Remote monitoring in chronic anaemia

Towards personalized transfusion strategies





Rik P.B. Tonino

Stellingen behorend bij het proefschrift

Remote monitoring in chronic anaemia
Towards personalized transfusion strategies

1. Hoewel het beschikbare bewijs beperkt is, lijkt een stijging van het hemoglobine-gehalte tot 12 g/dL (7.5 mmol/L) bij anemische patiënten te leiden tot significante verbeteringen in VO2max en vermoeidheid/kwaliteit van leven – *dit proefschrift*

2. Het gebrek aan duidelijke richtlijnen voor bloedtransfusies bij chronisch transfusieafhankelijke patiënten leidt tot een brede variatie in behandelstrategieën, met potentieel suboptimale uitkomsten en inefficiënt gebruik van bloedproducten tot gevolg – *dit proefschrift*

3. Biosensoren worden goed geaccepteerd, ook door oudere patiënten, en vormen daarmee een veelbelovend middel voor het verzamelen van longitudinale data – *dit proefschrift*

4. De combinatie van het gebruik van biosensoren met webgebaseerde platforms voorPROMs en cognitieve testen faciliteert de verzameling van hoogwaardige data – *dit proefschrift*

5. Draagbare biosensoren zijn in staat klinisch relevante fysiologische effecten na bloedtransfusies, zoals veranderingen in hartslag, betrouwbaar te meten – *dit proefschrift*

6. Een uniforme transfusiestrategie doet onvoldoende recht aan de heterogeniteit van symptomen en functionele beperkingen bij chronisch anemische patiënten; een gepersonaliseerde transfusiestrategie vereist meer dan een hemoglobinewaarde alleen – *Staibano et al., Transfusion Medicine Reviews, 2019*

7. De snelle technologische ontwikkeling van biosensoren maakt dat onderzochte apparaten vaak reeds verouderd zijn tegen de tijd dat onderzoeksresultaten worden gepubliceerd – *Murray et al., American Journal of Preventitive Medicine, 2016*

8. Niet alles wat eenvoudig te meten is, is klinisch relevant; biosensoronderzoek moet daarom worden gestuurd door klinische vragen en niet door technologische mogelijkheden – *Coravos et al., npj Digital Medicine, 2019*

9. De implementatie van digitale gezondheidszorg wordt vaker beperkt door klinische validatie en integratie in zorgprocessen dan door technologische mogelijkheden – *Greenhalgh et al., Journal of Medical Internet Research, 2017*

10. Elke schijf is een remschijf

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Rik Paulus Bernardus Tonino

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Towards personalized transfusion strategies

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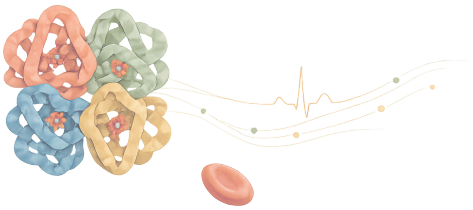

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

"The blood is the life"

– Bram Stoker

General introduction and outline of this thesis

"The blood is the life" – *Dracula (Bram Stoker)*. Indeed, we would simply perish without blood running through our veins. Whereas Dracula needs human blood to restore his youth, a non-vampiric person requires haemoglobin-containing red blood cells to transport oxygen to the body's cells in order to stay alive. Besides survival, Dracula uses blood to stay young, hence a more nuanced version of the phrase would also apply: Blood is, besides life itself, also quality of life.

Anaemia, defined as a haemoglobin (Hb) of <13.0 g/dL for adult men and <12.0 g/dL for adult, non-pregnant women[1] can have a substantial impact on a patient's quality of life. The main function of Hb in red blood cells (RBC) is to transport oxygen. Anaemia, leading to a reduced transport of oxygen, commonly presents with symptoms like fatigue, shortness of breath, dizziness and reduced physical function.[2–5] Various treatments can be used to increase the Hb level: if in shortage, iron and vitamin supplementation may aid the erythropoiesis, erythropoiesis-stimulating agents like EPO can activate the bone marrow to produce more red blood cells, and RBC transfusions, ultimately, directly replenish the red cell volume in a patient. While a higher Hb level is correlated to better outcomes like lower mortality[6] and better QoL,[7] increasing Hb does not necessarily lead to better outcomes, and the balance between the benefits and side effects of Hb-increasing treatments is disputed.[8] In this regard, RBC transfusions–apart from the associated costs and side effects–are even associated with worse outcomes themselves.[9] The latter has led to an as much as possible restrictive transfusion policy.

Patient blood management (PBM) is an evidence-based, multidisciplinary approach aimed at optimizing the care of patients who might need transfusion and hence limit this need as much as possible. Many PBM guidelines promote the use of restrictive transfusion strategies in various clinical settings. Previously, common medical practice was to use higher Hb transfusion triggers, approaching 10.0 g/dL. During the last three decades, clinical trials in acute and critical care settings showed that lower thresholds for patients in these settings did not cause harm. For example, an updated Cochrane review in 2018 found that transfusing RBCs at a restrictive threshold of Hb 7.0–8.0 g/dL, compared to a liberal Hb threshold of 9.0–10.0 g/dL, did not adversely affect 30-day mortality, or any other adverse outcomes measured.[10] These findings have led to a restrictive transfusion threshold of 7.0–8.0 g/dL to be the current standard for hemodynamically stable patients.[11]

Traditionally, trials focus on hard endpoints like mortality as primary outcomes and show that interventions that increase Hb generally do not influence these hard endpoints. Softer, patient-reported outcomes like Health-Related QoL, and Quality-Adjusted Life Years (QALYs) have gained territory over the past two decades, but are still largely underreported.[12]

As well described by Mo et al.,[11] There are different patient subgroups that are likely to have different pathophysiological responses to anaemia and transfusion. For example, a critically ill patient may not directly benefit from a higher haemoglobin level in terms of mortality, stroke, cardiac events and recovery, and QoL in the ICU will be low, regardless of the Hb level. The PBM guidelines therefore apply to this type of patient. Chronically anaemic patients, however, like those with myelodysplastic syndrome, who face symptoms like fatigue on a daily basis, may gain a lot from a higher Hb transfusion threshold. The restrictive threshold, promoted by the PBM guidelines may not apply in these cases: Less may not always be more. Indeed, the PBM guidelines acknowledge a lack of evidence for chronically anaemic patients and advise an individual transfusion policy based on the perceived quality of life. Nonetheless, adverse events of RBC transfusions, like transfusion reactions,[13–15] iron overload,[16–18] and poor clinical outcomes in studies with liberal transfusion thresholds in patients with acute anaemia[19–22] remain reasons for a default restrictive transfusion strategy, also in chronically transfusion-dependent groups.

However, even if a more liberal transfusion threshold would negatively influence the life expectancy, it could be argued that hard endpoints are not always the most important endpoints: If QoL increases with a higher Hb level, a liberal transfusion strategy might increase QALYs in spite of the hypothesized shorter life expectancy. In this respect, focussing on a hard endpoint like survival may decrease QALYs, and thus actually harm chronically transfusion-dependent patients. Thus, hard endpoints are important, but need to be balanced with other effects of the treatment, of which QoL is arguably the most important parameter for the patient.

The question now is: how do we determine this optimal balance that results in the most QALYs? Again, different patient subgroups are likely to have different pathophysiological responses to anaemia and transfusion. Consequently, a single strategy for all patients is off the table. Furthermore, within these subgroups, different patients experience different symptoms at comparable Hb levels. So stratifying PBM guidelines across patient subgroups may also not be the answer, but rather we should look at individuals instead of patient groups. In addition, a common criticism of transfusion guidelines is that we do not know the precise effect of transfusion, and have no means to measure the effect, and thus cannot determine a goal. In other words, when do we know the transfusion had the desired effect? What actually is the desired effect?

To get to an understanding of the desired effect of transfusion, let's first look at the Hb level as an evaluation parameter of transfusion strategies. The Hb level represents the concentration of Hb in the total blood volume. This means that if a patient has an increased plasma volume, the Hb level will decrease, even though the total Hb volume remains the same. The Hb level is therefore a suboptimal measure for a patient's total Hb volume. Besides, the function of all red blood cells is not the same, so also in this

regard the total Hb volume does not equal the oxygen transport capacity. Finally, the total oxygen transport is dependent on more than the red cell volume, like cardiac output and vascular distribution. It can therefore be concluded that the ultimate goal of a transfusion–increased delivery of oxygen in the tissues that have a suboptimal oxygen supply before transfusion–is insufficiently represented by an Hb level. On the other hand, with current techniques it is not feasible to monitor oxygen concentration in all tissues of all patients that might require transfusion. Therefore, we need to look at other objective, clinically relevant, proxy parameters to measure the need and effect of RBC transfusions.

In search of parameters that may be clinically relevant and represent oxygen transport we could look at the reaction of the end-users of oxygen: organs. Objective physical parameters like heart rate, respiratory rate, and patient activity levels might represent the oxygen availability in patient tissues. After all, a lack of oxygen, due to anaemia, will cause the respiratory system to increase oxygen uptake by a higher respiration rate, and will increase the cardiac output with a higher heart rate to enhance oxygen transport. Another organ highly dependent on oxygen is the brain. Possibly, a reduced oxygen availability may impair cognitive functions.

While this physical parameter approach may very well yield an effective method to determine the physiological effect of a transfusion, or Hb modulation through other treatment, we also need to evaluate the perceived effect on the patient. Subjective measurements of fatigue levels and overall QoL must also be assessed to ultimately balance the benefits against the side effects and costs.

Summarizing, it has been shown that there is no harm in transfusing restrictively in terms of hard endpoints for the critically ill and surgical patients. For patient groups that are chronically anaemic, we lack the means to evaluate transfusion strategies for loss of QoL and hence QALYs. This hampers us to effectively balance the pros and cons of transfusion.

Scope of the thesis

In **Chapter 2**, we start with evaluating current evidence and knowledge gaps of the effect of Hb modulation on human physiology and patient-reported outcomes. In an umbrella review we give an overview of reviews that have assessed changes in haemoglobin by various treatments: ESAs, iron supplementation, altitude training and transfusion in anaemic patients, non-anaemic patients and healthy subjects, and patients with polyglobulia.

Given the interpretative latitude within PBM guidelines for transfusing chronically anaemic patients, we investigate the haemoglobin thresholds and targets that physicians employ in clinical decision-making, as well as the motivations guiding these decisions in **Chapter 3**.

The feasibility of remote monitoring of chronic transfusion-dependent patients with wearables and eHealth techniques is tested in **Chapter 4**, while **Chapter 5** reports the first physiological and patient-reported effects of RBC transfusions.

In **Chapter 6**, in search of a haemoglobin optimum, we assess the effect of phlebotomies and blood donation on heart rate, activity and QoL in patients with a primary polyglobulia and healthy blood donors.

In **Chapter 7,** a dose-dependency of RBC transfusion amount and physiological and patient-reported outcomes is analysed. We evaluate the effect of a patient-specific standard amount of RBC transfusion and compare the effect on physiology, cognition and QoL with +1 and +2 RBC units in a multicentre randomised crossover trial.

Chapter 8 offers a comprehensive summary and discussion of the key findings outlined throughout this thesis. In addition, it explores future directions and provides recommendations for further research, as well as strategies to enhance healthcare delivery and advance personalized approaches in transfusion medicine.

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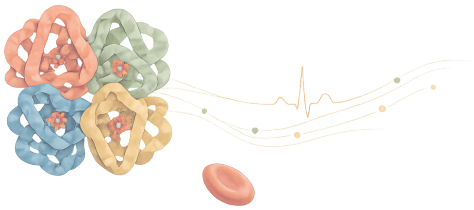

HAEMOGLOBIN MODULATION AFFECTS PHYSIOLOGY AND PATIENT-REPORTED OUTCOMES IN ANAEMIC AND NON-ANAEMIC SUBJECTS: AN UMBRELLA REVIEW

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Abstract

Background

An abnormal haemoglobin concentration has a substantial effect on a person's quality of life and physiology. Lack of tools that effectively evaluate haemoglobin-related outcomes leads to uncertainty regarding optimal haemoglobin levels, transfusion thresholds and treatment targets. We therefore aim to summarize reviews that assess the effects of haemoglobin modulation on the human physiology at various baseline haemoglobin levels, and identify gaps in existing evidence.

Methods

We conducted an umbrella review of systematic reviews. PubMed, MEDLINE (OVID), Embase, Web of Science, Cochrane Library and Emcare were searched from inception to the 15th of April 2022 for studies that reported on physiological and patient-reported outcomes following a haemoglobin change.

Results

Thirty-four reviews were included of which 7 were scored as of high quality and 24 of critically low quality using the AMSTAR-2 tool. The reported data generally show that an increase in haemoglobin leads to improvement of patient-reported and physical outcomes in anaemic and non-anaemic subjects. At lower haemoglobin levels, the effect of a haemoglobin modulation on quality of life measures appears more pronounced.

Conclusion

This overview has revealed many knowledge gaps due to a lack of high-quality evidence. For chronic kidney disease patients, a clinically relevant benefit of increasing the haemoglobin levels up until 12 g/dL was found. However, a personalized approach remains necessary due to the many patient-specific factors that affect outcomes. We strongly encourage future trials to incorporate physiological outcomes as objective parameters together with subjective, but still very important, patient-reported outcome measures.

Introduction

The main function of haemoglobin (Hb) in red blood cells (RBC) is to transport oxygen. The Hb level is biologically maintained between 12.0 and 16.0 g/dL in females, and 13.0–16.5 g/dL in males. However, an abnormal Hb level is frequently found. Globally, the prevalence of anaemia (Hb < 12.0/13.0 g/dL for F/M, respectively) is estimated to be 23.2% (Safiri et al., 2021) and the prevalence of erythrocytosis (defined as Hb > 16.0/16.5 g/dL or Hematocrit (Hct) > 48%/49% for F/M, respectively) is estimated to be in the range of 0.8%–3.4%, in various populations (Ruggeri et al., 2003; Wouters et al., 2019). Both a low and a high Hb concentration may have a substantial effect on a person's quality of life. For instance, impaired oxygen transport due to anaemia may cause symptoms of fatigue and decreased physical and cognitive function (Penninx et al., 2004; Denny et al., 2006; Thein et al., 2009; Soni et al., 2010). On the other hand, erythrocytosis may result in hyperviscosity, which may cause, amongst other symptoms, shortness of breath, and physical and cognitive deterioration (McMullin et al., 2005).

For abnormal Hb levels, often only symptomatic treatments are available: for anaemic patients, RBC transfusions, erythropoietin stimulating agents (ESAs), iron and vitamin supplementation can be utilized, amongst other therapies, typically with the goal to increase Hb levels and hence QoL, and/or decrease morbidity/mortality. Moreover, athletes may try to enhance their exercise capacity by increasing their Hb to supraphysiologic levels. For patients with erythrocytosis, on the other hand, phlebotomies and cytoreduction may be utilized to reduce hyperviscosity symptoms and the risk of thrombo-embolic complications.

The relationship between the total Hb-mass and the absolute O2 transport is influenced by numerous factors like age, macro-/microvascular performance and type of Hb. e.g., HbF, and HbH have a higher oxygen affinity than HbA, with HbH having an extremely high affinity, leading to tissue hypoxia even at normal Hb levels. Contrastingly, HbS has a lower oxygen affinity compared to HbA, facilitating tissue O2 delivery at a lower PaO2. Within a single subject, however, it can be assumed to some extent that this relationship between the total Hb-mass and oxygen transport is linear (Calbet et al., 2006). The lower the Hb-mass, the less O2 transport. Indeed, it has been reported that in patients with chronic anaemia, red blood cell transfusions improve walk test distances and fatigue scores (Lezin et al., 2019). Moreover, studies showed a decrease in VO2max following isovolumic hemodilution and an increase in VO2max following RBC transfusions (Calbet et al., 2006), and studies evaluating blood donors have shown that blood donation increases the resting heart rate 24 h after donation, and decreases VO2max (Gordon et al., 2010). Therefore in these groups, it has been established that a change in Hb has an effect on the O2 transport capacity. What we do not know, however, is the magnitude of this effect at different Hb levels. Do these effects correlate linearly to the change in Hb level, and is there a

certain level above which an increase will not exert a beneficial but even a negative effect on the patient? Does O2 transport decrease at a certain supraphysiological Hb level due to rheological reasons hampering microcirculatory perfusion by the more viscous blood? And if so, how do we find the patient specific Hb balancing the best possible O2 transport vs. microcirculatory perfusion and hyperviscosity risk?

Likewise, there is an ongoing debate about transfusion thresholds. In patients with reversible anaemia restrictive transfusion strategies have become the default because of the intrinsic costs, the lack of better outcomes at higher thresholds and the small but remaining risks of blood transfusion. In contrast, in chronic deeply anaemic and transfusion-dependent patients, it can be argued that a more liberal strategy might increase the QoL (Wood and McQuilten, 2020; Oliva et al., 2021). Of course, negative side effects of Hb-modulating therapies have been established: There are well known risks in transfusion like transfusion reactions and iron overload; ESAs increase the risk of venous thromboembolism or may cause polycythemia putting the patient at risk for heart attack, stroke, or even death; and both iron and ESAs may cause tumors to grow in patients who have cancer (Salamin et al., 2018; Wilson et al., 2018). However, the balance between beneficial effects of a higher Hb level and the negative effects, costs and logistics is complex, especially if the benefits are yet unknown or challenging to quantify.

Assessing functional outcomes, like VO2max, exercise capacity, heart rate, and patient-reported outcomes like HRQoL, fatigue and dyspnea, at various Hb levels may help to understand what effect changes in total Hb-mass have on the physiology of human beings, whether or not they are anaemic. While a reduction in Hb level from 16 to 15 g/dL may not be clinically relevant for the subject itself, documentation of its effect will help to put the puzzle of Hb optimization together. If we would have data on every shift in Hb level in every patient group with any start off Hb level, we could predict the outcomes in patients for whom an increase or decrease in Hb level is considered. Consequently, we could make an evidence-based decision on Hb thresholds and targets.

In conducting this umbrella review, we took into consideration that there are many accompanying effects of the included therapies, the disorders and the different treatments. Hence, the measured effects might not always primarily or only reflect the Hb change. Moreover, while we do not want to compare interventions, i.e., whether ESAs are more effective than iron or transfusion, we looked per Hb modulating intervention at the hematological outcome and the consequential effect on outcomes. Due to the many patient-specific factors that affect the outcomes of Hb levels (Figure 1), a personalized approach to the patient is always a necessity for good healthcare. Notwithstanding this, combining data from all types of interventions, patient groups and outcomes creates an overview, after which we can put the individual's situation into perspective. Still, in a way we are comparing apples and

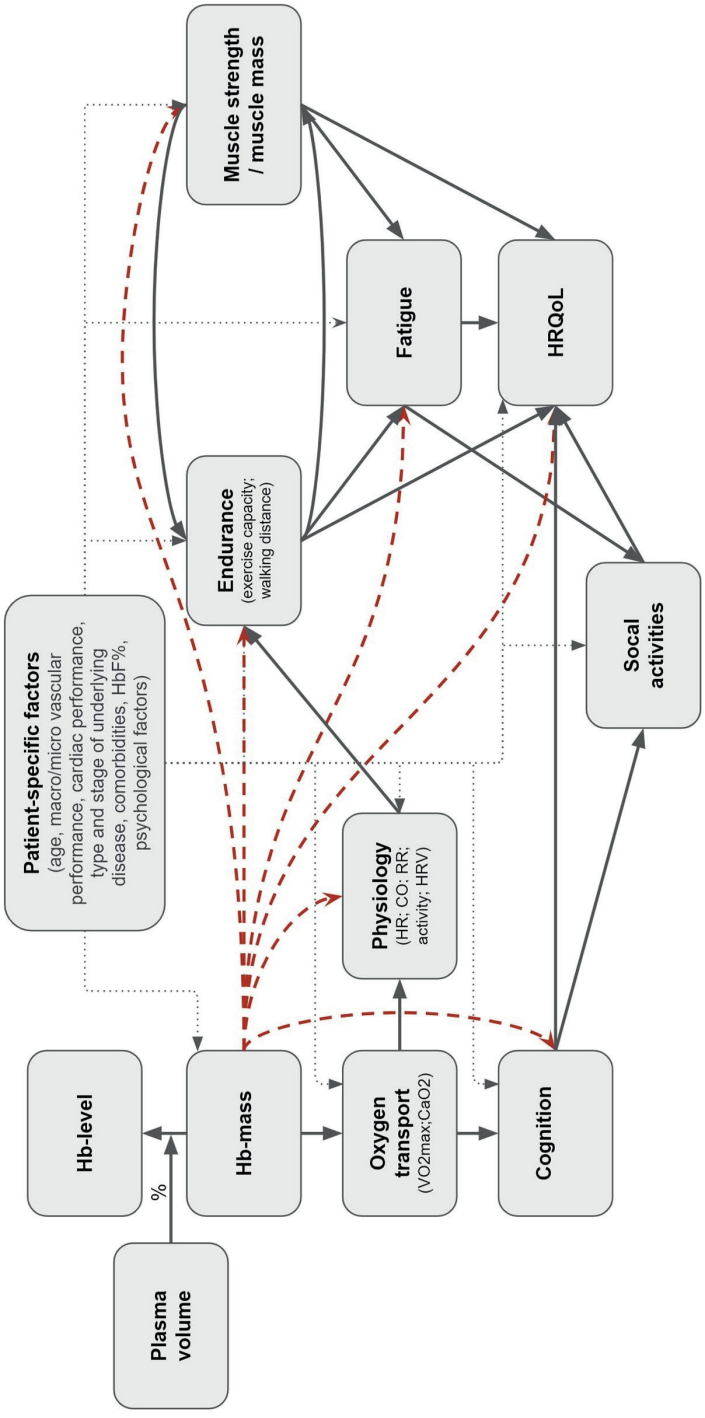

Figure 1. Proposed causal pathway in black arrows. The red dashed arrows are the (indirect) effects this umbrella review is intended to reflect on.

oranges, however, this approach might tell us a great deal about our fruit–Hb modulation and the effect on outcomes–in general (Holly, 2021).

In Figure 1 we propose a hypothetical causal pathway of effects of changes in Hb on various outcomes, and show the individual effects we intend to investigate. Since we did not find comprehensive summaries of existing research on this topic, we aimed to review reviews that examined the effects of Hb modulating interventions on physiology in anaemic and non-anaemic subjects, assess whether sufficient evidence is available for evidence based guidelines, and therewith to identify gaps in existing evidence.

Methods

Protocol and registration

An umbrella review was conducted, based on the Joanna Briggs Institute methodology (Ioannidis, 2009). The predefined protocol, published in PROSPERO International prospective register of systematic reviews (CRD42022299392), adhered to the PRISMA-P guidelines (Moher et al., 2009).

Information sources and search strategy

PubMed, MEDLINE (OVID), Embase, Web of Science, Cochrane Library and Emcare were searched from inception to the 15th of April 2022 for studies that reported on physiological and patient-reported outcomes following an Hb change. Additionally, we used hand-searching and screened reference lists and guidelines for finding additional potential inclusions for our umbrella review. There were no language or publication year restrictions. The detailed search strategy is reported in Supplementary Material S6.

Eligibility criteria and outcomes

Studies were eligible if they were published systematic reviews (SRs) or meta-analyses which included primary studies that evaluated the clinical effect of interventions that change the Hb level. Non-systematic reviews, reviews in which no Hb levels were reported, or in which Hb change was solely due to blood loss in surgery or other forms of acute bleeding (other than intended phlebotomies) were excluded. We aimed to include systematic reviews on all types of anaemias, non-anaemias and polycythemia. Eligible interventions that change the Hb level are transfusion, phlebotomy, isovolumic hemodilution, altitude training, EPO, and iron and vitamin supplementation.

