient nature of transfusion-induced changes, we hypothesize that sustained higher, more stable hemoglobin levels with less cardiopulmonary compensation may yield cumulative benefits over time, reducing physical and even mental fatigue, with downstream gains in QoL. In this context, heart rate and other cardiopulmonary parameters—alone or combined with additional clinical measures—may serve as sensitive markers to guide transfusion timing and dosing beyond hemoglobin level alone. Conversely, persistent tachycardia consistent with hypoxemic stress may limit activity and contribute to gradual functional decline. These hypotheses require confirmation in studies with longer follow-up evaluating whether strategies that stabilize hemoglobin and attenuate compensatory tachycardia translate into meaningful clinical improvements.

Importantly, as this analysis presents interim findings, measures were taken to reduce the risk of Type I error from multiple testing in both interim and final analyses. Notably, significant reductions in heart rate were observed despite conservative statistical adjustments, underscoring the robustness of this effect.

The results therefore indicate that higher hemoglobin levels may confer meaningful clinical benefits by alleviating cardiopulmonary compensation in transfusion-dependent anemic patients. To our knowledge, this is the first trial to objectively demonstrate such benefits in this population. While SoC + 2 appears to offer improved clinical outcomes over SoC + 1 and SoC, SoC being the current default restrictive transfusion strategy in The Netherlands, a cost–benefit analysis was not conducted, and the long-term risk–benefit balance of higher transfusion volumes remains to be determined.

In conclusion, the findings in this interim analysis ($n = 12$) suggest a dose-dependent effect of RBC transfusions on heart rate. Moreover, wearables appeared sensitive to clinically relevant differences in heart rate supporting their use to quantify transfusion effects. Trends in secondary outcomes are hypothesis-generating and should be interpreted cautiously given the small sample size and variability in patient responses. Completion of enrolment and adequately powered follow-up studies with longer follow-up periods are required to fully understand the clinical significance of these trends and to determine whether increased hemoglobin levels can lead to sustained benefits in heart rate, physical endurance, cognitive function, and ultimately an improved quality of life.

AUTHOR CONTRIBUTIONS

RPBT, MRS, and JJZ conceived the study design. All authors participated in including patients. The study was carried out by RPBT. RPBT, MRS, and JJZ participated in the interpretation of the results. RPBT wrote the first draft. All authors reviewed the draft.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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