Outcomes that were recorded in this umbrella review are: VO2max, heart rate, respiratory rate, heart rate variability, exercise capacity, fatigue, patient-reported outcome measures, patient-reported experience measures, quality of life and hematological outcomes (Hb/Hct/transfusions). Within-subject designs and placebo/standard of care/other comparator-controlled designs are included. Screening, data extraction and quality assessment were performed independently in duplicate by two authors (RT and LZ). Discrepancies were discussed and when necessary, resolved with the help of a third author.

Data management and selection process

We screened all titles and abstracts of retrieved citations to assess suitability for inclusion. Two authors (RT and LZ) independently screened the full texts of articles potentially meeting eligibility criteria. Before data extraction, articles meeting eligibility criteria were checked whether they were qualitatively sufficient using the JBI Critical Appraisal checklist for systematic reviews and research syntheses. If articles were scored less than 33% on the JBI checklist, they were excluded. In case of discordant reviews, the Jadad decision algorithm was used to ascertain which meta-analysis represented the best evidence (Jadad et al., 1997). CADIMA software (Julius Kühn Institute, Germany) was used to manage records and data. The data extraction was conducted according to a modified JBI extraction tool (Supplementary Material S6).

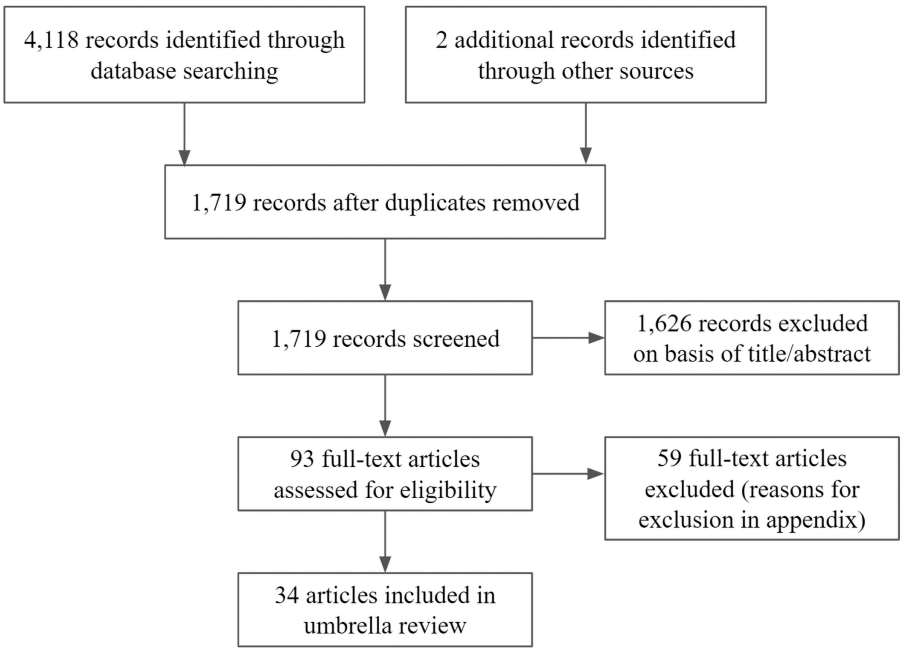

Figure 2. Flow diagram of study selection.

Author, year, type of participants, control groups, number of participants, description of intervention and control, number of studies, types of studies, databases searched, country of origin of the included studies, outcomes and findings, type of effect model used in the meta-analysis (fixed or random), between study heterogeneity estimates (I2 values), any presented measure of publication bias, Grading of Recommendations Assessment Development and Evaluation (GRADE) rating, and sources of funding and conflicts of interest were extracted from the studies. We assessed whether the studies evaluated possible sources of heterogeneity across studies and whether the authors conducted a sensitivity analysis.

Assessment of methodological quality and quality of evidence

Methodological and reporting quality was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR)-2 tool. This tool rates systematic reviews/meta-analyses on literature search, study selection, data extraction and transparency of the studies (Shea et al., 2007). The GRADE score was utilized to score the quality of the evidence found in the included studies (Guyatt et al., 2009). We evaluated the quality on five items: risk of bias, imprecision, inconsistency, indirectness and publication bias using the GRADE Handbook (Schünemann et al., 2013).

Data synthesis and meta-biases

We performed a narrative umbrella review. Meta-analyses were not feasible with the included heterogeneous data. However, forest plots of PROMs and physiological outcomes were conducted without a meta-analysis for overview purposes. In these forest plots, the effect sizes have been transformed to standardized mean differences (SMD) using R's "MBESS" and "esc" packages, depending on available data. If sample sizes for intervention and control groups were not available separately, we assumed equal groups to estimate the confidence interval for the SMDs. Moreover, with these computed SMDs, we produced funnel plots for PROMs and physiological outcomes separately, to evaluate the possibility of publication bias.

Sensitivity analysis

Though a formal sensitivity analysis was not possible without a meta-analysis, we assessed whether outcomes were notably different when selecting only high-quality SRs, to reduce confounding and bias, or when leaving out SRs that evaluated ESAs. ESAs, a group of drugs that has been evaluated in larger studies with more pharmaceutical company sponsorship, may give biased results due to conflicts of interest, or contrastingly, less biased more adequate results due to proper financing for larger, methodologically superior trials.



Figure 3. Individual systematic review assessment with the AMSTAR-2 tool.

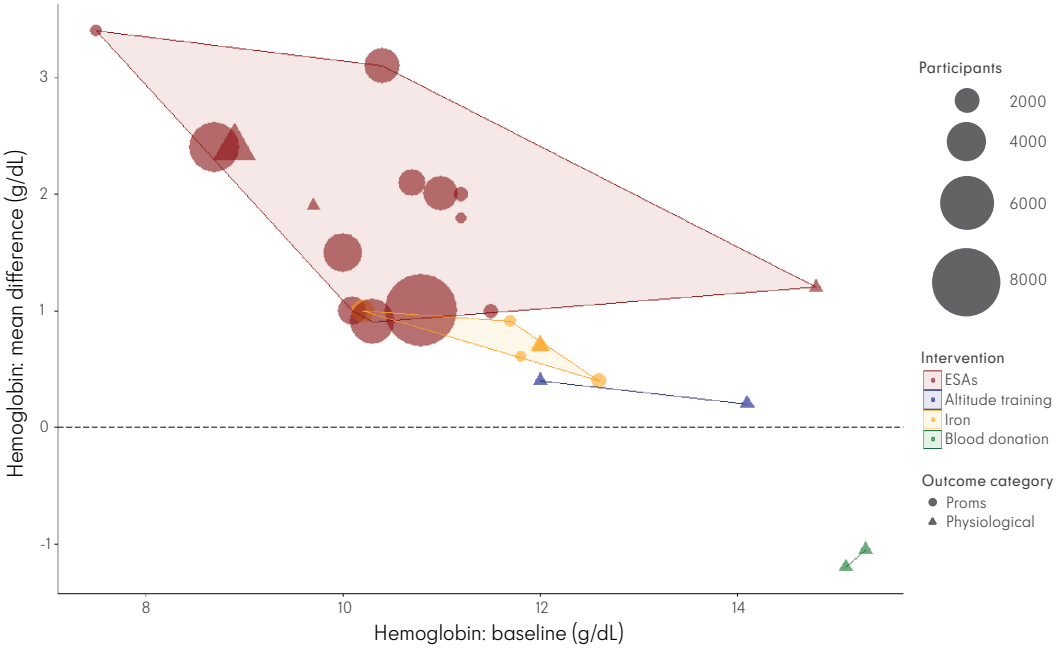

Figure 4. Bubble plot of haemoglobin baseline (pre-intervention) and haemoglobin mean difference (post-intervention—pre-intervention). At lower baseline levels, higher Hb-increments were achieved. Furthermore, systematic reviews evaluating ESAs contributed the majority of included evidence. For the purpose of overview, when an Hb mean difference was not reported, we used the (target—baseline) instead in this figure. Moreover, not all baseline values were reported, in which case we used inclusion criteria cut-offs. As 10/34 studies only reported heterogeneous data of primary studies or percentages without an absolute Hb level, we could only include 26/34 reviews in this figure. ESAs, erythropoietin stimulating agents; PROMs, patient-reported outcome measures.

Results

Review selection

The search strategy yielded 4,120 results. After screening of titles and abstracts, the full texts of 93 articles were further evaluated. Of these, 34 studies with 169,878 participants met the inclusion criteria (Figure 2). The included studies were published from 2009 to 2020. The majority of primary studies were conducted in Europe and North-America and 24% (8/34) of the included reviews declared pharmaceutical company sponsorship. We included quantitative reviews with meta-analyses for the interventions ESAs, iron supplementation, altitude training and blood donation. The included patient groups comprising patients with cancer, hematological malignancies, bone marrow failure, chronic kidney disease, chronic heart failure, autoimmune disorders, critical illness in the ICU, iron-deficiency and healthy subjects. We did not encounter suitable SRs that covered hemochromatosis, polycythemia, thalassemia, sickle cell disease and other haemoglobinopathies and subtypes of anaemias.

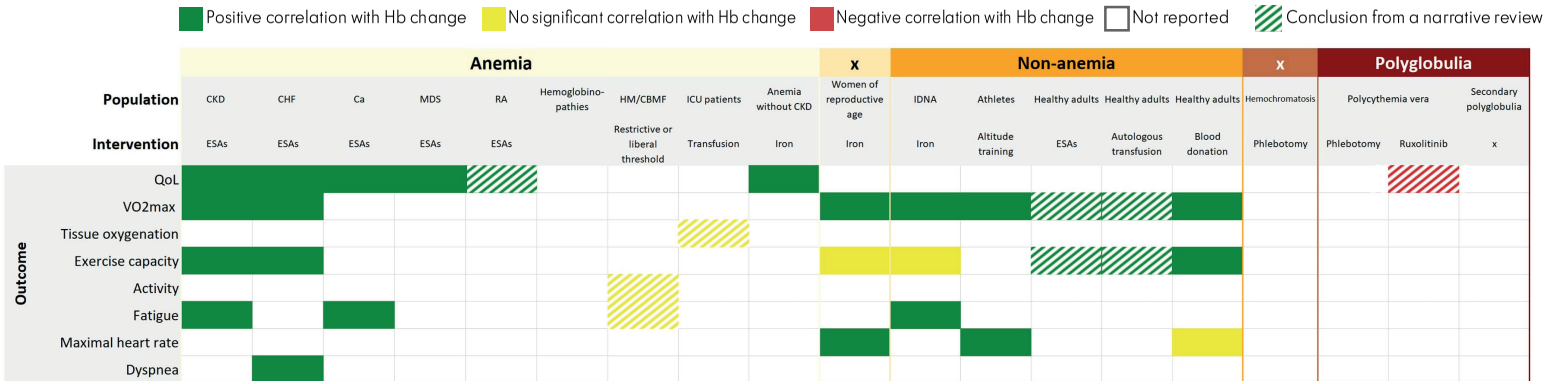

Figure 5. Overall findings of the umbrella review by outcome measures and interventions. CKD, chronic kidney disease; CHF, chronic heart failure; RA, rheumatoid arthritis; HM, hematological malignancies; CBMF, chronic bone marrow failure; ICU, intensive care unit; IDNA, iron deficiency non-anaemia; ESAs, erythropoiesis-stimulating agents.

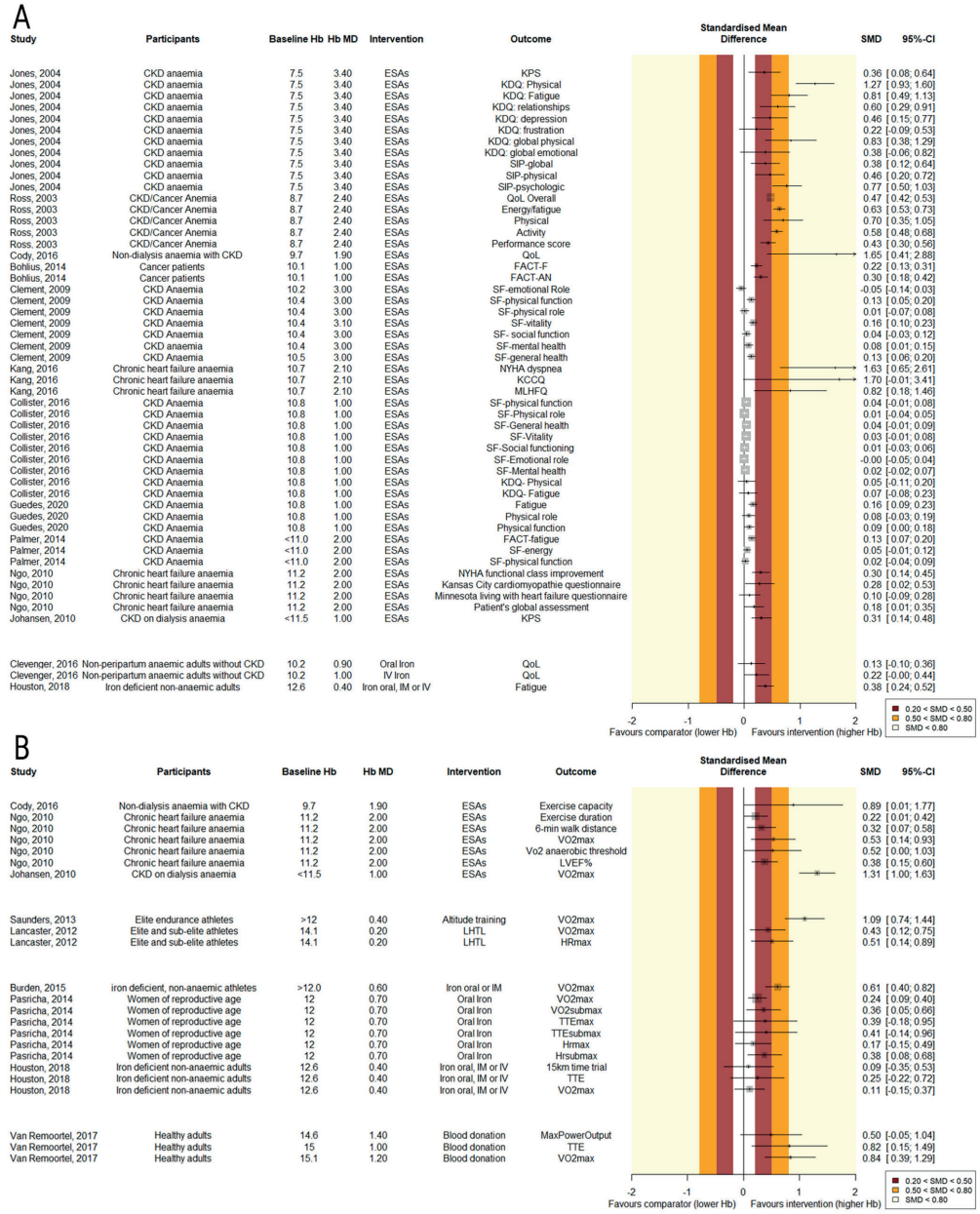

Figure 6. Forest plot of quantitative (A) PROM and (B) physiological outcomes. Results are grouped per intervention, listed from lowest to highest baseline haemoglobin level. The effect of Hb changes appears more pronounced at lower baseline Hb levels. Standardized mean differences were computed by transforming the reported effect sizes using R "MBESS" or "esc" packages, depending on the available data. SMD values of 0.2–0.5 are considered small, 0.5–0.8 medium, and values >0.8 are considered large. For overview purposes, if an Hb mean difference was not reported, we used the target instead in this figure. Also, not all baseline values were reported, in which case we used inclusion criteria cut-offs.

For red cell transfusion only narrative reviews were included. No relevant reviews were encountered on the subjects of vitamin supplementation and phlebotomy. Details of studies included for review are shown in Supplementary Material S1. A full reference list of the excluded studies with reasons for exclusion is provided in Supplementary Material S2.

Critical appraisal and risk of bias

The individual assessment for each SR with the AMSTAR-2 critical appraisal tool is shown in Figure 3. The quality was found to be high in seven SRs, two SRs scored low and 24 SRs were appraised as of critically low quality. Furthermore, we plotted all quantitative data in funnel plots to assess possible publication bias (Supplementary Figures S1, S2). For physiological outcomes, we found no signs of publication bias (Egger's test: $p = 0.277$). Patient-reported outcome measures, however, showed clear signs of publication bias. The funnel plot in Supplementary Figure S1 has a very pronounced asymmetry, with less powerful studies finding larger effect estimates, suggesting substantial bias. This is supported by the Egger's test: $p < 0.001$.

An overview of the baseline Hb levels and the achieved Hb-increment by intervention per study is presented in Figure 4. The mean increase in Hb after ESA-treatment lies between 1 and 3 g/dL. Iron treatment and altitude training show mean increases in Hb of <1 g/dL. The colored areas in this figure indicate per intervention what increment per baseline-Hb has been studied. These areas do not overlap, creating a patchwork-like image. While the lack of overlap shows that we cannot accurately compare the interventions with one another, this supports the combining of these data: to get a more complete picture of the effect of various increments at different baseline Hb's.

ESA treatment

Twenty citations that investigated the effect of ESA treatment were eligible for evaluation (Supplementary Materials S1, S3). The SRs were published between 2003 and 2020, and AMSTAR-2 quality of reporting ranged from critically low to high, the GRADE quality of evidence was generally low, ranging from very low to high. ESAs were compared with placebo, lower targets or no ESAs. Results are depicted in Figures 5, 6. Due to heterogeneity of the investigated subjects, we summarized the outcomes per patient group (Supplementary Figures S3, S4).

Chronic kidney disease

Eight quantitative (Jones et al., 2004; Ross et al., 2007; Clement et al., 2009; Johansen et al., 2010; Palmer et al., 2014; Cody and Hodson, 2016; Collister et al., 2016; Guedes et al., 2020) and four qualitative (Gandra et al., 2010; Johansen et al., 2012; Pergola et al., 2019; Staibano et al., 2020) SRs that investigated chronic kidney disease patients were included. QoL, VO2max, exercise capacity and fatigue were reported to improve with an increase in Hb in quantitative analyses. Intriguingly, however, the

review with the most participants found no significant correlation between the Hb change and PROMs, although the most important items did approach significance (SF-General health: MD = −1.9, CI: −4.1, 0.4, SF-physical function: MD = −2.6, CI: −5.6, 0.4, SF-Vitality: MD = −2.0, CI: −4.4, 0.4)(Collister et al., 2016). Effects of Hb modulation on PROMs at baseline levels >10 g/dL appear less pronounced than at Hb levels <10 g/dL. However, the increase in Hb level is greater at lower levels than at higher baseline levels. Furthermore, two SRs reported that HRQoL benefits associated with haemoglobin targets of >12 g/dL appeared modest and of uncertain clinical significance (Clement et al., 2009; Pergola et al., 2019).

Anaemia with underlying malignancy

One quantitative SR of critically low quality investigated ESA-induced Hb modulation in patients with underlying malignancies. Fatigue and QoL improved after an increase in Hb from a mean baseline of 10.1 g/dL (Bohlius et al., 2014). Two qualitative SRs reported on Hb modulation in patients with myelodysplasia, reporting that patients that had a hematological response to ESAs improved on QoL-scores.

Other: Chronic heart failure, healthy subjects, rheumatoid arthritis

Two quantitative SRs investigating chronic heart failure patients reported that QoL, VO2max, exercise capacity and dyspnea improved significantly after a mean Hb increase of 2.0–2.1 g/dL at a mean baseline Hb of 10.7–11.2 g/dL (Ngo et al., 2009; Kang et al., 2016). In healthy subjects, two qualitative SRs evaluated the effect of ESAs on VO2max, exercise capacity and the maximal heart rate. All these parameters were suggested to be positively affected by an increase in Hb, although no meta-analyses were performed to support this (Heuberger et al., 2013; Sgrò et al., 2018). Finally, in rheumatoid arthritis, QoL was suggested to be positively correlated to Hb in a qualitative SR (Martí-Carvajal et al., 2013).

Iron treatment

Five SRs evaluating iron treatment were eligible (Supplementary Materials S1, S3) (Gurusamy and Richards, 2013; Pasricha et al., 2014; Burden et al., 2015; Clevenger et al., 2016; Houston et al., 2018). Treatment with intravenous, oral and intramuscular iron was compared with placebo, iron oral, or no iron in anaemic and non-anaemic patient groups. The articles were published between 2013 and 2018. AMSTAR-2 scores ranged from critically low to high and the evidence was graded very low to moderate. In Figures 5, 6 the effects of iron on various outcomes are depicted. Clevenger et al. investigated the effect of iron on QoL in anaemic patients without chronic kidney disease and found that these patients benefit significantly from parenteral iron (Hb MD = 1.04 g/dL, CI: 0.52, 1.57, n = 1744), but oral application (Hb MD: 0.91 g/dL, CI: 0.48, 1.35, n = 851) did not lead to a significant difference in QoL. Pasricha et al. (2014) evaluated studies with women of reproductive age, anaemic and non-anaemic together, and concluded that oral iron supplementation increased the

Hb level and had a significantly positive effect on VO2max (MD = 2.35, CI: 0.82, 3.88) and the heart rate (MD −4.05 CI:–7.25, −0.85). Pasricha et al. (2014) also mentioned the role of iron in the mitochondrial respiratory chain, suggesting that improved tissue iron might improve exercise capacity, independent of an Hb modulation. The exercise capacity showed a positive trend, although this was not significant. Two SRs evaluated iron treatment in iron deficient non-anaemic groups. These groups significantly benefited from the iron-induced Hb change for the outcomes VO2max and fatigue. The exercise capacity, however, again did not change significantly.

Transfusion

Two narrative SRs were eligible for evaluation with regard to transfusion (Supplementary Materials S1, S3). Nielsen et al. (2017) evaluated the effect of transfusion on tissue oxygenation in critically ill ICU patients with anaemia compared to similar controls. They found no significant effect on tissue oxygenation (Figure 5). However, nine of the primary studies revealed a consistent pattern–patients with abnormal tissue oxygenation prior to transfusion improved with transfusion, whereas those with normal pre-transfusion indices did not. The authors conclude that this supports a strategy for future clinical trials which focuses on abnormalities of tissue oxygenation or microcirculatory parameters rather than haemoglobin levels as the trigger for transfusion. Solheim et al. (2019) evaluated the effect of autologous transfusion on the VO2max and exercise capacity in trained and untrained adults, compared to controls that did not receive an autologous blood transfusion. They reached the conclusions that the magnitude of change in Hb explains the increase in VO2max, and reinfusion with as little as 135 mL packed red blood cells increases time-trial performance by elevating CaO2. The AMSTAR-2 scores were critically low for both SRs, the GRADE quality of evidence was very low.

Restrictive versus liberal threshold

Of the retrieved citations evaluating restrictive (7.0–9.0 g/dL) and liberal thresholds (9.6–12.0 g/dL), two SRs were eligible for review (Supplementary Materials S1, S3). The SRs were published in 2015 and 2017, and both evaluated the effect of transfusion thresholds on quality of life. Estcourt et al. (2017) concluded to be very uncertain whether a restrictive threshold reduces quality of life in a population with hematological malignancies: one trial, 89 participants, fatigue score: restrictive median 4.8 (IQR 4–5.2); liberal median 4.5 (IQR 3.6–5) (very low-quality evidence). Gu et al. (2015) aimed to evaluate fatigue in a myelodysplastic syndrome population, but reported only one study which was terminated early due to poor recruitment and reported no results for their primary outcome measure. Both SRs are of high quality as scored with the AMSTAR-2 tool, but produced very low GRADE quality evidence due to small sample sizes and low quality primary studies.

Altitude training

Two SRs, published in 2012 and 2013, evaluated altitude training in athlete populations (Supplementary Materials S1, S3). Whereas Saunders et al. (2013) investigated several types of altitude training together, Lancaster and Smart (2012) focused only on live-high train-low altitude training. The AMSTAR-2 scores for both SRs were critically low, and GRADE quality of the evidence was low. Both SRs reported a small increase in Hb (0.57–0.69 g/dL and ~3%). Lancaster reported an improvement in maximal heart rate (MD = 1.77, CI:0.50, 3.03) and both SRs concluded that altitude training improves VO2max significantly (MD = 1.51, CI: 0.44, 2.58 and slope = 0.48, CI: 0.30, 0.67) in athletes, compared to normoxic training (Figures 5, 6).

Blood donation

Two SRs evaluating blood donation were eligible for review (Supplementary Materials S1, S3). The AMSTAR-2 scores of both articles were critically low. The GRADE quality of the evidence ranged from very low to low. Van Remoortel et al. (2017) evaluated several studies that compared healthy adults that underwent blood donation before and after donation, and one study that used sham bleeding as comparator. Johnson et al. (2019) performed a similar SR with comparable eligibility criteria. The results and conclusions presented by Johnson et al. (2019) were not completely understood, and Johnson et al. (2019) could unfortunately not be reached for comments. Intriguingly, Johnson and Van Remoortel reached contrasting conclusions. With much overlap in primary studies, we selected the review with the best data synthesis on the basis of the JADAD decision algorithm. Hence, we selected Van Remoortel's SR. The latter concluded that the VO2max and time to exhaustion decreased significantly after blood donation. Maximum power showed no significant difference pre- and post-donation (Figures 5, 6).

Sensitivity analysis

Systematic reviews evaluating ESAs make up for a large part of the included evidence. Therefore, we decided to additionally evaluate what the outcome of this umbrella review would have been without these SRs evaluating ESAs. A forest plot, funnel plot and an overview table of results, all without ESA-related trials, are shown in Supplementary Material S5a (Supplementary Figures S5–S8). Remarkably, very little evidence remains regarding PROMs and regarding anaemic patients in general. Too few reviews could, however, be included to create a funnel plot for PROMs in this sensitivity analysis. Nonetheless, there is no evident change of significance direction notable.

Furthermore, for a second sensitivity analysis, we selected only high-quality SRs. In doing so, no data for non-anaemia were left (Supplementary Figures S9–S12). For anaemic patients, however, the outcomes again remained similar in this analysis.

Discussion

The present umbrella review examined the body of evidence on the effect of changes in Hb levels on physiological and patient-reported outcomes. The gathered evidence suggests that an increase in Hb is generally followed by better physiological and patient-reported outcomes (Figures 5, 6). Likewise, a decrease in Hb would lead to inferior outcomes. The magnitude of the effect appears more pronounced at lower baseline Hb levels. Although, the increment was also higher at lower baseline Hb levels, which might be an important confounder. Despite rigorous and systematic methodology, we were only able to identify 34 eligible systematic reviews, mainly reporting on the effect of ESAs. Therefore, as illustrated by Figure 5, our umbrella review reveals many gaps in evidence. Of many interventions, the effects are not yet well evaluated. The added value of this umbrella review, illustrated by Figure 4, is that through a patchwork of data from studies that evaluate Hb changes with different interventions, we can imagine an extrapolated effect in our knowledge gaps. The present overview thus provides us with what might be expected of the general effect of an Hb-shift, regardless of the cause/intervention, which should be considered in the light of numerous patient-specific factors that affect the outcome for the individual. More importantly, this overview demonstrates that currently there is very little high quality evidence on this subject and identifies the knowledge gaps that require further research.

The domains of fatigue and physical functioning are reported to be affected most in PROMs. When focusing on physiological outcomes, VO2max and exercise capacity have been studied most frequently, but hardly in patient groups with Hb levels <10 g/dL. While a trend towards a positive correlation between Hb-increment and physiological outcomes is apparent, this is not always significant, possibly due to underpowering. VO2max improves significantly with an increase in Hb in both anaemic and non-anaemic patients. Exercise capacity is not always improved after an increase in Hb. Perhaps, longer standing Hb-improvements are needed to have a noticeable effect on the exercise capacity. While a reduction in fatigue and increase in VO2max will lead to increased activity, an increased muscle mass will only ensue later.

We found no eligible SRs evaluating the effect of an Hb change on physiological outcomes in polycythemia patients. Intriguingly, no SRs evaluated the effect of Hb changes on respiratory rate, resting heart rate, heart rate variability, cardiac output or other basic physiological outcomes in any of the patient groups.

Limitations

The reporting of evidence is generally scored by the AMSTAR-2 checklist to be of critically low quality, and meta-analyses with substantial sample sizes are mostly restricted to one intervention: ESAs. We did not impose any restrictions by language

or publication year and used very wide eligibility criteria to decrease the chance of selection bias. However, because of the wide eligibility criteria for this overview, the included populations are very heterogeneous. It is therefore emphatically not our intention to compare the included reviews with each other. Likewise, all quantitative outcomes–from VO2max to PROMs–have been presented together in the forest plots in Figure 6. The intention here is to give a visual overview of the standardized effect sizes of all results, not for meta-analytic purposes. Moreover, due to incomplete reporting in several reviews, multiple assumptions had to be made to compute SMDs from the reported effect sizes, limiting possibilities and accuracy of deeper analyses. Nonetheless, we believe this gives a good overview of the available evidence. Furthermore, it was commonly noted by the included narrative SRs that studies and outcomes were often too heterogeneous to be compared in meta-analyses. International cooperation and standardization of methods for producing and reporting outcomes would thus be helpful to reach more meaningful conclusions and to compare outcomes with other trials. As per custom for umbrella reviews, we chose to only include systematic reviews and meta-analyses to compare and contrast published reviews and to provide an overall examination of a body of information that is available for this topic (Hartling et al., 2012). Therefore, primary studies may exist that have assessed areas that we identified as gaps in evidence. Reviewing primary studies in these identified gaps, preferably in a meta-analysis, may be a next step for future research. Furthermore, the Hb-increment was higher in groups with a lower baseline Hb than in groups with a higher baseline Hb (Figure 4). This is important to realize when interpreting the forest plots in Figure 6: the effect of an Hb change seems more pronounced at lower baseline-levels. However, as the increment is higher at lower baseline Hbs, a dose-dependency effect might have confounded this result. Other bias may have been introduced by side effects of the investigated therapies. With current techniques it is impossible to determine whether an improvement in QoL is caused solely by an Hb modulation. It is conceivable that other metabolic effects of iron supplementation or treatments like ESAs may cause this change in QoL.

Our meta-bias analysis suggests that reviews analyzing PROMs are prone to publication bias, whereas physiological outcomes do not show meta-biases in the funnel plot or sensitivity analysis. Indeed, PROMs are a subjective tool, and therefore easily biased if the methodology of the primary study lacks blinding and such. Possibly, larger primary studies were methodologically sounder than those with small sample sizes, in which case, the funnel plot is a result of information bias. The other option is that non-significant meta-analyses were not published. Either way, as this issue did not occur with the physiological outcomes, we recommend for future primary studies to at least incorporate physiological outcomes, preferably in combination with PROMs. With fast emerging wearables, eHealth and remote monitoring options (Tonino et al., 2019), incorporating physiological outcomes has rapidly become more feasible and may provide intriguing new insights.

Our sensitivity analyses underline the fact that there is a lack of high-quality evidence to support guidelines. Selecting high quality SRs only, the results for anaemic patients were similar. However, there were no high quality SRs that assessed Hb changes in non-anaemic patients. After removing ESA-related reviews there were hardly any reviews left that assessed PROMs and very little evidence for anaemic patients in general. Since ESA-studies are predominantly funded by pharmaceutical companies, this demonstrates the importance of funding by pharma for research. Even though pharma-funded studies may be prone to conflicts of interest, they do contribute significantly to current knowledge. Nonetheless, independent high-quality evidence is very scarce.

In search of evidence-based guidance for haemoglobin optimisation, whether for transfusion thresholds, ESA-targets, hyperviscosity management or optimal athletic performance, we found that for a quantitative benefit-harm assessment, we lack the data to draw meaningful conclusions. In some cases, as in ESA treatment in chronic kidney disease, there are sufficient data for a moderately certain conclusion that there is benefit in increasing the Hb level up until about 12 g/dL for both patient-reported and physiological outcomes. With the heterogeneity, confounding and scarce high quality evidence, it is difficult to compare and/or extrapolate these findings to Hb levels >12 g/dL. Additionally, due to data suggesting an increased thrombotic risk above 12.0 g/dL in ESA-treated chronic kidney disease-patients, we would advise against Hb-targets >12.0 g/dL in this patient group (Palmer, 2010). For other treatments and patient groups, and the subjects of donation and phlebotomies, the evidence is thin or non-existent, and no conclusions about optimal Hb levels can be drawn.

Critics may state that the Hb level is an inadequate measure to begin with. Indeed, the total Hb-mass is not affected by changes in plasma volume and would be more stable and render more accurate insights (Prommer et al., 2008). However, most studies use the Hb level as a proxy for total Hb-mass due to its ready availability. And while less accurate, it can be insightful in larger samples. In the future, however, we need to look at alternative objective parameters for oxygen transport optimization. With current technology, wearable devices are able to remotely measure basic physiology parameters like heart rate, heart rate variability, respiration rate, tissue oxygenation, capillary oxygenation and many more. Collecting these parameters and using big data algorithms may be a step towards a more accurate assessment of the patients' treatment requirements when it comes to oxygen transport optimization. As this umbrella review shows, we still have many data gaps to fill.

In conclusion, this overview has revealed many knowledge gaps due to a lack of high-quality evidence. For chronic kidney disease patients, a clinically relevant benefit of increasing the Hb levels up until at least 12 g/dL on PROMs and physiological outcomes was found. However, a personalized approach of patient care remains a necessity due to the many patient-specific factors that can affect the tolerance to

deviating Hb levels. In non-anaemic patients, the evidence suggests that increasing the Hb level improves physiological and patient-reported outcomes, but the effect is less pronounced. Decreasing the Hb level has a clear inverse effect on physiological outcomes in non-anaemic subjects. For supraphysiological Hb levels, no eligible reviews were found. Because of the many knowledge gaps in general in the reported data sets, we strongly encourage future trials to incorporate physiological outcomes as objective parameters together with subjective, but still very important, patient-reported outcome measures.

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Author contributions

RT, MS, and JJZ conceived the study design. The study was carried out by RT and LZ. All authors participated in the interpretation of the results. RT and LZ wrote the first draft. All authors reviewed the draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The supplementary material for this article can be found online at:
frontiersin.org/articles/10.3389/fphys.2023.1086839/full#supplementary-material

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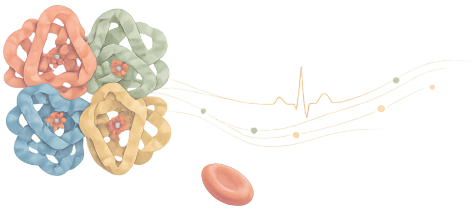

CLINICAL PRACTICE FOR OUTPATIENTS THAT ARE CHRONICALLY RED CELL DEPENDENT: A SURVEY IN THE NETHERLANDS

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Abstract

Background

Limited data are available to guide physicians on how to determine the red blood cell (RBC) transfusion regimen in chronically transfusion-dependent patients. The lack of clarity on thresholds and targets to be used for transfusion could easily result in either under- or over transfusion in these patients. The aim of our survey is to investigate (1) transfusion thresholds; (2) number of RBC units given per transfusion episode; (3) interval between transfusions and (4) patient factors, like decreased cardiac function modulating the former.

Materials and Methods

We sent a web-based 44-question survey to members of the Dutch Haematology Association.

Results

Fifty physicians responded between June and October 2020 (response rate 30%), well-distributed between community and academic hospitals. A wide variation in transfusion strategies was reported: Most patients received 1–2 RBC units (range: 0–3 units) every 2–4 weeks (range: 1–12 weeks) with a median threshold of 8.0 g/dL ranging from 6.4 to 9.6 g/dL. Patient-specific clinical factors that are most frequently reported to influence the transfusion strategy are angina pectoris, cardiac failure and dyspnoea. Softer parameters that are of influence are the quality of life and self-sustainability.

Conclusion

The results of this survey indicate a broad variation in RBC transfusion strategies in Dutch patients with chronic transfusion dependency. While the current variation in transfusion strategies may be unavoidable in an individualized approach, randomized trials and better defined usable parameters to evaluate the effect of transfusion strategies are required to reach a consensus on how to determine the transfusion strategy.

Introduction

Patients who receive red blood cell (RBC) transfusions on a regular basis typically suffer from diseases like myelodysplastic syndrome (MDS), myeloproliferative diseases (MPN), thalassaemia, sickle cell disease or aplastic anaemia. Although these patients receive 20%–30% of all RBC transfusions in Europe,[1,2] limited data are available to guide physicians on how to determine a chronic RBC regimen.[3-7] As studies on restrictive RBC transfusion strategies show no disadvantages in other patient categories,[8-12] physicians tend to use a restrictive transfusion policy based on the perceived Quality of Life (QoL) of the individual patient.[13-15] The effect of this individualized transfusion policy is hard to quantify and depends on the haemoglobin (Hb) threshold, the timing of transfusion and the number of RBC units administered.[6,7,16] Factors like anaemia-related symptoms, the (estimated) cardiopulmonary compensation capacity and the presence of iron overload might further influence the transfusion policy.[17,18] The lack of clarity on thresholds and targets to be used for transfusion will easily result in either under or over transfusion in these patients. Both, moreover, will have negative effects: with on one hand anaemia-related symptoms[19-22] and on the other iron-overload and other transfusion-specific side effects.[23,24,25]

We performed a survey amongst haematologists in the Netherlands to investigate their current standard of care for patients dependent on chronic transfusions, regarding the applied (1) transfusion thresholds; (2) number of RBC units given per transfusion episode; (3) interval between transfusions and (4) patient factors, like decreased cardiac function modulating the former.

Materials and methods

Study design

In this cross-sectional study, a structured, 44-question online survey was conducted amongst members of the Dutch Society of Haematology (NVvH) that treat patients with chronic transfusion dependency due to a haematological disorder. The questionnaire was sent to 169 haematologists in the Netherlands (Appendix S1). The questions were related to both clinical and soft outcomes that might influence the transfusion policy, that is, the Hb threshold, amount of transfusions given and the interval between transfusions. In addition, respondents were asked to fill out a set of questions about one or more of their own transfusion-dependent patients to test for consistency of actual practice with responses to similar general questions. To allow for quantitative answers, Likert scales were used.[26] Incomplete surveys were included in the analysis. Free-text responses were interpreted and summarized by the authors. The study was conducted using a Castor Electronic Data Capture (Castor, Amsterdam, the Netherlands) based survey (Appendix S1).

Statistical analysis

Categorical variables are summarized as frequencies and percentages or median with range and statistically evaluated with the chi-square test, continuous variables are reported as means and standard deviations and were statistically evaluated with unpaired t-test, Welch's t-test and Pearson's correlation coefficient. Statistical methods were conducted using SPSS (version 25.0, SPSS Inc., Chicago, IL), p-values <0.05 were considered significant.

Results

Study cohort

We sent out a survey to 169 members of the NVvH in the Netherlands of which 50 physicians responded between June and October 2020 (response rate: 30%). A total of 56% of the responding physicians work in an academic medical centre, 44% in a community hospital. Seven out of eight academic centres in the Netherlands were represented in the responses. The physicians completed questions on a cumulative total of 58 transfusion-dependent patients. Out of the respondents, 42/50 were haematologists, 6 were haematologists in training and 2 were specialists in internal medicine. Including the years in training, 12 respondents had <5 years of experience with transfusion-dependent patients; 19 respondents between 5 and 10 years; 9 between 10 and 19 years and 10 respondents had >20 years of experience.

General response

In the first part of the survey, we asked physicians to indicate, which of a set of 19 given factors affects their transfusion strategy in general. In Figure 1, these factors are depicted. Clinical factors that are reported to strongly influence the transfusion threshold are angina pectoris, cardiac failure and dyspnoea. Soft outcomes that are reported to influence the threshold mostly are a decreased quality of life and self-sustainability. Factors that are reported to be of no, or little, influence are gender, emotional state (fear and depression), renal disease, peripheral vascular disease, iron parameters and a bleeding tendency.

We stratified by years of experience of the haematologist and academic versus community hospital to evaluate for effect-modification by these factors. While responses from academic- and community hospitals yielded comparable outcomes, the amount of experience of physicians did have an influence on the weight they attributed to certain factors: patient activity, mobility and self-sustainability were scored as 'moderate-strong influence on the Hb-threshold' in 8/9 (89%, $p = 0.01$), 10/10 (100%, $p <0.01$) and 9/10 (90%, $p = 0.17$) by physicians with >20 years of experience, while physicians with <20 years of experience scored 17/39 (44%), 23/39 (59%) and 29/40 (74%), respectively.

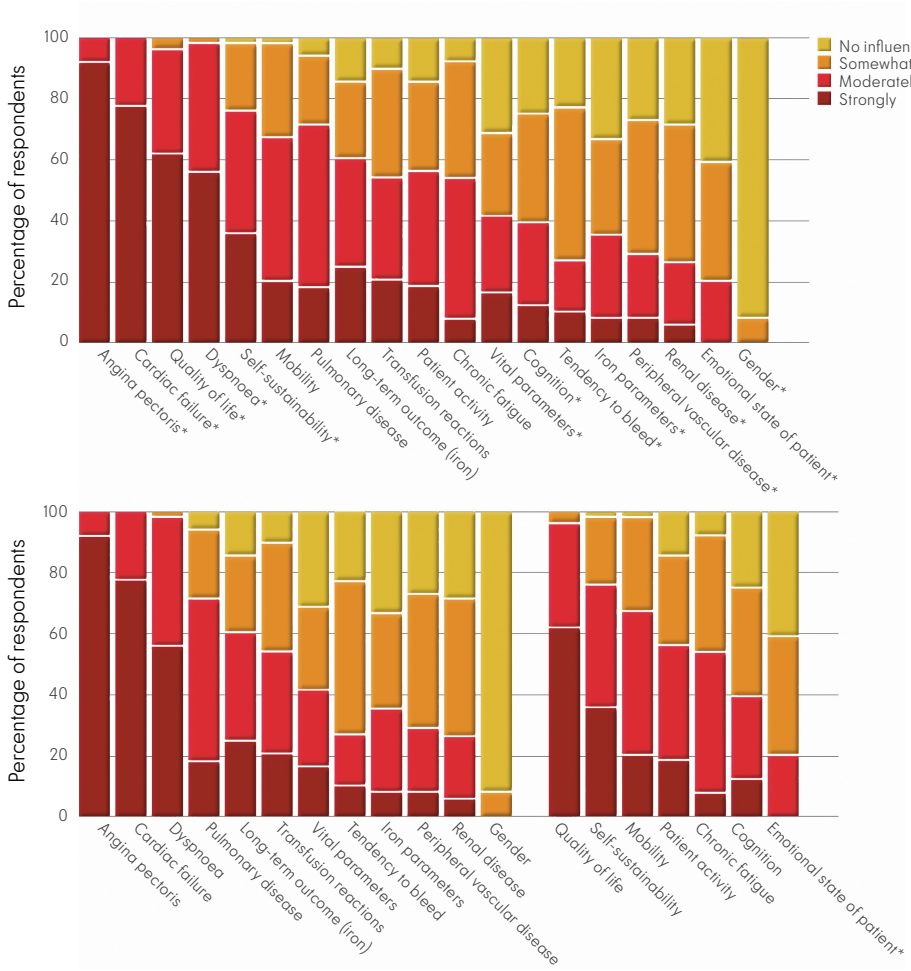

Figure 1. Responses to how much the indicated factors affect the choice for a red blood cell transfusion threshold, arranged from strongly to least influential (top); and subdivided in clinical and soft parameters (bottom). *p < 0.05 compared to the responses of all other parameters.

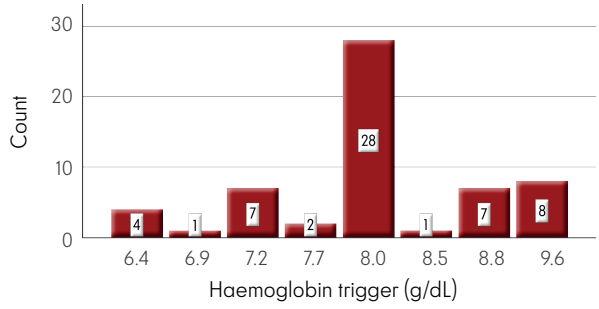

Figure 2. Haemoglobin thresholds used in daily practice (n = 58).

Table 1. Overview of various individual transfusion regimes.

	Number of RBC transfused		
	1 RBC	2+ RBCs	Total
Interval (weeks)	g/dL ± SD (*n*)	g/dL ± SD (*n*)	g/dL ± SD (n)
1	8.3 ± 1.0 (4)	8.6 ± 0.9 (3)	8.4 ± 0.9 (7)
2–4	8.0 ± 0.7 (15)	8.3 ± 0.7 (22)	8.2 ± 0.7 (37)
5–12	8.9 ± 1.1 (2)	7.9 ± 1.2 (10)	8.1 ± 1.2 (12)
Total	8.1 ± 0.8 (21)	8.2 ± 0.9 (35)	8.2 ± 0.8 (56)

Note: A mean threshold is given per transfusion regime.
Abbreviation: RBC, red blood cell.

Table 2. Amount of red blood cells (RBCs) transfused when the haemoglobin level drops <0.8, 0.8–1.6 or >1.6 g/dL below the patient's personal threshold.

	Number of RBCs transfused per transfusion episode				
Hb level below the patient's personal threshold	0 RBCs *n* (%)	1 RBCs *n* (%)	2 RBCs *n* (%)	3 RBCs *n* (%)	Cumulative count of transfused RBCs (mean per patient)
<0.8 g/dL	1 (2%)	21 (36%)	34 (59%)	2 (3%)	95 (1.6 pp)
0.8–1.6 g/dL	0	8 (14%)	41 (71%)	9 (16%)	117 (2.0 pp)
>1.6 g/dL	0	0	26 (45%)	32 (55%)	148 (2.6 pp)

Note: A significant increase in transfused RBCs is seen with lower Hb levels ($p < 0.001$, for both <0.8 compared to 0.8–1.6 and >1.6 g/dL, and 0.8–1.6 compared to >1.6 g/dL). Abbreviation: RBC, red blood cell.

Long-term outcomes were taken into consideration more often by physicians with <5 years of experience: they scored a 'moderate-strong influence' in 9/11 (82%) cases versus 20/37 (54%) for >5 years of experience ($p = 0.07$). Furthermore, 8/48 (17%) of the respondents (all of which have <10 years of experience) reported to measure post-transfusion Hb levels.

Patient-specific response

The reported Hb thresholds for RBC transfusion-dependent patients are depicted in Figure 2. The most-reported threshold (28/58; 48%) was 8.0 g/dL (range: 6.4–9.6 g/dL). Four patients received transfusions only when their Hb dropped below 6.4 g/dL, seven patients had a threshold of 7.2 g/dL. Sixteen patients had a threshold higher than the median, of these, eight were transfused when their Hb level dropped below 9.6 g/dL.

Regarding the transfusion interval: 7/56 patients (13%) received transfusions on a weekly basis, 11/56 patients (20%) every 2 weeks, 13/56 (23%) patients every 3 weeks, 13/56 (23%) patients every 4 weeks and only 12/56 (21%) patients have an interval of at least five weeks (Table 1).

The number of transfused units was strongly correlated with the pre-transfusion Hb level ($p < 0.001$). Table 2 shows the amount of RBCs transfused per episode, depending on how much the Hb level dropped below the patient's threshold. When the pre-transfusion Hb is <0.8 g/dL below the patient's personal threshold, a mean of 1.6 RBC units was transfused. When the observed Hb level was between 0.8 and 1.6 g/dL below the threshold, a mean of 2.0 RBC units was transfused. When the Hb level was >1.6 g/dL below the threshold, the mean number of transfused units was 2.6.

The threshold, interval and number of units transfused together form a transfusion strategy. The various transfusion strategies are cross-tabulated in Table 1 and depicted in Figure 3. The mean threshold/(interval × transfusion amount) does not show a particular trend, suggesting that the variation in thresholds is independent of these two factors and more dependent on patient-specific parameters. Although no single strategy prevails most, a common frame can be identified: 63% of the reported patients are transfused 1–2 units every 2–4 weeks.

Parameters associated with changes in transfusion strategies

We asked the respondents to complete a set of questions on a patient of theirs to test for consistency with the general responses on the abovementioned factors. For patients without angina pectoris, the mean threshold was 8.0 g/dL whereas patients with moderate angina had a threshold of 8.8 g/dL ($p = 0.047$). This suggests that physicians indeed increase the transfusion threshold when a patient suffers from angina. Whether or not patients had any form of cardiac failure only did not impact the threshold in a significant manner ($p = 0.28$): a mean threshold of 8.1 g/dL for no cardiac failure versus 8.4 g/dL for patients with cardiac failure. Pulmonary disease had an, if any, inverse effect: 8.2 g/dL was the mean threshold for patients without the pulmonary disease, 8.0 g/dL for patients with pulmonary disease. The patient group without pulmonary disease did, however, have a higher prevalence of cardiac failure and angina pectoris.

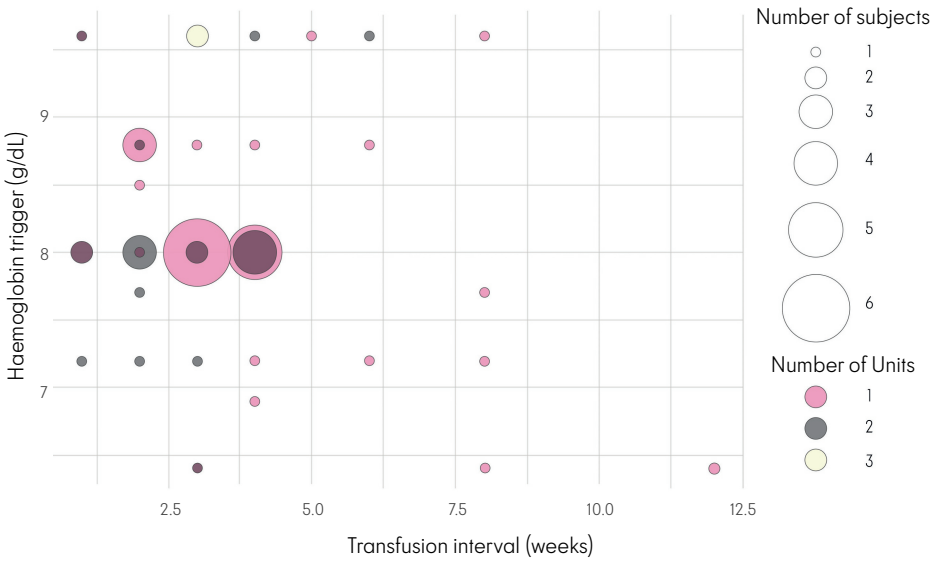

Figure 3. Bubble plot of the reported transfusion strategies. Most responses were focussed on a threshold of 8 g/dL every 2–4 weeks. Patients with thalassaemia and Sickle Cell Disease were reported to receive transfusions with a larger interval with also a lower mean threshold, which explains some of the outliers.

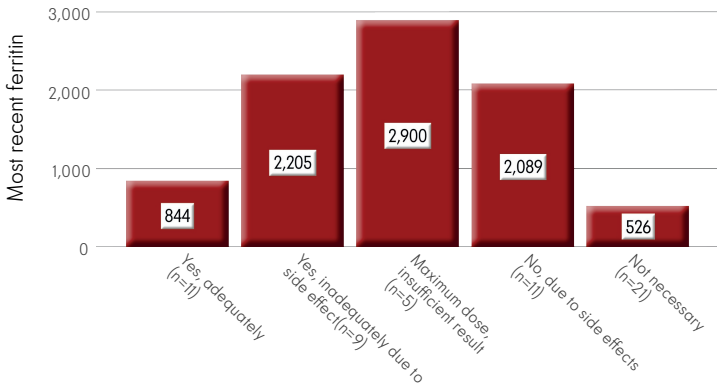

Figure 4. Mean ferritin per response to the question of whether the patient receives chelation therapy. The mean transfusion burden is given per response group. Patients that do not require chelation therapy have the highest mean transfusion burden (P = 0.042 compared to those who do receive chelation therapy).

The underlying disease, the cause for the patient's chronic anaemia, strongly impacts the transfusion strategy. While the overall median transfusion interval is 3 weeks, for 5/8 thalassaemia patients, the transfusion interval is 5 weeks or more (median = 6 weeks, range: 2–12, P = 0.038). Thalassaemia and sickle cell patients (n = 8 and 3, resp.) also have a lower transfusion threshold (7.2 ± 0.7; P = 0.001, and 7.5 ± 1.2 g/dL; P = 0.19, respectively). Other disease groups (MDS n = 22, MPN n = 13, AML n = 2, CMML n = 2, and other n = 7) all had a mean threshold between 8.2 and 8.6 g/dL with a median interval of 3 weeks (range: 1–8 weeks), except for one aplastic anaemia patient: threshold 9.7 g/dL, interval 1 week. Not all patients have a structured transfusion strategy: 2/3 sickle cell patients receive transfusions on demand.

Whether a patient received active treatment other than RBC transfusions for their underlying disease appears to affect the threshold too. The mean threshold for patients that received a form of chemotherapy was 7.6 ± 0.6 g/dL (n = 11, P = 0.02 compared to no treatment), while receiving immunomodulatory drugs leads to a threshold of 8.5 ± 0.6 g/dL (n = 8) and no treatment to 8.3 ± 0.9 g/dL (n = 38).

Although most physicians report that they try to adjust transfusion strategies to avoid long-term negative outcomes due to iron overload, they also report not necessarily taking iron parameters into the equation (Figure 2). Nonetheless, our data do show a mild effect of ferritin level on the threshold. When patients had a ferritin <1000 µg/L, the mean threshold was 8.3 ± 0.6 g/dL, while ferritin levels >1000 µg/L lead to a mean threshold of 8.0 ± 0.4 g/dL (P = 0.24). In addition, we evaluated the ferritin levels per response to the question 'how many RBC units the physician would transfuse to their patients if the Hb level dropped more than 1.6 g/dL below their personal threshold': the 32 patients that would receive three RBCs had a mean ferritin level of 1140 ± 944 µg/L while the 25 patients that would receive 2 RBCs had a mean ferritin level of 1647 ± 1948 µg/L (P = 0.20). Stratification for the transfusion burden yielded the same results. While the main cause for elevated ferritin levels is the transfusion burden, it is also dependent on how effective and/or tolerated chelation therapy is (Figure 4). Interestingly, the patients that were deemed not to need chelation therapy because of the still low mean ferritin levels did have the highest transfusion burden (2.9 units / 4 weeks; P = 0.046 compared to patients that do receive chelation therapy). These three findings suggest that patients with higher ferritin levels are in fact transfused more restrictively. Most parameters individually did not render an association with the transfusion threshold, interval or number of units transfused. However, trying to pinpoint what type of patients are most likely to deviate from the mean, we noticed that patients with a threshold <7.2 g/dL did not suffer from pulmonary or cardiac problems, and had few risk factors overall. Amongst patients with thresholds up to 8.0 g/dL, 3/14 (21%) suffered from cardiac and/or pulmonary problems, compared to 26/44 (59%) patients with thresholds above or equal to 8.0 g/dL (p = 0.014). This indicates that an important prerequisite for maintaining a maximally restrictive transfusion policy is a sufficient (estimated) cardiopulmonary

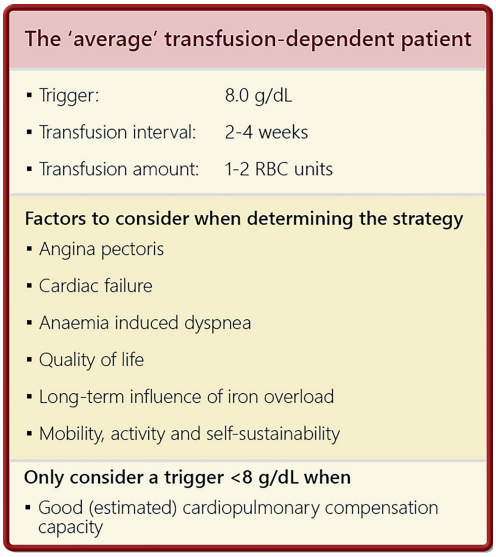

Figure 5. The average transfusion-dependent patient according to the present survey; *RBC, red blood cell.*

compensation capacity. Conversely, as stated before, the presence of angina pectoris and cardiac failure may lead to a higher threshold. Other than that, we could not identify consistent motives for increasing the threshold above 8.0 g/dL.

Regarding physician factors, academic hospitals and community hospitals reported similar strategies. There are, however, some nuanced, non-significant, differences: academic hospitals transfuse every 3.6 weeks (mean), while community hospitals transfuse every 4.4 weeks without a change in the mean transfusion threshold (both 8.2 g/dL). Physicians with <5 years of experience in the field appear to transfuse more units (1.8 units every 3.9 weeks) but at a more restrictive = lower threshold (8.0 g/dL), compared to colleagues with more experience, especially compared to those with >20 years of experience (1.6 units every 3.9 weeks, threshold 8.2 g/dL). We found no correlation between outliers in thresholds and the experience level of the physicians.

Because we included incomplete surveys, we performed a non-response error analysis to evaluate whether bias might have been introduced by non-responders. A relatively high number of respondents failed to report the patient's most recent ferritin (5/58; 9%). We did not find a difference between those who did not report the ferritin level and those who did. Other questions were not left unanswered more frequently than others.

Discussion

This survey amongst Dutch haematologists shows an average transfusion strategy of 1–2 RBC units (range: 0–3 units) every 2–4 weeks (range: 1–12 weeks) with a median threshold of 8.0 g/dL but a large reported variation (range: 6.4–9.6 g/dL). Patient-specific clinical factors that affected the found variability in the transfusion strategies are angina pectoris, cardiac failure and dyspnoea, but also ferritin levels, underlying disease and the concurrent treatment influenced transfusion regimen. Softer parameters of influence are quality of life and self-sustainability. More experienced physicians take patient activity, mobility and self-sustainability into account more often than less experienced colleagues.

Regarding the underlying disease, patients suffering from sickle cell disease and thalassaemia had a lower mean threshold (7.2 and 7.5 g/dL, resp.) and longer interval (median 6 weeks) compared to the other included patients (Hb-threshold >8.2 g/dL, interval = 3 weeks). This may be explained by a lifelong need of these patients to cope with lower Hb levels but also by the known higher alloimmunization levels of these patients and thus more focus on restriction. In addition, transfusion goals differ between different indications: whereas an MDS patient receives transfusions to improve the oxygen-transportation capacity, the aim in patients with sickle cell disease is also to decrease the proportion of sickle Hb relative to Hb A to prevent or reverse vaso-occlusive disease.

Patients receiving chemotherapy are transfused at a lower mean threshold (7.6 g/dL) as compared to those with immunomodulatory drugs or no active therapy (8.5 and 8.3 g/dL, resp.). The suppression of haematopoiesis by chemotherapy, although more severe, is also more likely to be reversible. Physicians may thus accept a lower Hb level as a rise is to be expected when the chemotherapy's side effects wear off.

There may be various arguments to transfuse at a higher more liberal threshold: a physician might aim to increase the patient's QoL; or to counter a patient's poor tolerance of low Hb levels. Vice versa, restrictiveness with thresholds below 8 g/dL seems only enforced if there are no clear risk factors such as a reduced estimated cardiopulmonary compensation capacity (Figure 5).

Clearly, the exact effect of a transfusion on the patient is hard to quantify. As few physicians report to measure post-transfusion Hb levels, this also appears to be a parameter of little value. Therefore, there is a dire need for clinically relevant outcome measures to evaluate transfusions and transfusion strategies.

Interestingly, an increased ferritin level did somewhat influence the threshold and transfusion burden, in spite of the fact that physicians score ferritin as one of the least influential factors. A possible relation indeed is not clear-cut. Indeed, high ferritin

levels could cause a more restrained transfusion strategy to avoid iron overload and consequent long-term organ damage, while for patients with lower ferritin levels, a more liberal transfusion strategy could be allowed. On the other hand, the need for chronic transfusions is bound to lead to higher ferritin and iron overload, which could already urge the physicians to transfuse more restrictively as a precaution. Therefore, the observed but only moderate impact of elevated ferritin levels on the transfusion strategy might be an underestimation of iron overload awareness. In addition, whether chelation therapy is used, effective and/or tolerated further complicates this question, as it greatly affects ferritin levels. Assuming transfusion burden should be guided by the present or expected iron overload a new question could be raised: could patients in whom chelation therapy is effective be transfused at a higher threshold? The theoretical benefits of a higher Hb level, which have yet to be established, may indeed outweigh the side effects if they can be limited. In addition, an established gain in quality-adjusted life years might balance the extra labour and costs of transfusions. Clearly, not all variations of transfusion strategies can be accounted for by the investigated factors. Besides patient factors, the current variation in transfusion strategies is likely also due to a lack of evidence-based guidelines for this group of patients. Some physicians may base their choice to transfuse more restrictively on multiple studies conducted in other patient groups where restrictive RBC transfusion strategies show no disadvantages on the accumulated parameters like morbidity and mortality.[8-12] Others may choose a more liberal strategy because a higher Hb level is believed to be beneficial for the transfusion-dependent patient.[27] While variability in transfusion strategies between patients may not be a problem at all, the lack of guidelines should not lead to large interphysician differences, as this will cause both under and over transfusion. Nevertheless, the observed range of thresholds does not find a base in Dutch or international guidelines.[13, 28] Currently, the Dutch guideline advises to use a threshold between 7.0 and 8.0 g/dL for reversible anaemia of haematological patients other than the chronically dependent group; importantly, its only advice for chronic anaemia is to apply an individual strategy based on the perceived quality of life.

This is the first survey amongst haematologists in the Netherlands in which important questions regarding RBC transfusion support in chronic transfusion-dependent patients are addressed. Though some presented results may have been expected, it is important that they are documented in search of proper guidelines.

Regarding this paper's limitations, first, as is the case in most surveys, this study is limited by the moderate response rate. Aiming for respondents who take an interest in transfusion policies, and are, therefore, likely to treat a relatively high number of the low-prevalent transfusion-dependent patients, we believe, we have included a representative portion of the target population. Second, our data may be subject to response bias as physicians who do not maintain standard transfusion strategies, or who do not use transfusion thresholds may not have responded. Third, as only the

responses of the physicians were collected, the actual clinical practice could differ. We should, for example, be cautious with the interpretation of ferritin levels, since we have no means of verifying these numbers. Fourth, because we included incomplete surveys, bias could have been introduced by non-response errors. However, our non-response error analysis suggests that this is not the case.

A survey looking into the transfusion thresholds of patients with haematological malignancies in general in the Netherlands yielded similar results.[29] However, the median threshold for outpatient care was lower (7.2 g/dL). Mo et al. performed a survey investigating thresholds for specifically MDS patients in Australia. In agreement with our results, they concluded a typical transfusion threshold of 8.0 g/dL, with higher thresholds typically used for patients with cardiovascular disease or anaemia symptoms.[30] In both the abovementioned surveys, the investigation of parameters associated with changes in transfusion strategies, however, was much more limited than the present study. Both these previous surveys reported on existing institutional transfusion guidelines and/or used case scenarios to elicit transfusion thresholds. The present study, in contrast, asked for actual patient examples, which might be a better reflection of the true spectrum of currently used transfusion strategies for chronic transfusion-dependent patients. These new, original data could allow professionals to benchmark their transfusion practices and reflect on them, and may be helpful in organizing haematologists' training.

The observed variation in less restrictive transfusion strategies ultimately stems from the variable use of non-evidence-based parameters to counter the cons of transfusions. While it is clear that fewer transfusions prevent transfusion reactions and iron overload, this results in a lower Hb level, which negatively impacts patients' well-being.[10, 19-22] Softer outcomes describing well-being like health-related quality of life, though reportedly important as shown by Figure 2, however, are harder to quantify.

Our findings hence address the need for prospective randomized trials to develop evidence-based guidelines for RBC transfusions in patients with chronic transfusion dependency with the goal of improving their QoL while limiting unnecessary transfusions without compromising the outcome. To date, there have only been two small randomised controlled trials (13 and 38 patients) comparing restrictive versus liberal thresholds in chronic transfusion-dependent patients. Although not adequately powered to detect clinically relevant differences, results are suggestive of an improved QoL with higher Hb levels.[31, 32] Currently, several studies with chronic transfusion-dependent patients are conducted (REDDS-2, ACTRN12619001053112; REMOTE 2, NL9289; EnhanceRBC, NCT02099669; SMD-Transfu, NCT03643042; PTQA, NCT03660228). Results of these studies will yield better insight into the effects of transfusion strategies on the well-being of this chronically transfused group of patients. We encourage international collaborations for trials investigating patients

with chronic transfusion requirements. Such collaboration is likely required to achieve a large enough sample size to detect meaningful, clinically relevant differences in transfusion strategies.

In conclusion, the results of this survey indicate a broad variation in RBC transfusion strategies in Dutch patients with chronic transfusion dependency. While the current variation in transfusion strategies may be unavoidable in an individualized approach, randomized trials and better defined usable parameters, amongst which a measure for QoL, to evaluate the effect of transfusion strategies are required to reach a consensus on how to determine the transfusion strategy.

Conflict of interest

All authors attest that they have no conflict of interest to declare.

Supporting information

Additional supporting information may be found in the online version of the article at the publisher's website.

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RT, MS and JJZ conceived the study design. RT performed the research and wrote the first draft. MS and JJZ supervised the research, and reviewed and edited the manuscript.

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Supplementary material

The supplementary material for this article can be found online at:
https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fvox.13220&file=vox13220-sup-0001-supinfo.docx

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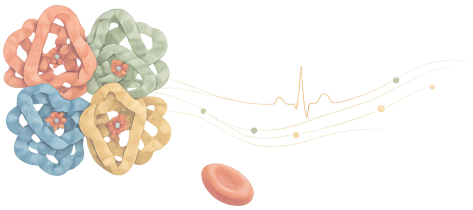

REMOTE PATIENT MONITORING IN ADULTS RECEIVING TRANSFUSION OR INFUSION FOR HEMATOLOGICAL DISORDERS USING THE VITALPATCH AND ACCELERATEIQ MONITORING SYSTEM: QUANTITATIVE FEASIBILITY STUDY

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Abstract

Background

Frequent vital sign monitoring during and after transfusion of blood products and certain chemotherapies or immunotherapies is critical for detecting infusion reactions and treatment management in patients. Currently, patients return home with instructions to contact the clinic if they feel unwell. Continuous monitoring of vital signs for hematological patients treated with immunotherapy or chemotherapy or receiving blood transfusions using wearable electronic biosensors during and post-treatment may improve the safety of these treatments and make remote data collection in an outpatient care setting possible.

Objective

This study aimed to evaluate patient experiences with the VitalPatch® wearable sensor (VitalConnect) and to evaluate the usability of data generated by the physIQ AccelerateIQ™ monitoring system for the investigator and nurse.

Methods

A total of 12 patients with hematological disorders receiving red blood cell transfusions, an intravenous (IV) proteasome inhibitor, or an IV immunotherapy agent were included in the study and wore the VitalPatch® for 12 days. Patients completed questionnaires focusing on wearability and nurses completed questionnaires focusing on the usability of the VitalPatch®.

Results

A total of 12 patients were enrolled over 9 months, with 4 receiving red blood cell transfusions, 4 receiving IV proteasome inhibitors, and 4 receiving IV immunotherapy. These patients were treated for diseases such as multiple myeloma, myelodysplastic syndrome, and non-Hodgkin lymphoma. Of these patients, 83% (10/12) were aged 60 years and older. A total of 4 patients (4/12, 33%) withdrew from the study (3 because of skin irritation and 1 because of patch connection issues). Patients wore biosensor patches at baseline and for 1-week post-administration. Patient-reported outcomes (PROs) were collected at baseline, day 1, day 5, and day 8. No difference in the PRO was observed when nurses or patients applied the patch. PRO data indicated minimal impact on the patient's life. Ease of use, influence on sleep, impact on follow-up of health, or discomfort with continuous monitoring did not change between baseline and day 8. Changes in PRO were observed on day 5, where a 20% (2/10) increase in skin irritation was reported. Withdrawals because of skin irritation were reported in all cases when wearing the second patch. Nurses reported the placement of the VitalPatch® to be easy and felt measurements to be reliable.

Conclusions

Generally, the VitalPatch® was well tolerated and shown to be an attractive device because of its wearability and low impact on daily activities in patients, therefore making it suitable for implementation in future studies.

Introduction

Background

Although continuous patient monitoring is often thought to be reserved for intensive care units, the need for frequent assessment of vital signs is necessary in other clinical circumstances as well. Examples of these circumstances include during and after transfusion of blood products, and during and after transfusion of certain chemotherapies and immunotherapies.[1,2] Receiving these transfusions and infusions can result in untoward reactions that typically manifest as abnormal vital signs before or simultaneously with an adverse event (AE), also known as an infusion reaction.[3-5] For example, 2.1% of all recipients of blood products experience a transfusion reaction, some of which can be life-threatening. In addition, administration of many anticancer drugs has a risk for infusion reactions.[6] Therefore, frequent vital sign monitoring during and after treatment is essential to prevent poor patient outcomes.

Even when intensive vital sign monitoring occurs, infusion reactions can go unrecognized. One reason may be inconsistent vital sign assessment.[5,7-10] In one study, researchers found 27.4% (168/614) of nursing staff estimated respiration rate rather than measuring it.[11] In many cases, physicians sent patients home after transfusion and infusion therapy with instructions to contact the clinic if the patient became unwell.[6] This leaves the possibility of late detection of infusion reactions open. These findings demonstrate that strategies for patient assessment during and following transfusion and infusion are suboptimal.

To improve the detection of infusion reactions, various interventions have been explored, such as additional training on identifying possible infusion-associated AEs for nurses.[2] Increasing nurses' knowledge of risk factors for infusion-associated AEs[12]

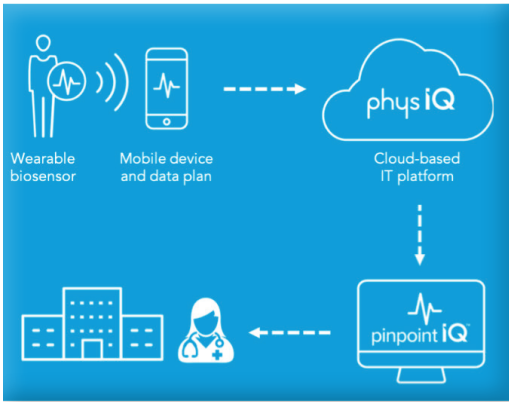


Figure 1. The AccelerateIQ™ end-to-end solution. IT: information technology.



Figure 2. VitalPatch® placement.

has been implemented, in addition to guidelines to intensify monitoring of infusion recipients at higher risk. Process changes, such as standardized handoff forms[1] and clinical decision support systems[13], are other strategies used to improve safety of transfusions and infusions. Nonetheless, the challenge of adequate assessment during transfusion and infusions remains.

The evolution of digital health and biosensors has opened the possibility of an easier and more effective way of monitoring and analyzing vital signs in patients during and after the receipt of transfusions and infusions. Using these technologies, a health care professional may have greater insight into a patient's health status. One such product is the AccelerateIQ™ and VitalPatch® system. AccelerateIQ™ is an end-to-end clinical-grade system that collects data from wearable sensors (in this case VitalPatch®). AccelerateIQ™ applies Food and Drug Administration–cleared artificial intelligence analytics to display indicators and data streams through a Web portal. Clinicians can then see any physiological changes indicative of clinical deterioration in patients outside of the acute setting (see Figure 1).

Objectives

The aim of this study was to evaluate whether the AccelerateIQ™ and VitalPatch® system is a practical way to monitor transfusion patients and whether patients find it acceptable to do so. We performed a pilot study to determine whether it was feasible to implement this system in the clinic and to support future studies, with a focus on wearability, usability of data, and safety. These pilot data will be used to inform a further definitive trial to optimize recruitment, treatment compliance, and follow-up protocols.

Methods

Study Design

This study was a three-arm, parallel, single center, observational, nonrandomized, open-label feasibility study. The study aimed to explore wearability, usability, and safety of use of the AccelerateIQ™ and VitalPatch® system in a population of transfusion and infusion patients.

The medical ethics committee, Zuidwest Holland, granted ethical approval, and the board of the Haga Teaching Hospital granted approval. The trial was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Patient data were anonymized to ensure patient privacy. Storage and handling of personal data complied with the General Data Protection Regulation and Medical Treatment Agreement Act, Dutch law.

Table 1. Baseline characteristics.

Characteristics	N0. of patients (% of total)
Age	
40-49 years	2 (17%)
60-69 years	6 (50%)
70-79 years	4 (33%)
Hematological disorder	
Multiple myeloma	4 (33%)
Myelodysplastic syndrome	*2 (17%)*
β-Thalassemia	1 (8%)
Non-Hodgkin lymphoma	5 (42%)
Treatment	
Red blood cell transfusion	4 (33%)
R-CHOP [a]	4 (33%)
Carfilzomib/Dexamethasone	3 (25%)
Carfilzomib/Lenalidomide/Dexamethasone	1 (8%)
Skin Color	
White	11 (92%)
Dark	1 (8%)
Sex	
Male	10 (83%)
Female	2 (17%)

[a] R-CHOP: doxorubicin, cyclophosphamide, vincristine, rituximab, and prednisone

The study population comprised 12 adult participants with a confirmed hematological disorder distributed over 3 different groups. Groups consisted of: (1) 4 patients receiving red blood cell transfusions; (2) 4 patients receiving intravenous (IV) proteasome inhibitors; and (3) 4 patients receiving IV immunotherapy. Patients with severe pulmonary comorbidities, arrhythmias, or other significant conductivity disorders, or with known skin allergies or conditions that might compromise the patient's safety or quality of data, were excluded. Patients were recruited by their own physician in the Haga Teaching Hospital and included after informed consent was obtained.

Intervention

Participants in the study received standard care in addition to vital sign monitoring through the AccelerateIQ™ and VitalPatch® system. This system consists of the VitalPatch®, a disposable adhesive patch biosensor that incorporates 2 surface electrodes with hydrogel and a thermistor on the bottom of the patch. A 4-day battery and an electronic module with an embedded processor, a microelectro-mechanical system tri-axial accelerometer, and a Bluetooth low-energy transceiver are also part of the sensor. The patch's sensors facilitate continuous, near real-time monitoring of heart rate, R-R interval, heart rate variability, respiratory rate, single-lead electrocardiography, skin temperature, body posture, fall detection, and activity. Data are sent via Bluetooth to a mobile phone (Samsung J327V, Android), which uploads the data over mobile data networks to the physIQ AccelerateIQ™ cloud platform.

A universal smartphone was provided to maintain quality systems and standards in clinical and trial use. When the phone to patch distance exceeds Bluetooth range, which is about 20 feet, the patch will store data and offload it when the phone is back in range. Raw data are then analyzed to extract further vital sign features and to detect vital sign anomalies in the patient physiological response. After that, the smartphone transmits data to the AccelerateIQ™ data platform. physIQ operates in line with national standards for the privacy of health information and regulations for electronic records and signatures, pursuant to the Health Insurance Portability and Accountability Act of 1996 and the Code of Federal Regulations (CFR), respectively.

Patients wore a VitalPatch® for a maximum of 12 days. The first patch was placed the week before the start of treatment and worn for 4 days to generate baseline data. The second patch was placed at the start of treatment (or the day before for transfusion patients), and a third patch, necessary because of battery life, was placed after 4 days by the patient at home (see Figure 2). The patch cannot be submerged in water, so while wearing the patch, patients could not swim or bathe. Showering was allowed.

Table 2. Questions on patients' experience with the VitalPatch®. Patients responded on a Likert-type scale whether they agreed (10) or disagreed (1) with the statement.

#	Question	Baseline (*n* = 10)	Day 1 (*n* = 12)	Day 5 (*n* = 10)	Day 8 (*n* = 8)	Total (*n* = 40)
1	Was it easy placing the patch?	9	9	7.8	8.5	8.6
2	Problems placing patch? *	1	1	2	1	1.3
3	Is it pleasant wearing the patch?	7.1	6.2	6.1	7.5	6.7
4	Sense that health is being monitored?	5.2	5.0	4.8	5.5	5.1
5	Discomfort wearing the patch?	2.0	2.3	2.5	1.9	2.2
6	Trouble sleeping due to the patch?	1.2	1.8	1.6	1.6	1.6
7	Was the patch in the way?	2.7	2.3	2.6	1.6	2.3
8	Do you experience skin irritability?	1.4	2.3	3.4	2.3	2.4
9	Did the patch stay in place?	7.8	8.3	7.7	8.8	8.1
10	Any restrictions in daily activities due to patch?	1.1	1.3	1.4	1.3	1.3
11	Do you have the sense of being watched due to the patch?	2.1	1.9	1.9	2.1	2.0

Q1 and Q3-Q11 Mean per question is given; scale 1-10; *Q2: cumulative yes = 1, no = 0.

A total of 2 nurses accessed AccelerateIQ™ through a standard Web browser that displayed a patient dashboard. Within the dashboard, the nurses had access to data and analytics to determine if there were any abnormal reactions or potentially dangerous AEs associated with the treatment. The nurses also generally assessed the accuracy of monitoring but did not treat subjects based on portal data.

Outcome Measures and Data Collection

To understand the acceptability of use of the AccelerateIQ™ plus VitalPatch® system by patients and health care professionals, we assessed wearability and usability. Wearability was measured by a questionnaire, completed by patients at baseline, day 1, day 5, and day 8. The questionnaire was in the participant's native language of Dutch. Questions focused on the patient's evaluation of their experiences with the VitalPatch®. They completed 11 questions by indicating on a Likert-type scale (except for question 2, which was binary [0/1]) whether they agreed (10) or disagreed (1) with the statement. There was one yes/no question.

Participating nurses completed a survey at the end of the study, evaluating their experience with the VitalPatch® as a health care professional. The survey consisted of 3 questions with a Likert-type scale and 3 open-ended questions. Both questionnaires were developed by the investigator and underwent face validity. Safety outcomes were also assessed by tracking AEs related to wearing the biosensor.

Statistical Analysis

No sample size calculation was performed as this was an exploratory study. However, data were reviewed for trends. Descriptive statistics were used and means compared. AEs were analyzed by describing timing and extent of skin reaction.

Results

Inclusion

From February to October 2018, 12 patients were enrolled in the study. Participants included 4 patients receiving red blood cell transfusions, 4 receiving proteasome inhibitors, and 4 receiving IV immunotherapy. These patients were receiving treatment for various diseases, including multiple myeloma, myelodysplastic syndrome, and non-Hodgkin lymphoma. A total of 83% (10/12) of the patients were aged 60 years and older, 83% (10/12) were male, and 92% (11/12) were non-Hispanic white (see Table 1). During the study, no abnormal reactions or AEs to transfusions and infusions occurred.

Wearability

Wearability was measured through patients completing an 11-question survey (see Table 2 and Multimedia Appendix 1). No difference in patient-reported outcomes (PROs) was observed when either the nurses or the patients applied the patch. Patients considered wearing the patch pleasant (mean 6.7/10), and the patch remained in place (mean 8.1/10). Patients reported little discomfort (mean 2.2/10) and little trouble with sleeping because of the patch (1.6/10). Patients did not feel the patch was in the way (mean 2.3/10) and did not experience restrictions in daily activities because of wearing the patch (mean 1.3/10).

Patients' reports of skin irritation did demonstrate a change over the patch-wearing period (mean of question 8 at baseline: 1.4; day 1: 2.3; day 5: 3.4). In fact, 3 patients withdrew from the study because of skin irritation. One of these dropouts had a case of relatively severe dermatitis with impacted skin integrity, the other 2 had mild discomfort with minor erythema. The mean of question 8 at day 8, however, normalized to 2.3. The dropout because of skin irritation caused a lower completion of PROs at day 8, biasing results. When withdrawals are excluded, the mean of question 8 at day 5 is comparable with that of day 8. This was also the case for prominent differences at question 3, question 5, question 7, and question 9 (corrected mean for withdrawal at

day 5: 2.0, 1.7, 2.5, and 9, respectively). In addition to the questionnaire, connectivity issues between the patch and the phone were reported by 2 patients as bothersome (17%, 2/12). For one of the patients, this led to withdrawal from the study.

Usability

Usability was measured by a survey completed by 2 research nurses. Placement of the patch was reported to be easy (9/10). Initially, connecting the patch to the phone was at times troublesome but not insurmountable. The ability to monitor patients' vitals in this study was considered moderately pleasant (6.5/10). Research nurses considered data measured by the VitalPatch® to be reliable (8/10).

A total of 4 patients (33%, 4/12) voluntarily withdrew from the study (3 because of skin irritation and 1 because of Bluetooth connection issues). Withdrawals because of skin issues were all reported when wearing the second patch. Withdrawals were evenly distributed over all 3 groups. Neither age, disease, therapy, nor other demographic factors showed a trend with withdrawal or skin irritation.

Discussion

Principal Findings

This feasibility study focused on the wearability and usability of the VitalPatch® in the outpatient setting in patients receiving transfusions or infusions. We quantified the user experience among 12 patients wearing the patch for 12 days. Apart from skin irritation related to the patch in 3 patients, there was positive feedback on comfort and usability of the patch, and emphasis on limited restrictions in daily activities because of the patch. Nurses reported ease of use and comfort with relying on data measured by the VitalPatch®.

The dropout rate was high compared with earlier work by Selvaraj[14], where out of 70 patients wearing the HealthPatch for 50 days, 6 patients withdrew. Selvaraj also revealed skin irritation issues but also found the need to shave chest hair, personal lifestyle choices, frequent travels, and compensation as reasons for withdrawing from the study.[14] The main reason for dropout in our study was skin irritation. Potentially because our study group patients mainly consisted of patients with hematological malignancies, they were burdened so heavily by their disease and treatment that even relatively small inconveniences were enough to withdraw. Another explanation could be that patients needed more guidance in the first week of wearing the patch. Patients who wore the patch for the whole duration of the study, and thus had gained experience with it, reported little to no inconveniences. Small inconveniences, while missing guidance and experience with the patch, could discourage a patient enough to contribute to discontinuation of use.

Commercial use of the VitalPatch® has revealed skin irritation in some subjects, which prompted physIQ's internal review of the VitalPatch® and its relationship to skin irritation. It was discovered that the number of skin irritation reports increased (while statistically nonsignificant) after the introduction of Cavilon as a skin barrier. Therefore, Cavilon use has since ceased to be part of the patch placement instructions. Nonetheless, Cavilon use in this study might explain the dermal issues. Furthermore, we found no correlation in demographics, treatment, or other known parameters with skin irritation. Taking into account that the HealthPatch used in Selvaraj's trial[14] is a precursor of the VitalPatch®, it is more plausible that the high dropout rate found in our study is simply caused by chance and the small sample size and not because of the product itself.

Strengths and Limitations

Sample size is a limitation of this study. Owing to the exploratory nature of the study, no sample size calculations and no inferential statistical analyses have been applied. Another restriction is that dropouts did not complete the PRO survey at day 8. When comparing the mean values of the PRO survey at day 5 and day 8, it appears time improved patients' experience with the VitalPatch®: PRO data at day 8 were clearly more favorable than those of day 5. However, when corrected for the withdrawals, the PRO means at day 5 and 8 remained the same. Thus, no changes in comfort and skin irritation were observed from day 5 onward. Furthermore, the fact that our cohort was predominantly comprised of older white men reduces its generalizability and is a limitation of this study.

Comparison to Previous Studies

Overall, comfort, wearability, and usability were comparable with the outcome of Selvaraj's trial, who also described encouraging feedback on patch-type biosensors for continuous home use.[14] Chan et al[15] looked into the accuracy and usability of measurements of the HealthPatch. These appear to be of comparable accuracy with those made by traditional, larger medical devices. They conclude their article noting that it is important that such a device must be easy to use if it is to be widely adopted. Our data demonstrated ease of use for patients and nurses alike.

Future Perspective

Besides aiding future studies, the VitalPatch® has great potential for in- and outpatient health care. For instance, patients undergoing intensive treatment, such as those receiving an autologous stem cell transplantation, might benefit from continuous monitoring through quick registration and management of adverse events. Finally, in time, when enough experience with the VitalPatch® has been gained, it may reduce nurses' workload by replacing frequent vital sign monitoring.

Conclusion

Among a variety of wearables[16], this report shows the VitalPatch® to be an attractive device because of its wearability and low impact on daily activities in patients, therefore making it suitable for implementation in future studies.

Acknowledgments

MS and KL conceived the study design. OE and MS performed the research. RT analyzed the data. RT and KL wrote the first draft. MS supervised the research. All authors reviewed the manuscript.

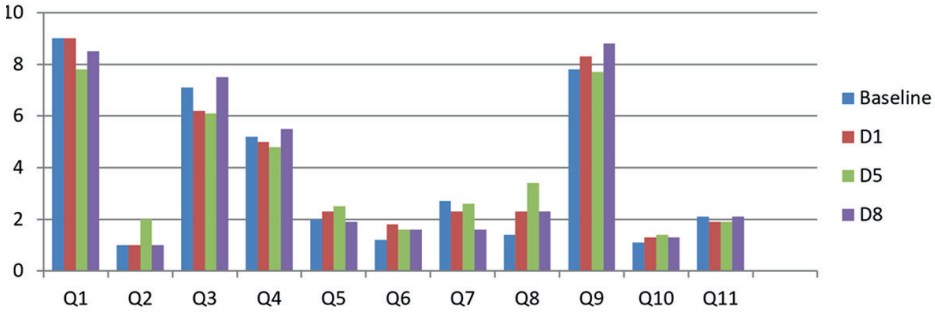
Funding information

This research was fully funded by Janssen Pharmaceuticals.

Conflicts of Interest

KL is an employee of physIQ, Inc.

Supplementary figure



Suppl. fig. 1. Means of responses. Patients responded by indicating on a Likert-type scale whether they agreed (10) or disagreed (1) with the questions (presented in Table 2). A change in skin irritability (Q8) over time is visible.

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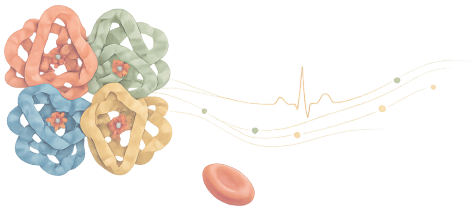

REMOTE MONITORING OF VITAL AND ACTIVITY PARAMETERS IN CHRONIC TRANSFUSION-DEPENDENT PATIENTS: A FEASIBILITY PILOT USING WEARABLE BIOSENSORS

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Abstract

Background

Little is known if, and to what extent, outpatient red blood cell (RBC) transfusions benefit chronic transfusion-dependent patients. Costs, labour, and potential side effects of RBC transfusions cause a restrictive transfusion strategy to be the standard of care. However, effects on the actual performance and quality of life of patients who require RBCs on a regular basis are hardly studied. The aim of this study was to assess if new technologies and techniques like wearable biosensor devices and web-based testing can be used to measure physiological changes, functional activity, and hence eventually better assess quality of life in a cohort of transfusion-dependent patients.

Methods

We monitored 5 patients who regularly receive transfusions during one transfusion cycle with the AccelerateIQ™ biosensor platform, the Withings Steel HR, and web-based cognitive and quality of life testing.

Results

Data collection by the deployed devices was shown to be feasible; the AccelerateIQ™ platform rendered data of which 97.8% was of high quality and usable; of the data the Withings Steel HR rendered, 98.9% was of high quality and usable. Furthermore, heart rate decreased and cognition improved significantly following RBC transfusions. Activity and quality of life measures did not show transfusion-induced changes.

Conclusion

In a 5-patient cohort of transfusion-dependent patients, we found that the AccelerateIQ™, Withings Steel HR, and CANTAB platforms enable acquisition of high-quality data. The collected data suggest that RBC transfusions significantly and reversibly decrease heart rate and increase sustained attention in this cohort. This feasibility study justifies larger validation trials to confirm that these wearables can indeed help to determine personalized RBC transfusion strategies and thus optimization of each patient's quality of life.

Introduction

Only few completed trials in the outpatient setting for transfusion-dependent patients have been conducted,[1,2] and there is little data in general about the value of outpatient transfusions.[3-7] Adverse events of red blood cell (RBC) transfusions, like transfusion reactions,[8-10] iron overload,[11-13] and poor clinical outcomes in studies with liberal transfusion thresholds in patients with acute anaemia[14-17] are reasons for a default restrictive transfusion strategy. Without objective parameters to measure the benefits of RBC transfusions, a restrictive transfusion strategy might not be the optimal choice for deeply anaemic patients that require RBC transfusions on a regular basis.

The current standard of transfusion care in these patients typically involves 1–3 units administered every 2–4 weeks and is based on a combination of haemoglobin concentrations and a subjective interpretation of clinical symptoms of anaemia. Validated measurements of quality of life and performance measures, however, might be more clinically relevant. More elaborated upon, thresholds for timing of transfusion could be the patient's vital signs and functional activity. Although such data can nowadays be obtained by wearable telemetric tools, systematic assessment of such tools and their data have not yet been performed. Moreover, this is a prerequisite for eventual randomized trials examining the impact of RBC transfusion on such outcomes in transfusion-dependent patients. Because haemoglobin concentration and VO2max are correlated,[18] the increased oxygen transport capacity following RBC transfusion may result in a reduced cardiac output, with, hence, a reduced heart rate. This may subsequently lead to an increase in quality of life (QoL) and activity parameters. Furthermore, since correlations between altitude and cognition, through altitude-induced hypoxia, have been established,[19-21] patients with chronic anaemia might endure similar hypoxia-induced cognitive changes.

The aim of this study was therefore to understand if new technologies and techniques like wearable biosensor devices and web-based testing can be used to measure physiological changes and functional activity in a pilot cohort of transfusion-dependent patients. To evaluate this, we hypothesized that patients' heart rates should decrease significantly after a single RBC transfusion, while returning to baseline before the subsequent transfusion. Furthermore, we tested whether the haemoglobin changes inherent to intermittent RBC transfusion also measurably modulate cognition, activity, and patient-reported QoL. Eventually, objective outcomes like a decrease in activity and vital sign changes due to chronic anaemia and the reverse after RBC transfusion may help inform guidelines on who, when, and how to transfuse as restrictively as possible without compromising QoL.

Table 1. Patient baseline characteristics.

		R001	R002	R003	R004	R005
Age (years)		70-79	70-79	70-79	20-29	70-79
Haematological disorder		MDS	MDS	MDS	Thalassemia	MDS
Uses a β-Blocker		No	Yes	No	No	No
RBCs per transfusion episode		2	2	1	1	2
Pre-transfusion haemoglobin	*V1*	9.0 g/dL	8.7 g/dL	8.7 g/dL	8.7 g/dL	10.0 g/dL
at	*V4*	7.7 g/dL	9.2 g/dL	8.7 g/dL	8.4 g/dL	10.0 g/dL
Sex		Female	Male	Male	Female	Male
Transfusion Interval		3 weeks	2 weeks	2 weeks	5 weeks	3 weeks

Methods

Study Design

The present study was a single-centre, observational, within-subject design, feasibility pilot study performed by the Haga Teaching Hospital. The study aimed to assess the feasibility of extracting and analysing data in a larger cohort and explore RBC transfusion-induced changes in vital sign, activity, cognitive, and QoL parameters. The study population was comprised of 5 patients with chronic dependence on RBC transfusion (at least one transfusion every 8 weeks) due to a haematological disorder. Patients with severe pulmonary comorbidities, arrhythmias, or other significant conductivity disorders, or with known skin conditions that might compromise the device's quality of data were excluded. Patients were their own controls as data before and after RBC transfusion were compared. Recruitment was between November 2019 and April 2020 by patients' own physician. The follow-up lasted until May 2020. Most of the data were collected remotely with the patients being at home.

Intervention

Patients received RBC transfusions according to their own usual transfusion regimen. This varied between 1 and 2 units every 2–5 weeks (Table 1). Conforming to the Dutch blood transfusion guidelines, transfusion-dependent myelodysplastic syndrome and thalassemia patients receive Rh and Kell compatible RBCs to prevent the formation of allo-antibodies.



Figure 1. The VitalPatch®, a single-lead, wet-electrode device that collects electrocardiogram and triaxial accelerometry data, used for the AccelerateIQ™ platform.



Figure 2. The Withings Steel HR watch. This device uses photoplethysmography to semi-continuously monitor heart rate and has a triaxial accelerometer for activity data.

Data Collection and Outcome Measures

Patients were monitored 7 days before the target RBC transfusion and up to the subsequent transfusion. Two wearable device platforms were used simultaneously to evaluate the usability of collected data: 1. The physIQ AccelerateIQ™ platform and 2. The Withings Steel HR watch. AccelerateIQ™ leverages the VitalPatch® (Fig. 1), a single-lead, wet-electrode device that collects electrocardiogram and triaxial accelerometry data to extract various physiological metrics such as heart rate, RR-interval, heart rate variability, respiratory rate, and activity measures (including but not limited to steps, bouts, gait). The Withings Steel HR watch (Fig. 2) uses photoplethysmography to semi-continuously monitor heart rate and a triaxial accelerometer for activity measures; every 10 min, the HR measures the heart rate for ± 30 s and summarizes this into a mean heart rate. The heart rate as measured by the Withings steel HR is divided into a sleeping and awake heart rate by default. The wearables' data are sent via Bluetooth to a mobile phone, which uploads the data over mobile data networks to either the Withings data cloud or the physIQ AccelerateIQ™ cloud platform.

The primary outcome of this pilot is the feasibility of capturing physiological data with wearable biosensors. Feasibility was established if the deployed devices captured high quality and usable physiological data >80% of the time in at least 4/5 of the included patients. Secondary outcomes are differences in heart rate, activity, cognition, and QoL before and after RBC transfusion. To assess the effect of RBC transfusion on cognitive and QoL parameters, the Rapid Visual Processing (RVP) task (CANTAB, Cambridge, online suppl. material 4; see www.karger.com/doi/10.1159/000526438 for all online suppl. material) and QoL questionnaires (QUALMS and PROMIS) were used. We selected the robust, validated RVP task to assess the cognitive domain of sustained attention as this has been shown to be impaired at high altitude.[20] The

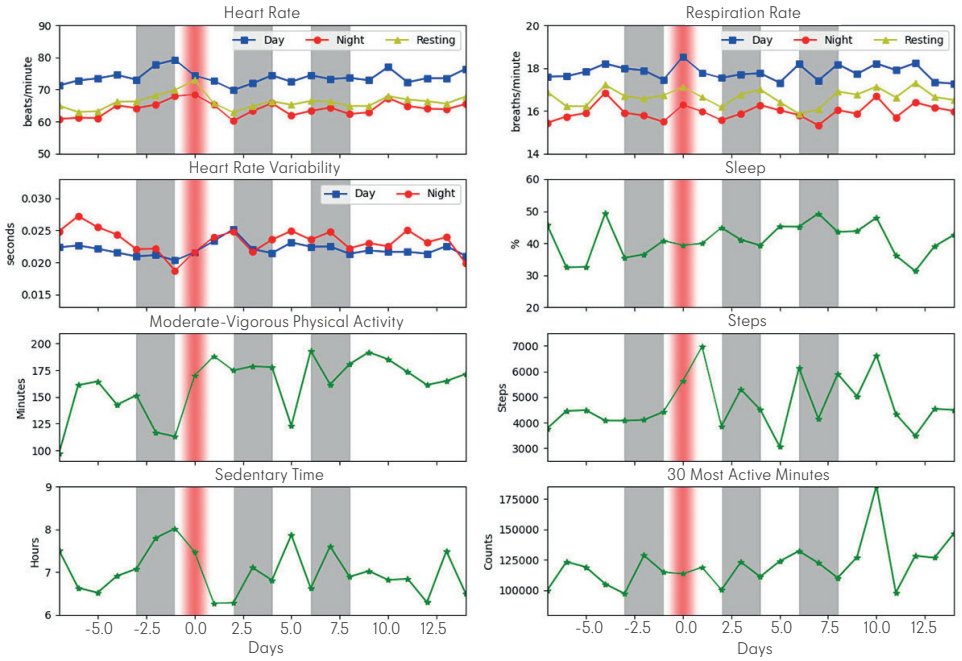

Figure 3. Population changes of various aggregated values from AccelerateIQ™ before and after transfusion. The graph shows data only until day 14 because 2/5 patients received another transfusion at day 15. Data summarized as V1, V2, and V3 are shown as grey areas; V4 is defined as the last 3 days before the next transfusion, which varies among patients, and can thus not be shown in this graph. Transfusion day results, indicated with the red zone, should be interpreted differently because of their clear aberrance with normal at home days (outcomes per individual in supplementary material 1).

QUALMS (Quality of Life in Myelodysplasia Scale) was created and validated to measure quality of life in myelodysplastic syndrome patients specifically.[22]

PhysIQ operates within the US standards for the privacy of health information and regulations for electronic records and signatures, pursuant to the Health Insurance Portability and Accountability Act of 1996 and the Code of Federal Regulations, respectively. Handling of the Withings data is in line with the European General Data Protection Regulation.

Statistical Analysis

Continuous data were summarized as medians per day with interquartile range (IQR) and categorical data as frequencies and percentages. A linear mixed model with random intercept analysis was performed to assess for inference and correct for predefined confounders: age, sex, activity (steps/24 hr), use of β-blocker, and cumulative number of RBCs received per transfusion episode. Data were reviewed for usability in further trials. We used linear interpolation for missing data.

Table 2. Outcomes per 3 days from AccelerateIQ™, Withings, CANTAB, and HRQoL questionnaires.

Feature	Visit 1		Visit 2		Visit 3		Visit 4	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
AccelerateIQ™								
Day heart rate (bpm)	77.5	9.9	74.9*	8.2	77.0	10.4	73.6	15.2
Night heart rate (bpm)	64.0	10.5	61.2	9.4	62.1	9.5	67.5	8.0
Resting heart rate (bpm)	67.9	9.3	66.7*#	9.9	65.5#	7.8	67.2	7.2
Day respiratory rate (rpm)	17.7	3.0	16.9	2.7	17.1	4.2	18.5	2.8
Night respiratory rate (rpm)	16.2	3.2	15.1	3.5	14.5	3.9	19.1	2.7
Resting respiratory rate (rpm)	16.8	2.1	15.8	2.8	15.4	3.7	18.9	1.8
Day heart rate variability (s)	0.019	0.005	0.019	0.008	0.021	0.005	0.016	0.008
Night heart rate variability (s)	0.018	0.010	0.021	0.009	0.019	0.018	0.011	0.009
Sleep Efficiency (%)	33.8	11.3	37.5	32.9	45.8	39.0	31.1	12.4
MVPA (min)	116.0	69.0	152.5	137.8	165.0*	96.0	182.0	130.0
Daily Steps (step count)	4513	2144	4751	1561	4852	1851	4664	920
Sedentary Hours (hrs)	7.3	1.9	6.8	2.3	7.6	1.7	7.7	3.5
30 Most active minutes (counts)	67007	24603	76923#	21466	60543	66597	59106	7440
Withings								
Day heart rate (bpm)	77.0	9.0	73.0*#	6.0	76.7	11.4	76.3	9.0
Night heart rate (bpm)	66.0	10.5	63.5*#	11.0	66.0	10.5	68.0	7.0
Daily Steps (count)	1764	2239	1626	1329	2033	2306	1368	1487
CANTAB								
RVPA (score)	8660	74	8948*	191	9057*#	411	8682	267
QUALMS								
QUALMS (score)	61.4	16.1	66.7	12.9	69.7	4.5	68.2	12.1
PROMIS								
Physical (score)	40.8	19	41.8	17.4	42.4	14.8	45.9	12.8

* P<.05 compared to V1; # P<.05 compared to V4, leveraging mixed models; MVPA = Moderate to Vigorous Physical Activity; Sleep efficiency = percentage of time spent asleep when in bed; bpm = beats per minute; rpm = respiratory rate per minute; 30 Most active minutes (counts) = a metric for motion; sum of 30 most active minutes per day.

Four "visits" were defined for the analysis: with 2 days before RBC transfusion as visit 1 (V1); 3 days after RBC transfusion as V2; 1 week after RBC transfusion as V3; and 2 days before the subsequent RBC transfusion as V4. To avoid bias due to the natural variability in heart rate and steps, for analysis we used the heart rates and activity of the 3 days around the defined day of visit.

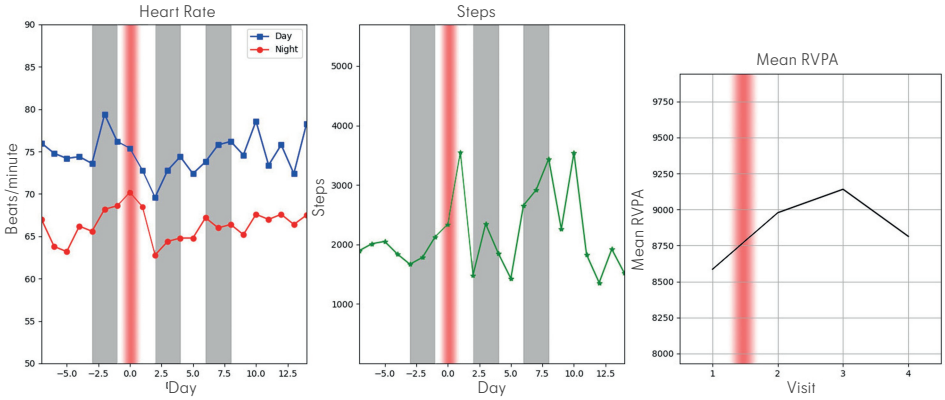

Figure 4. Population changes of mean heart rate per day/night (left), mean steps per day (middle right) as measured by the Withings Steel HR, and RVPA (right). The RVPA is the main outcome of sustained attention as measured by the CANTAB RVP. Transfusion day results, indicated with the red zone, should be interpreted with caution because of their clear aberrance with normal at home days (outcomes per individual in supplementary material 2 and 3).

Results

Baseline Data

Five chronic transfusion-dependent patients were included between December 2019 and April 2020 and completed follow-up. Four patients had myelodysplastic syndrome and one had β-thalassemia. RBC transfusion policies varied between one and two units every two to 5 weeks (Table 1). One patient did not complete the PROMIS-questionnaires.

VitalPatch® Findings

In a total of almost 132 captured subject days, 13,627,202 data points were collected. Each datapoint represents one RR-interval, and then beat-to-beat heart rate is calculated and windowed into 1-min averages. In total, there were 3,148 h of data, of which 97.8% was high quality, usable data as determined by applying an AI-based signal quality index (SQI) algorithm to the ECG waveform data. The low-quality data were sporadic and not confined to any single subject or time of day. Activity-based parameters were collected in a similar manner.

The heart rate across all subjects noticeably decreased following transfusions with, again, a steady increase in the days leading up to the next transfusion (Fig. 3; online suppl. Material 1). The mean difference in daily heart rate at V1 and V2 was −4.2 ± 0.6 bpm. For the heart rate at night, this was −2.1 ± 1.3 bpm. From V2 to V3, the daily heart rate increased by 2.3 ± 0.6 bpm. Activity levels, as measured by steps, lacked a consistent trend across the study period (Table 2).

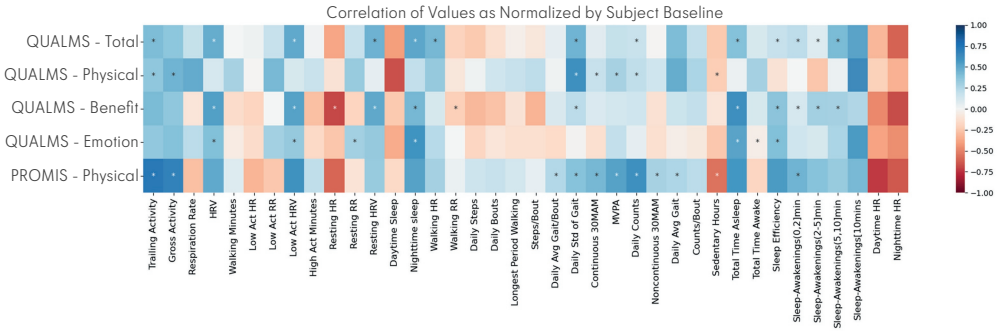

Figure 5. Heatmap of Spearman correlation coefficients when comparing questionnaire responses to physiological features, as compared to a subject's baseline. Significant positive correlations are mostly activity-based, indicating that a patient is more likely to score higher on HRQoL questionnaires when he/she is more active (significant correlations are indicated by * in the cells above).

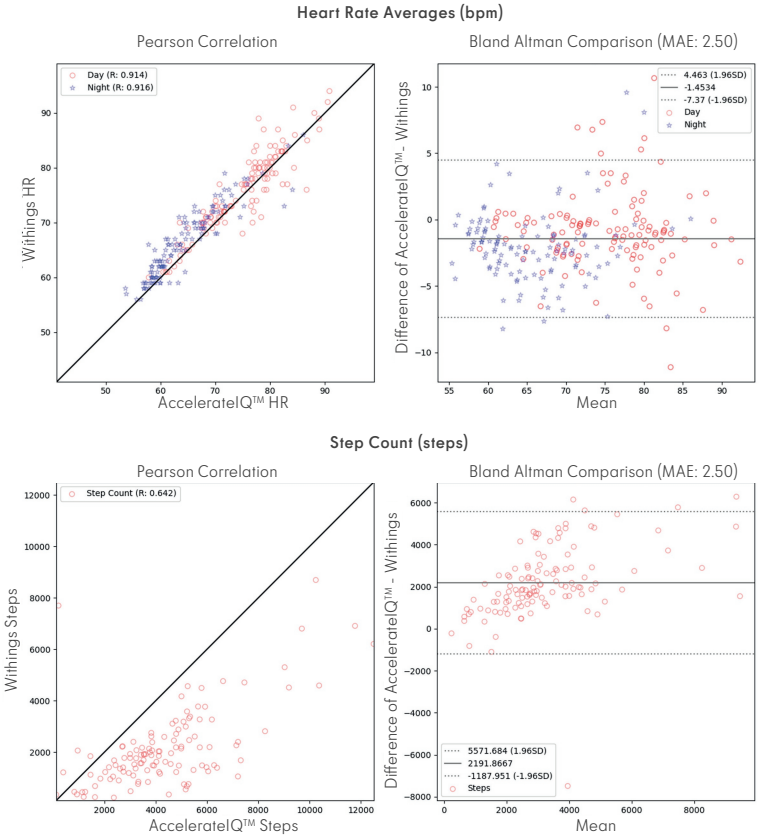

Figure 6. Correlation plot and Bland-Altman analyses for comparing daily heart rate (n = 238 samples; upper graphs) and step counts (n = 120; lower graphs).

Withings Steel HR Findings

In a total of 137 captured subject days, 33,181 data points were collected. Each datapoint is generated by calculating a heart rate for at least 30 s, once every 10 min. One day (0.7%) and two nights (1.5%) of heart rate data were insufficient to be included in the analysis. Data were assumed to be sufficient when the heart rate was captured more than 80% of the time. Activity data were collected continuously and summarized as steps per day.

A decrease in heart rate was observed 3 days after RBC transfusion (V2) compared to V1 (Table 2; Fig. 4). The mean difference in daily heart rates between V1 and V2 was −4.2 ± 0.5 bpm ($p = 0.016$). At night, the mean difference was −3.4 ± 0.7 bpm ($p = 0.023$). At V3, the daily heart rate was still lower than before transfusion but had increased compared to V2 (V3-V1: −1.1 ± 1.0 bpm, $p = 0.007$). The heart rate at V4 approximated that of V1. Comparing the patient's activity as the number of steps at the visits, an increase in activity is found after a week (V1: 1,860 ± 536 steps; V3: 3,004 ± 981). This is not significant, though ($p = 0.07$) and is visually not supported by Figure 4.

CANTAB Cognitive Evaluation

There was no missingness in our CANTAB data. All patients completed their cognitive tests on the appointed days of visit.

As depicted in Figure 4, patients appear to benefit cognitively from the transfusion. Compared to V1, the mean RVPA at V2 and V3 increased significantly ($p = 0.005$ and 0.003, resp., Table 2.)

QoL Questionnaires

QoL questionnaires were completed intermittently according to a weekly schedule apart from the visits. We were able to pair a completed QUALMS with each visit for each patient. One patient, unfortunately, did not complete the PROMIS-questionnaires and was omitted from the analysis. There were no significant changes over the study period for any of the derived features from the PROMIS or the QUALMS questionnaires, suggesting that subjective responses do not clearly reflect the detected objective physiological changes following RBC transfusion.

To further investigate how the physiological features are related to subjective quality of life metrics, spearman correlations were leveraged. We compared the change in physiological features to the change in questionnaire metrics at each visit from baseline. Changes in activity levels were identified as significantly correlated with changes in questionnaire responses more so than other physiological parameters (Fig. 5). The correlation coefficients were positive, indicating that subjects identified an increase in QoL when there was an increase in activity levels. Furthermore, though not significant, a negative correlation was found between questionnaire metrics and

heart rates, suggesting that patients are more likely to report higher QoL scores when having a lower heart rate.

VitalPatch®-Withings Comparison

Both AccelerateIQ™ and Withings produce a night-time resting and daily heart rate. To quantify similarities, Bland-Altman and Pearson correlation plots were leveraged. Overall, the mean absolute error is only 2.50 bpm (daily 2.23, nightly 2.76 bpm) where the AccelerateIQ™ device tends to calculate a lower heart rate than Withings by more than 1 beat per minute (Fig. 6).

Discussion

Key Findings

The present pilot study clearly validates the further use of wearables and data processing for larger cohort trials focussing on vital signs, activity, and cognitive performance as functions of the chronic red cell transfusion regimen. Data collection was without structural or troubling complications. In our group of just 5 patients, we found significant RBC transfusion-induced differences in cognition and heart rate. Low activity heart rate was clearly associated with the timing of RBC transfusion: a drop of ±7.15 bpm ($p = 0.011$) after RBC transfusion, which thereafter slowly returned to baseline. On the other hand, both the VitalPatch® and the Withings watch did not show transfusion-induced changes in activity data. While the absence of intraindividual changes is not illogical for the short observation period, activity parameters may be usable for stratification and confounding purposes. With regard to cognitive performance, the CANTAB RVP task showed a significant reversible increase in sustained attention after RBC transfusion. In contrast, QoL questionnaires did not show any direct correlation to the RBC transfusions.

Strengths and Limitations

As an explorative pilot, the small number of patients obviously limits the value of transfusion-induced effects, and more detailed investigation is needed. Furthermore, numerous confounders potentially influenced the heart rate activity, stress, fluid intake, etc. This makes the exact effect of RBC transfusion on heart rate dynamics uncertain, as illustrated by the day-to-day variability in heart rate in Figures 3 and 4. A larger group of patients followed over more transfusion episodes should even out the influence of extremes in and between single patients. On the other hand, the use of a within-subject design also limits bias: fixed characteristics, both measured and unmeasured, cancel out by using patients as their own controls.

Although the Withings' Steel HR is not medically validated for measuring continuous heart rates, we chose to use this smartwatch together with the VitalPatch®, to see if a photoplethysmography-based device could yield the same insight as an ECG-based

biosensor. The Withings Steel HR heart rate data correlate well with the VitalPatch's data. Step count data, on the other hand, do not correlate well at all. It is not known if the Withings Steel HR step count algorithm has been validated against a ground truth reference. However, the AccelerateIQ™ algorithm has been validated against reference data.

Interpretation

In terms of our primary objective, capturing usable data with these devices is certainly feasible. In view of the relevance of our data, the heart rate–although heavily confounded–showed a clear association with the RBC transfusions, as did sustained attention. These data support the logical assumption that an increase in haemoglobin concentration–and therewith oxygen transport capacity–by a RBC transfusion reduces the need for cardiopulmonary compensation, and thus results in a reduced heart rate. Likewise, the increase in oxygen transport capacity appears to have a beneficial effect on the patient's sustained attention. The fact that the haemoglobin concentration is only increased optimally once the excess plasma volume has been redistributed explains why we found the heart rate to be at its lowest 2–3 days post-transfusion. Significantly modulated in a group of 5 patients, heart rate and cognition seem very promising parameters to be further investigated in a larger group.

Being probably better associated with more structural and longer-standing changes in haemoglobin, neither quality of life nor activity parameters showed useful trends in our short follow-up study with only reversible haemoglobin improvement. It should, moreover, be noted that the present study was partly conducted during a COVID-19 lockdown, which undoubtedly decreased the patient's activity. Moreover, activity levels are heavily impacted by weather, lifestyle choices, and daily schedules, but also by the gradual building of fitness.

Zooming in on the usability of the data, the absolute value of steps data is uncertain, while also the AccelerateIQ™ and Withings data show large differences. These findings, consistent with current literature, can be attributed to differences in device location, walking speeds, and differences in algorithms.[23-25] Additionally, step counts are susceptible to high levels of noise and are challenging to ensure accurate counts. However, trends are comparable between devices. The absolute value of steps may be less important than the relative value, though, because we are interested in changes in activity, not the absolute number of steps. As there is no gold standard for step measurements to compare the devices to, it is difficult to confidently state which device–if any–is more accurate and able to detect meaningful change. It is important to realize, however, that we cannot compare data from different devices without a penalty.

Whether and how actigraphy can be used to measure substantial quality of life improvements remains an actual question.[26-28] A larger sample size and longer observation periods with structural improvement of anaemia should help to reduce confounding effects and improve the sensitivity for possible benefits of RBC transfusion modulation.

When choosing a device for remote monitoring, we advise to take into consideration the types of data streams that can be captured, device usability, data availability, and the data acquisition approach. In our study, we used accerateIQ™, which recorded a richer set of data types (respiratory rate, heart rate variability, and more) with higher granularity than the Steel HR. Capturing the high-fidelity multivariable data that AccelerateIQ™ provides enables deeper exploration of parameters and the relationship with therapies, but at the cost of additional patient guidance and regular charging of the device, not necessarily required for a consumer device like the Steel HR with a battery life of ± 28 days.

When comparing the heart rate as captured by AccelerateIQ™ to the Withings Steel HR, the outcome was similar. Small variations in the heart rate can be explained by differences in device location and algorithmic processing. In addition, neither device system yielded perfect subject compliance as occasional gaps of data were present– attributed to either the patients not wearing a device or struggling with connectivity issues. Depending on the objectives of the study, we found both devices to be usable for future studies.

Regarding generalizability, the present study focusses on patients with chronic anaemia due to a haematological disorder, which is a select group of patients that has been structurally excluded from previous studies. A well-designed larger study may yield generalizable results for this population.

In conclusion, in a 5-patient cohort of transfusion-dependent haematological patients we found that the AccelerateIQ™, Withings Steel HR and CANTAB platforms enable acquisition of high-quality data. The device platforms identified a significant and reversible decrease in heart rate and increase in sustained attention following RBC transfusions in this cohort. This feasibility study justifies larger validation trials to confirm that these wearables indeed can help to determine personalized RBC transfusion strategies and thus optimization of each patient's QoL.

Statement of Ethics

Ethical approval was granted by the Medical Ethics Committee Leiden-Den Haag-Delft, approval number: NL70534.098.19. The trial was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki 2013. Written informed consent was obtained from all participants before enrolment.

Conflict of Interest Statement

Mackenzie Tweardy and Stephan Wegerich are employees of physIQ, Inc. Rik Tonino, Martin Schipperus, and Jaap Jan Zwaginga have no conflicts to disclose.

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Author Contributions

Rik Tonino, Martin Schipperus, Jaap Jan Zwaginga, and Stephan Wegerich conceived the study design. The study was carried out by Rik Tonino. Rolf Brouwer contributed patient inclusions. Rik Tonino and Martin Schipperus verified the underlying data and ran the statistical tests. All the authors participated in the interpretation of the results. Rik Tonino and Mackenzie Tweardy wrote the first draft. All the authors reviewed the draft.

Data Availability Statement

Individual participant data that underlie the results reported in this article will be available after deidentification (text, tables, figures, and supplementary material) in our University's data warehouse but without investigator support other than deposited metadata. Other documents that will be available are the study plan and statistical analysis plan. Data will be available following publication, no end date. It will be shared with researchers who provide an approved methodologically sound proposal.

Supplementary material

The supplementary material for this article can be found online at:

https://ndownloader.figstatic.com/files/38020374

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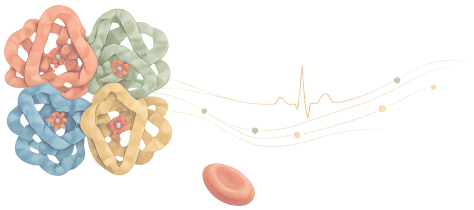

HEART RATE CHANGES AFTER PHLEBOTOMY IN POLYCYTHAEMIA VERA AND HEALTHY DONORS, AN OBSERVATIONAL CASE-CROSSOVER PILOT STUDY

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Abstract

Background

Haemoglobin plays a crucial role in oxygen transport, and any acute deviation will trigger compensatory hemodynamic functions. While the consequences of anaemia are well-documented, the effects of haemoglobin reduction in individuals without anaemia remain less explored. Patients with polycythaemia vera and healthy blood donors, who both undergo regular phlebotomies, offer a valuable model for studying these effects.

Methods

This observational case-crossover study assessed short-term physiological and quality-of-life changes following phlebotomy in five patients with polycythaemia vera and six healthy blood donors. Participants were remotely monitored using a smartwatch and completed daily quality-of-life assessments. The primary outcome was heart rate, while secondary outcomes included step count and quality-of-life measures.

Results

Patients with polycythaemia vera exhibited stable heart rates, with only minor variations in physical activity and quality of life after phlebotomy. In contrast, healthy blood donors experienced a significant increase in heart rate, which returned to baseline within a week. Physical activity remained clinically unchanged in both groups, and quality-of-life scores were stable.

Conclusions

This pilot study demonstrates that any acute haemoglobin reduction even within the normal range induces measurable heart rate changes that are directly related to probably the most optimal oxygen delivery state. Moreover, our studies show that wearable technology is sensitive enough to detect these effects. Hence, this nowadays readily available telemetry allows monitoring subtle physiological changes in research setting but it also offers a path towards optimising QoL for patients with anaemia, polyglobulia and for blood donors.

Introduction

Low haemoglobin levels can lead to impaired oxygen delivery, and consecutively to fatigue, dyspnoea, lack of concentration and therewith a reduced quality of life.[1–3] Even in healthy blood donors, frequent donations cause an increase in symptoms like tiredness, dyspnoea and restless legs.[4] To combat these adverse outcomes in anaemic patients, RBC transfusions are used to improve functional outcomes in anaemic patients.[5–7] However, excessively high haemoglobin levels, such as in polycythaemia vera (PV), can cause hyperviscosity, potentially limiting oxygen transport.[8] Normal levels are maintained between 12.1–15.1 g/dL in females and 13.8–17.2 g/dL in males.

The relationship between haemoglobin mass and physiological effects, especially cardiorespiratory outcomes, remains insufficiently explored in non-anaemic populations.[9] In athletic contexts, strategies such as altitude training and the use of erythropoiesis-stimulating agents have been employed to enhance Hb mass and thereby increase maximal oxygen uptake.[10–12] Nonetheless, the optimal Hb concentration for maximizing physiological function remains unclear. Similarly, the appropriate target Hb level in anaemic patients has long been a subject of clinical debate. Investigating the relationship between Hb mass and physiological effects across different clinical settings and baseline Hb levels may provide valuable insights into the optimisation of haemoglobin.

Blood donors and patients with PV, who undergo regular therapeutic phlebotomies, present a valuable model for studying these effects. The regulated removal of 500 mL of blood allows for precise assessment of its impact on various physiological parameters without further interventions. In healthy donors, an average reduction in Hb of 8.8±1.9% has been observed post-donation.[13] Indeed, previous studies of healthy donors show changes in heart rate and VO_2max 24-48 hours post-phlebotomy,[9,14] whereas no comprehensive evaluations of physiological outcomes in PV patients undergoing phlebotomies have been documented.[15]

Given these observations, the aim of this exploratory study is twofold: firstly, to investigate the impact of haemoglobin mass reduction on heart rate, physical function and quality of life in patients with PV as well as healthy blood donors, and secondly to explore whether current wearable techniques are sensitive enough to detect these effects.

Methods

Study Design and recruitment

This observational case-crossover pilot study assessed the physiological and quality-of-life changes associated with phlebotomy in patients with PV and healthy donors in the Netherlands.

Patients with PV were identified by their treating physicians at the Leiden University Medical Centre and referred to the local investigator (author RT). Donors were recruited from Sanquin, the national not-for-profit organisation responsible for the collection and distribution of blood and plasma. Donors who were invited to participate in another study (FAINT [16]–a parallel study conducted by author EHitV, investigating predictors of vasovagal reactions to needles), were invited to also participate in the current study.

Eligibility criteria for both groups included adults aged 18 years or older. For PV patients, exclusion criteria included poor functional status (ECOG ≥3), the presence of arrhythmias or significant cardiac conduction disorders, a life expectancy of less than 3 months, and concurrent participation in other clinical trials likely to interfere with this study. Patients with secondary polycythaemia or patients who were scheduled for oncological treatments or surgeries during the study period were also excluded. This study adhered to the principles of the Declaration of Helsinki and complied with the General Data Protection Regulation.

Data Collection and Procedures

Following enrolment, participants were provided with a smartwatch by the local site investigator. They were instructed to wear the device continuously, beginning one week prior to the intervention and continuing until one week following the intervention. The seven-day period preceding each intervention was designated as the baseline monitoring phase. Continuous data collection resumed immediately post-intervention and continued for an additional seven days, constituting the follow-up period.

Data collection for PV patients was conducted over three phlebotomy sessions per participant. However, for the healthy donors, data collection was limited to a single blood donation session due to logistical constraints, as the FAINT study did not follow donors over repeated donations. All phlebotomies were conducted as part of standard care, with no alterations to clinical procedures. The questionnaires were sent on a daily basis to the private e-mail addresses of the participants through CASTOR EDC, an electronic data management platform.

Heart rate measurements

Continuous heart rate and step count monitoring was conducted using the Withings Steel HR smartwatch, a commercially available wearable device previously employed by the authors in both completed and ongoing clinical trials.[5] Biosensor data were transmitted through Withings' GDPR-compliant platform. Continuous data were processed to obtain daily median heart rates and total daily step counts. In addition, mean heart rates were calculated separately for nighttime and daytime periods to account for potential confounding effects of physical activity on daytime heart rate measurements.

Quality of life

Participants completed a daily quality-of-life assessment using the EQ-5D-5L questionnaire, which evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale, ranging from no problems to extreme problems, producing a 5-digit health state profile. These responses were converted into an EQ-5D-5L index score, adjusted for the Dutch population (range: -0.329 to 1.000). In addition, participants rated their overall health using the EQ visual analogue scale (VAS; range: 0-100%), a self-reported measure ranging from 'the best health you can imagine' to 'the worst health you can imagine'. To adjust for possible activity-related confounding in heart rate outcomes, we also asked our participants to complete an activity VAS (0-100%) ranging from 'the least active you can imagine' to 'the most active you can imagine'.

Haemoglobin levels

Haemoglobin levels were measured prior to each intervention as part of routine clinical assessments for both PV patients and healthy donors via venipuncture and fingerprick measurement, respectively.

Demographic information and confounders

Additional demographic data, β-blocker usage and adverse reactions were collected for confounding and baseline characterization.

Statistical Analysis

The sample size calculation indicated a requirement of 9 participants per group; however, due to logistical constraints of this low-budget study, this pilot study included 5 PV patients and 6 healthy donors.

To minimize variability, each participant acted as their own control due to the case-crossover design, repeated measures across three phlebotomy sessions further strengthened the analysis. To mitigate potential bias from natural variability, as well as the effects of a particular day which may not be reflective of daily life (e.g. a visit to

a theme park), heart rate and activity data were summarized per 3 days for analysis. The day of phlebotomy was excluded from analysis, as the procedure induces acute volume depletion and puncture-related stress, both of which are known to transiently affect heart rate through mechanisms unrelated to the physiological effects under investigation.

Primary and secondary endpoints were analyzed using linear mixed models with random intercepts to account for repeated measures. Statistical significance was set at $p < .05$. A linear mixed-effects model with random intercepts for participants was used to assess the effect of phlebotomy on median heart rate, with fixed effects for time (baseline vs. 1-3 days and 4-7 days post-phlebotomy), sex, and β-blocker usage. Days –1 to –3 were used as baseline, days <–3 were used as a control period.

Results

A total of 55 patients scheduled for phlebotomy were screened, of whom 42 were excluded due to indications other than PV, four did no longer need phlebotomies, two patients only incidentally required phlebotomies, and two patients declined participation. Of 444 healthy donors invited, 25 participated in the FAINT study; six of these also enrolled in this add-on study. Ultimately, eleven participants were enrolled, comprising five PV patients who were stable on regular phlebotomy (at least every four months) and six healthy donors. Inclusion started July 19th, 2022 and follow-up ended March 20th 2023. Baseline data are presented in table 1.

Data collection

Following excellent compliance, sufficient day- and nighttime data were collected throughout the observation period (day –7 to 7). On day –7, data acquisition was incomplete, with two daytime and one nighttime intervals lacking sufficient measurements due to delayed device initiation, preventing calculation of a valid mean heart rate. No further data loss or connectivity issues occurred.

Primary outcome: Heart Rate

As illustrated in Figure 1, healthy donors exhibited a significant increase in median heart rate during the immediate post-donation period (days 1–3), with an estimated change of $\beta = 4.9$ bpm (95% CI: 2.4 to 7.5; $p < .001$), followed by a return to near-baseline levels by days 4–7. Absolute heart rate values are presented in Table 2, and the results of the linear mixed model analysis are detailed in Table 3. This pattern was observed consistently in both daytime and nighttime heart rate measurements ($p = .008$ and

$p = .010$, respectively), with a more pronounced increase noted during daytime hours. In contrast, heart rate in patients with polycythaemia vera remained stable throughout the observation period, ranging from 63 to 65 bpm, with only minor variation between daytime and nighttime measurements (Figure 2).

Table 1. Baseline characteristics.

	Polycythaemia Vera (n = 5)	Healthy Donors (n = 6)
Age, median (range)	64 (48-72)	50 (34-56)
Female gender, n (%)	1 (20%)	6 (100%)
β-blocker use, n (%)	2 (40%)	1 (17%)
Phlebotomies, cumulative	13	6
Pre-phlebotomy haemoglobin level, median (range)	15.1 g/dL (13.2-17.9)	14.0 g/dL (13.1-14.8)

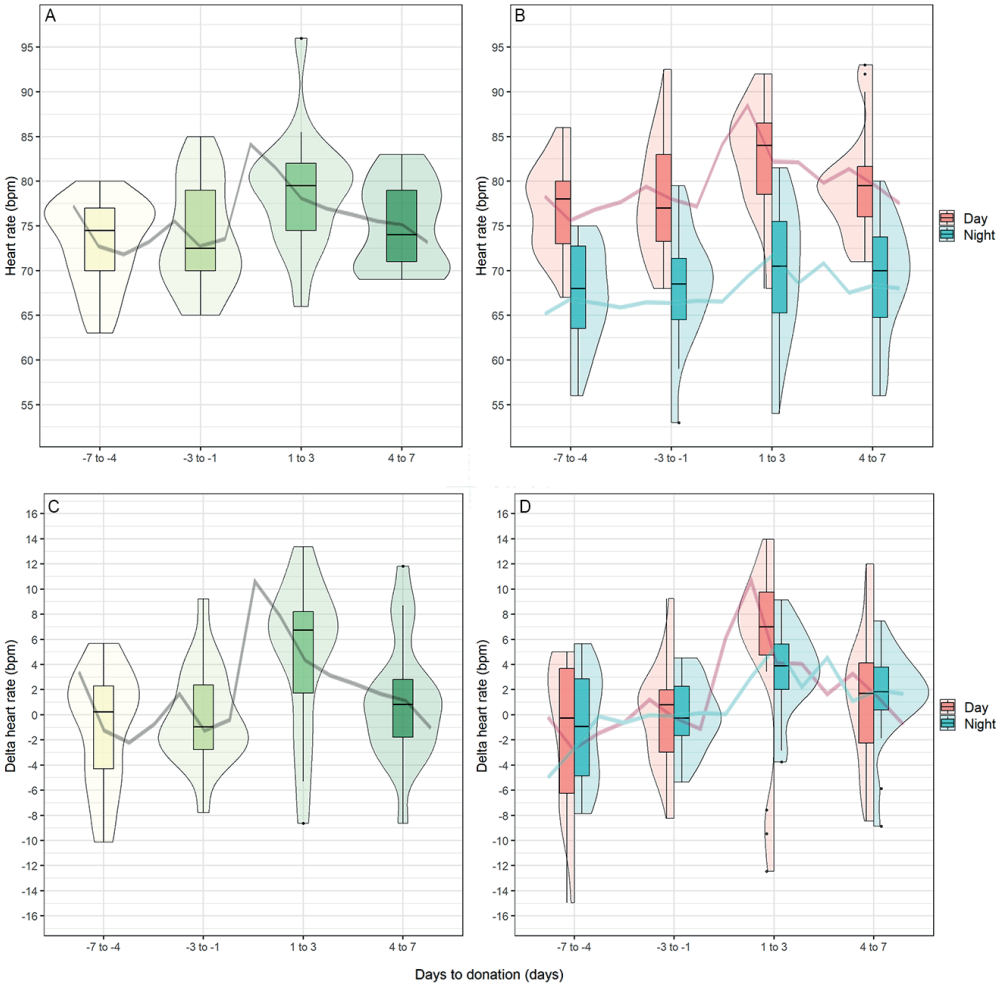

Figure 1. Donor heart rates: Violin- and boxplots summarizing the median heart rates per three days (A) and stratified for day (06:00-23:59) and night (00:00-05:59) (B) and Δheart rates (C and D). The line graphs correspond to the median heart rates per day. Day 0 was not included in the violin- and boxplots due to the direct phlebotomy-related confounding effects on heart rate.

Table 2. Outcomes.

Donor			Control *(D-7 – D-4)*	Baseline *(D-3 – D-1)*	Visit 1 *(D1 – D3)*	Visit 2 *(D4 – D7)*
	Heart rate (bpm, median)	*Total*	75 (70 - 77)	73 (70 - 79)	80 (75 - 82)	74 (71 - 79)
		Day	78 (73 - 80)	77 (73 - 83)	85 (78 - 88)	80 (76 - 82)
		Night	67 (61 - 73)	68 (62 - 71)	71 (65 - 76)	70 (64 - 74)
	Steps (amount/24hr)		6650 (2433 - 8327)	5394 (3521 - 8999)	6679 (4890 - 9450)	5612 (2991 - 9189)
	QoL (range: -0.33 to 1.00)	*EQ-5D-5L index score*	1.00 (0.87 - 1.00)	1.00 (0.87 - 1.00)	1.00 (0.87 - 1.00)	1.00 (1.00 - 1.00)
		VAS-QoL	0.9 (0.82 - 0.94)	0.92 (0.87 - 1.00)	0.84 (0.73 - 0.93)	0.91 (0.78 - 1.00)
		VAS-Activity	0.64 (0.59 - 0.8)	0.60 (0.51 - 0.70)	0.71 (0.61 - 0.82)	0.70 (0.61 - 0.84)
Polycythemia Vera						
	Heart rate (bpm, median)	*Total*	63 (62 - 67)	63 (63 - 65)	64 (63 - 66)	65 (64 - 67)
		Day	64 (63 - 69)	66 (63 - 69)	66 (63 - 69)	67 (66 - 69)
		Night	62 (60 - 64)	60 (56 - 63)	63 (61 - 65)	62 (58 - 64)
	Steps (amount/24hr)		4990 (3172 - 6569)	5319 (3800 - 6159)	3992 (2656 - 5396)	4472 (2897 - 5926)
	QoL (range: -0.33 to 1.00)	*EQ-5D-5L index score*	0.89 (0.88 - 1.00)	0.92 (0.88 - 1.00)	0.91 (0.88 - 1.00)	0.89 (0.85 - 1.00)
		VAS-QoL	0.70 (0.67 - 0.80)	0.72 (0.70 - 0.77)	0.72 (0.68 - 0.80)	0.71 (0.70 - 0.82)
		VAS-Activity	0.70 (0.61 - 0.71)	0.70 (0.65 - 0.75)	0.70 (0.62 - 0.80)	0.74 (0.70 - 0.79)

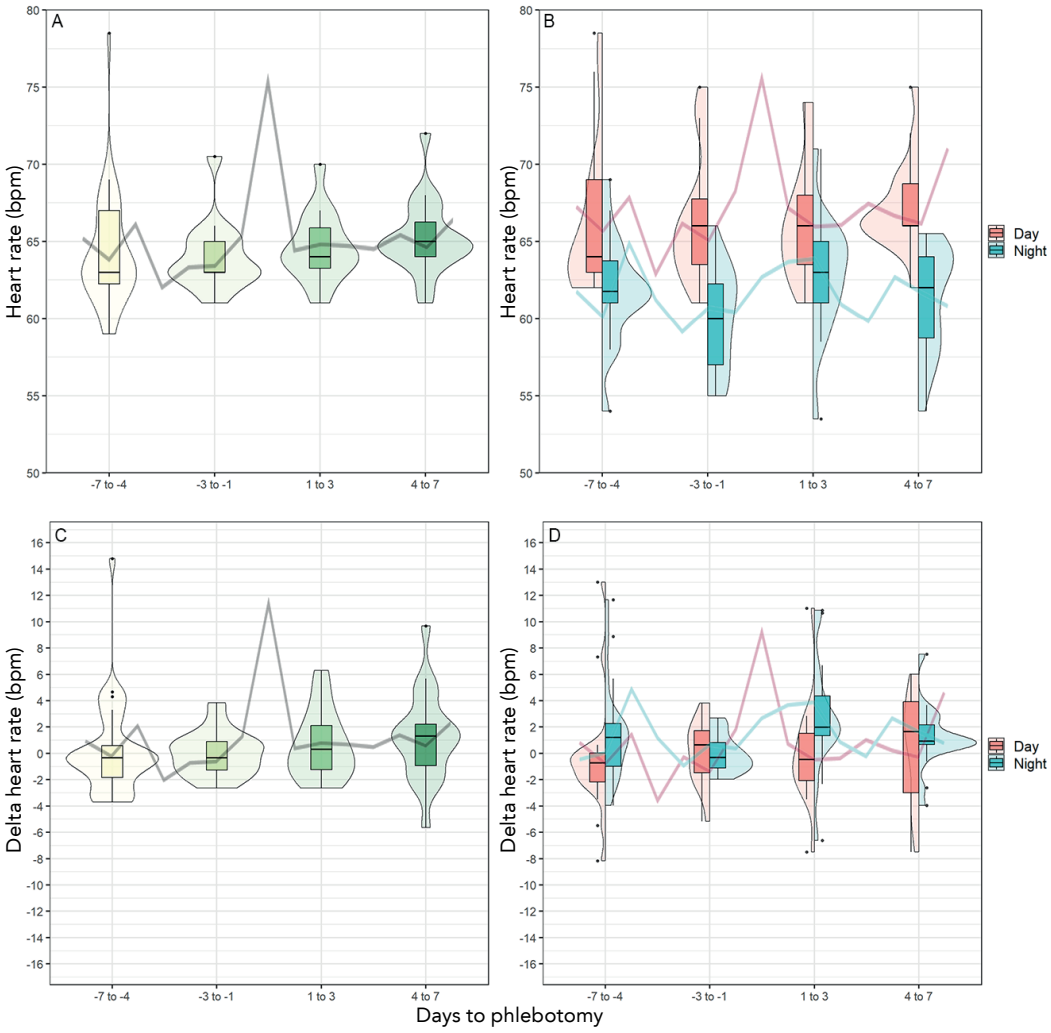

Figure 2. Phlebotomy heart rates: Violin- and boxplots summarizing the median heart rates per three days (A) and stratified for day (06:00-23:59) and night (00:00-05:59) (B) and Δheart rates (C and D). The line graphs correspond to the median heart rates per day. Day 0 was not included in the violin- and boxplots due to the direct phlebotomy-related confounding effects on heart rate.

Table 3. Linear mixed model outcomes for heart rate.

Donors						
Parameter	β	SE	95% CI	p-value	estimated means	marginal
Intercept	73.89	0.91	72.1 - 75.7	<.001		
Control	-0.86	1.28	- 3.4 - 1.7	.502	73.0	
Baseline	ref	ref	ref	ref	73.9	
Day 1 - 3	4.94	1.29	2.4 - 7.5	<.001	78.8	
Day 4 - 7	1.18	1.22	-1.2 - 3.6	.337	75.1	
Polycythemia Vera						
Parameter	β	SE	95% CI	p-value	estimated means	marginal
Intercept	63.63	0.563	62.5-64.7	<.001		
Control	0.23	0.655	-1.1 - 1.5	.725	64.1	
Baseline	ref	ref	ref	ref	64.3	
Day 1 - 3	0.63	0.692	-0.7 - 2	.362	64.7	
Day 4 - 7	1.23	0.647	-0.1 - 2.5	.061	65.3	
β-blocker	0.5	0.511	-0.5 - 1.5	.326		
Sex	0.35	0.624	-0.9 - 1.6	.573		

Baseline = days –3 to –1; control = days –7 to –4; Day 0 was excluded due to direct phlebotomy effects on heart rate like volume depletion and puncture induced stress; In the donor group, all participants were female and none were using β-blockers. Therefore, sex and β-blocker use were not included in the model.

Secondary outcomes: Physical activity and Quality of life

As depicted in Figure 3, step counts slightly, non-significantly, increased from baseline to day 1-3 before declining slightly to baseline at day 4-7 in healthy donors. PV patients showed an opposite trend, with step counts decreasing post-phlebotomy, followed by a partial recovery at day 4-7.

EQ-5D-5L index scores remained stable in healthy donors (1.00 across all periods), whereas PV patients had lower baseline QoL scores (0.70, IQR: 0.65–0.75) with slight improvement post-phlebotomy. VAS-based QoL ratings in donors declined from 0.92 to 0.84 post-phlebotomy but returned at day 4-7 (0.91). PV patients maintained stable VAS-QoL scores (0.89–0.92) across all periods. VAS-activity ratings in donors increased post-phlebotomy whereas they remained stable in PV patients.

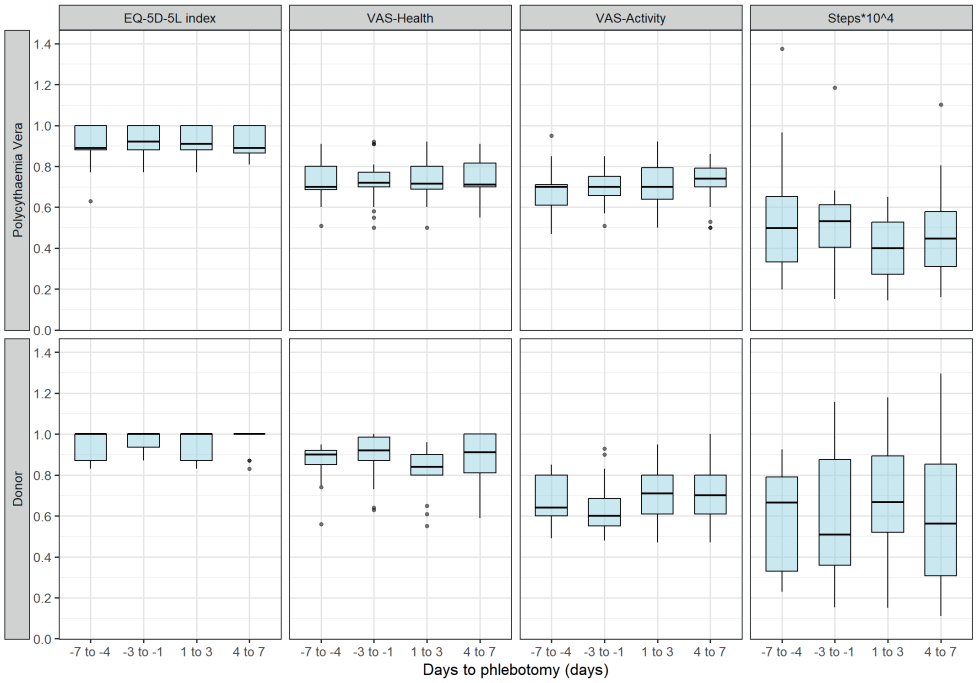

Figure 3. Boxplots summarizing secondary outcomes per three days.

Discussion

This study aimed to explore the short-term physiological and quality-of-life effects of phlebotomy in PV patients and healthy donors. However, due to resource constraints, recruitment was prematurely halted, resulting in a limited sample size of eleven participants. While this restricts the generalizability of findings, the data provide valuable insights into the short-term physiological effects of haemoglobin reduction. Notably, the outcomes demonstrated that the wearable technology used was sensitive enough to detect even small haemoglobin mass reductions within the normal range, highlighting its potential for larger scale future research and validation of changes in more patient specific treatments.

Our primary outcome, heart rate, demonstrated a transient physiological response to phlebotomy in both PV patients and healthy donors. However, a key distinction was observed between the two groups: while PV patients exhibited no sustained heart rate elevation post-phlebotomy, healthy donors experienced a prolonged increase lasting almost up to one week.

While the PV and donor groups cannot be compared due to the small sample size and baseline differences, the observed difference in heart rate response to phlebotomy is intriguing. We therefore present the following as an exploratory consideration: This difference in heart rate response might be explained by their respective baseline haemoglobin levels (table 1). Healthy donors–who had lower haemoglobin levels at baseline than PV patients–experienced a more pronounced and sustained increase in heart rate after phlebotomy. Another possible explanation is that donors experienced higher stress levels than PV patients seems less likely because the sustained increase in heart rate for nearly a week in blood donors is atypical for such a transient stress response.

The transient heart rate elevation observed on the day of phlebotomy in both groups is likely attributable to the acute volume depletion rather than haemoglobin reduction, as PV patients' heart rates returned to baseline within 24 hours–the plasma volume is typically completely replenished within 24-48 hours.[17] The sustained elevation in healthy donors interestingly suggests that even modest reductions in haemoglobin within the normal range can lead to measurable hemodynamic changes, especially so because this sustained elevation was not found in the PV group, potentially due to reduced oxygen-carrying capacity. This aligns with the timing of restoration of the Hb mass; the duration of complete restoration of Hb-mass has been documented to be between 20 to 59 days, although restoration starts in the first week.[13]

Phlebotomy in PV is primarily prophylactic, aimed at preventing hyperviscosity-related complications rather than alleviating symptoms. While it has been suggested that reducing hyperviscosity may lower cardiac workload and heart rate, this effect was not observed in our treated cohort, likely due to their minimal baseline symptom burden as they were stably treated. Hypothetically, in newly diagnosed PV patients - with higher baseline Hb masses - this effect might be measurable.

Consistent with this, quality-of-life assessments showed no clinically significant differences between groups or periods. A slight improvement in EQ-5D scores observed in PV patients during Period 4 may suggest a delayed symptomatic benefit of phlebotomy. However, given the small sample size, this finding should be interpreted with caution.

Similarly, step count measurements fluctuated across study periods, but the variability was substantial, making it unlikely that the observed differences reflect clinically meaningful changes in physical activity levels. These findings suggest that while phlebotomy effectively manages hematologic parameters in PV, its immediate impact on quality of life and physical activity remains limited.

Study Limitations and Future Directions

The primary limitation of this study is the small sample size, which restricts the ability to draw definitive conclusions. Furthermore, the lack of diversity with 6/6 donors being female restricts generalizability. Additionally, the absence of comparable studies makes it challenging to contextualize the findings. Furthermore, an adequate comparison between donors and PV patients would require comparable baseline characteristics. To better detect phlebotomy-induced correction of suboptimal oxygen delivery, PV patients with even more supraphysiological Hb and Ht values–e.g. those starting therapy and not in maintenance like ours–should be considered. Likewise, to investigate QoL and physical exercise changes as a function of suboptimal oxygen transport and the correction of the latter we do not necessarily need many more patients but certainly longer prospective observation periods starting with initiation of phlebotomy treatment. For the observed and reported changes in HR, however, with patients being their own control, it is not likely that higher sample sizes would alter our conclusions. Additionally, Hb measurements at predefined moments like day 3 and 7 could be helpful to correlate future studies.

Despite these limitations, our findings show that even minor haemoglobin reductions can elicit measurable physiological responses in healthy individuals, while stable and chronically treated PV patients may be less affected due to their higher baseline haemoglobin levels. These findings contribute to our understanding of haemoglobin mass changes across diverse clinical contexts. Notably, wearable technology proved sensitive enough to detect these effects. Hence, this nowadays readily available telemetry not only allows monitoring subtle physiological changes in research settings, but it also offers a path towards optimizing QoL for patients with anaemia, polyglobulia and for blood donors.

Conflict of interests

None of the authors have a conflict of interest to disclose.

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Author contributions

RT, MS, and JJZ conceived the study design. RT, JJZ and EHV participated in the inclusion of patients. The study was carried out by RT. RT, MS, and JJZ participated in the interpretation of the results. RT wrote the first draft. All authors reviewed the draft.

Data availability statement

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

Ethical approval statement

Ethical approval was granted by the medical ethics committee Leiden-Den Haag-Delft on 20-05-2022. Reference number: N22.055/HL/hl.

Patient consent statement

Informed consent from all participants was obtained.

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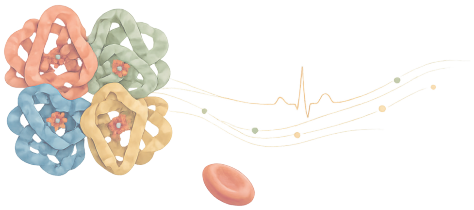

HEART RATE CHANGES IN CHRONICALLY RED CELL TRANSFUSION-DEPENDENT PATIENTS: A DOSE-DEPENDENT EFFECT OF RED CELL TRANSFUSION–A RANDOMIZED CROSSOVER TRIAL, INTERIM ANALYSIS

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Abstract

Background

Restrictive red blood cell transfusion strategies are widely recommended for acute anaemia but may not adequately address the needs of chronically anaemic patients with transfusion-dependent myelodysplastic syndromes or myeloproliferative neoplasms. For these patients with chronic anaemia, alleviating symptoms and improving quality of life are key objectives. This study evaluates the impact of additional 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, multicentre, within-subject, crossover trial evaluated twelve 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 haemoglobin augmentation was associated with significant reductions in heart rate, with the largest decrease in patients receiving the 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 haemoglobin is associated with lower heart rate, reflecting enhanced oxygen delivery. Wearable monitoring was sensitive to these changes. Non-significant, hypothesis-generating trends towards improved QoL, fatigue and cognition were observed.

Introduction

Restrictive red blood cell (RBC) transfusion strategies in haemato-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 as the default for patients with acute and reversible anaemia, 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 anaemic 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 anaemia-related symptoms.

Despite the well-documented impact of anaemia 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 haemoglobin concentrations may simply indicate a more advanced disease, with consequently poorer QoL scores independent of the anaemia. 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 anaemia-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 favourable 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-centred 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.

Study design and methods

This multi-centre, randomized, within-subject, crossover 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.

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 crossover design to increase precision by within-subject comparison, thereby reducing between-subject variability

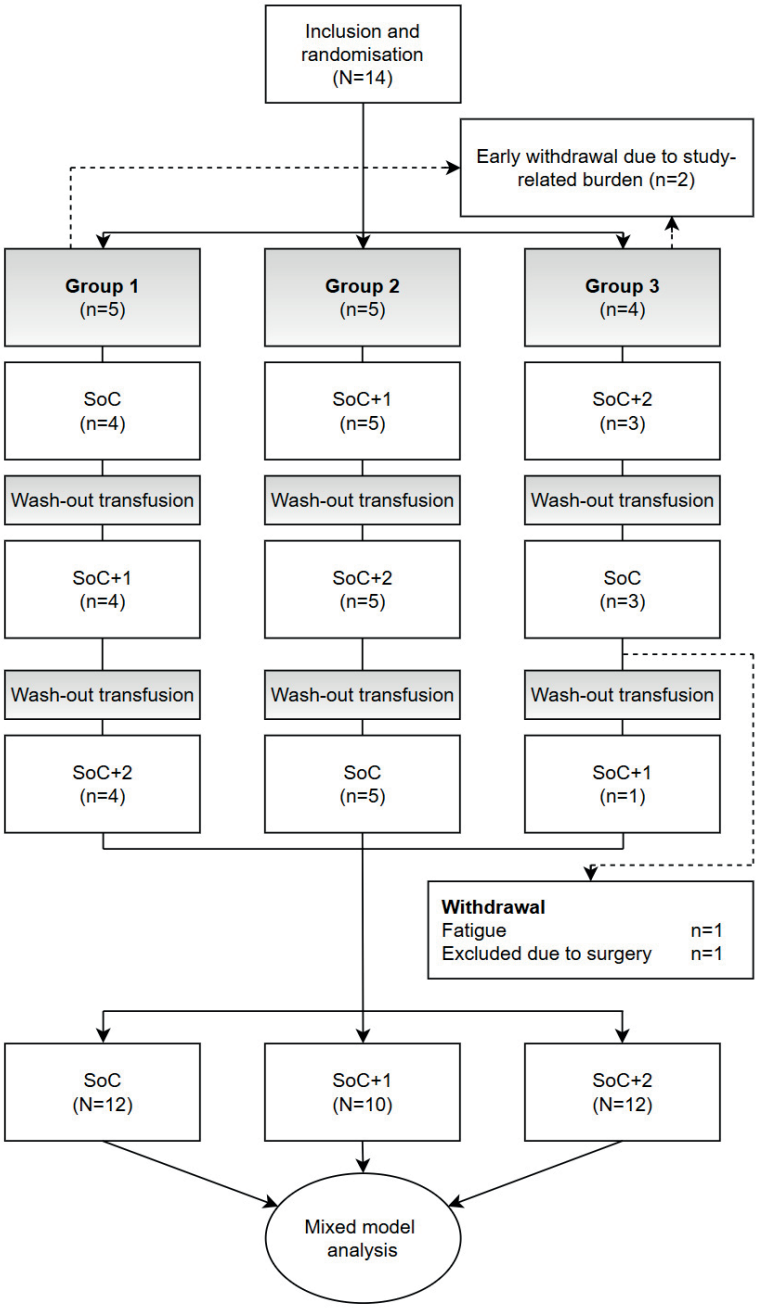

Figure 1. Flowchart of patient inclusion and randomisation.

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.

Outcomes

Heart rate and physical activity were continuously monitored by a biosensor–the Withings Steel HR smartwatch–starting one week before transfusion until the subsequent transfusion. Patients also completed the QUALMS and MFI (Multivariate Fatigue Index) questionnaires. Cognitive function was assessed via CANTAB tasks (RVP, SWMS, OTS). Haemoglobin 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: two days before the intervention transfusion (V1) seven days after transfusion (V2) and two 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 two 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.

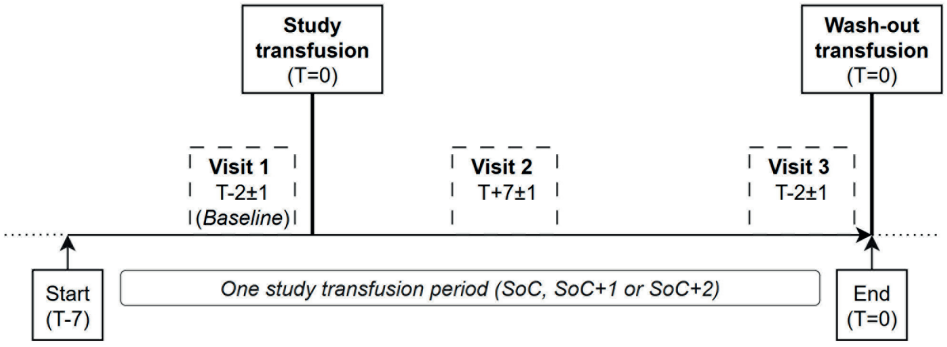

Figure 2. Visualisation of one study transfusion period. The duration is according to the patient's standard transfusion regimen. For our included population this varied from 1 to 6 weeks.

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.

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. We compared visits and differences between transfusion regimens and corrected for predefined confounders: age, sex, 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 (supplementary material 1).

Results

Baseline data

Between September 2021 and December 2023, 14 patients were enrolled across four centres. Two 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. Haemoglobin levels at V1 were comparable across the intervention groups (Supplementary material 2). No transfusion reactions or other adverse events due to transfusions or use of study materials were observed. We performed a Benjamini-Hochberg procedure to correct for multiple testing with a false discovery rate of .025 which yielded a threshold for significance of P = .0047.

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; non-significant). 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

Table 1. Patient baseline characteristics.

Median Age, years (range)	74 (64–89)
Haematological disorder	
MDS n(%)	8/12 (67%)
MPN n(%)	2/12 (17%)
CMML n(%)	1/12 (8%)
Undefined n(%)*	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 β-blocker n(%)	1/12 (8%)
Sex Women (%)	5/12 (42%)
Pre-transfusion 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)

MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasmata; CMML, chronic myelomonocytic leukaemia; RBCs, red blood cells; SoC, standard of care; Hb, haemoglobin.

*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.

both in the SoC+1 and SoC+2 group 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 supplementary material 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 analysing the normalized change in heart rate (Δheart rate) relative to the mean at V1, the dose-dependent effect of RBC transfusion became more pronounced (Supplementary material 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 3 RBC units as SoC were administered 2, 3, and 4 RBC units during the study instead of 3, 4, and 5 RBC units, to mitigate the risk of complications associated with transfusing 5 RBC units.

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.

Cognition

Three of the twelve 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 visualised 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.

Table 2. Outcomes per visit from Withings HR smartwatch, CANTAB, and HRQoL questionnaires.

		V1 (T = -2±1 days)	V2 (T = 7±1 days)	V3 (T^2 = -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)

		V1	V2	V3
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)
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)

Leveraging mixed models for absolute heart rate data, corrected for multiple testing with the Benjamini-Hochberg procedure; (see supplementary material 4 for mixed model outcomes for the Δheart rate analysis).

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

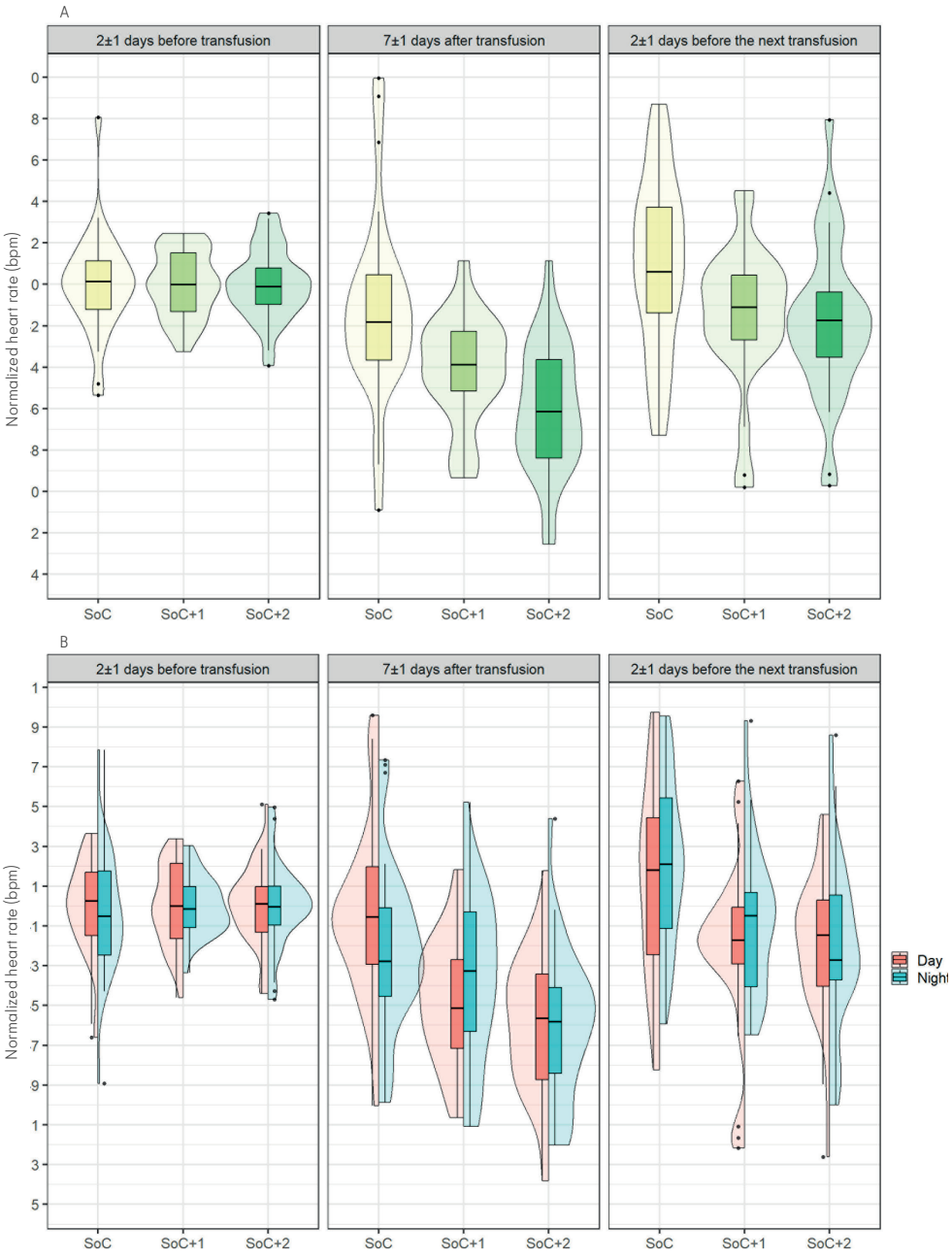

Figure 3. Median heart rate across study visits, normalized to the mean heart rate recorded during the first visit. This figure presents the summary of heart rate measurements at three time points: two days prior to transfusion, seven days following transfusion, and two days prior to the subsequent transfusion. 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-hour period. Figure 3B stratifies the normalized median heart rate into daytime (06:00–23:59) and nighttime (00:00–05:59) periods.

For the Spatial Working Memory Strategy task, SoC+2 showed a trend toward reversible 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.

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.

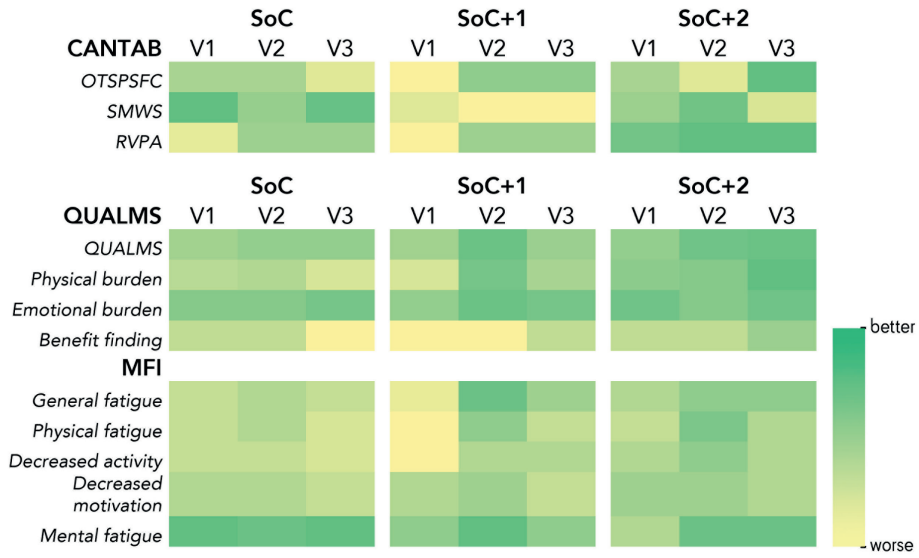

Figure 4. Heatmap of QUALMS, MFI and CANTAB outcomes with green indicating better outcomes and yellow indicating worse outcomes.

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

Discussion

The primary objective of this study is to explore the impact of varying transfusion regimens on heart rate in chronic transfusion-dependent anaemic 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 haemoglobin 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 haemoglobin 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 haemoglobin-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 anaemia 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 haemoglobin-driven changes. Alternative measures, such as the 6-minute 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, haemoglobin 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 haemoglobin level augmentation. These findings are consistent with the hypothesis that higher haemoglobin levels may alleviate fatigue by improving oxygen delivery and reducing the compensatory demands of anaemia. 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 anaemia 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 haemoglobin levels alone simply do not translate into meaningful improvements. However, we should also acknowledge that striving towards smaller 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 haemoglobin 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 anaemia-related deterioration and unnecessary transfusions in patients who tolerate lower haemoglobin 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 haemoglobin 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 haemoglobin 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 haemoglobin 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 haemoglobin levels may confer meaningful clinical benefits by alleviating cardiopulmonary compensation in transfusion-dependent anaemic 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 haemoglobin levels can lead to sustained benefits in heart rate, physical endurance, cognitive function and ultimately, an improved quality of life.

Author contributions

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

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Conflict of interest

All authors have no conflicts to declare.

Data availability statement

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

Supplementary material

The supplementary material for this article can be found online at:

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Ftrf.70023&file=trf70023-sup-0001-Supinfo.docx

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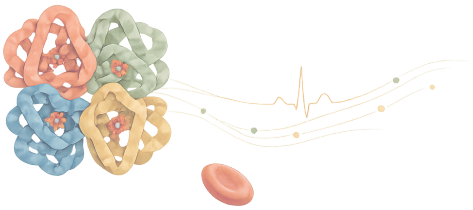

GENERAL SUMMARY AND DISCUSSION

For a large part based on the published article:
"Toward personalized transfusion strategies: The emerging role of wearable biosensors in chronic anaemia management"

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Introduction

Throughout this thesis, we have tried to answer several pressing questions: what are the effects of haemoglobin modulation? Is there a causal relationship between Hb level and physiological or patient-reported outcomes? How can we measure these outcomes effectively and accurately? And how should we interpret these measurements to inform and optimize transfusion or donation strategies?

As Bram Stoker, author of Dracula, might have put it: *"The blood is the life" – but how much life is actually in the blood?* Here we summarize our findings and reflect upon their implications.

Chapter 2

Haemoglobin modulation affects physiology and patient-reported outcomes in anaemic and non-anaemic subjects: An umbrella review

Background and context

Both low and high haemoglobin concentrations are known to affect physiological performance and quality of life. Yet, despite decades of research, uncertainty remains regarding how Hb modulation through interventions such as transfusion, phlebotomy, iron supplementation or erythropoiesis-stimulating therapy, or even altitude exposure, translates into measurable physiological and patient-reported outcomes. Existing clinical thresholds for transfusion or target Hb levels often rely on arbitrary or disease-specific conventions rather than on integrative physiological evidence.

To address this gap, we conducted an umbrella review synthesizing evidence from published systematic reviews and meta-analyses that evaluated the relationship between Hb modulation and both physiological and subjective outcomes in adults with and without anaemia. The goal was to determine whether changes in Hb concentration are consistently associated with improvements in measurable function and perceived well-being across populations and interventions.

Study summary and findings

A systematic search across six databases up to April 2022 identified 33 systematic reviews, comprising diverse populations (anaemic, non-anaemic, and polycythaemic) and interventions aimed at modulating Hb levels. Eligible reviews reported at least one physiological endpoint (e.g., VO_2max, heart rate, exercise capacity) or a patient-reported outcome (e.g., fatigue, dyspnoea, Quality of Life).

Quality assessment using AMSTAR-2 revealed that only 7 reviews were rated as high quality, whereas 24 were judged critically low, highlighting substantial methodological limitations within the available literature.

Across the included reviews, increases in Hb concentration were generally associated with improvements in both physiological measures and patient-reported outcome measures. These benefits were, as might be expected, most pronounced among individuals with low baseline Hb levels, where modest Hb increases translated into gains in functional capacity and perceived vitality. For example, in chronic kidney disease, raising Hb toward 12 g/dL (7.5 mmol/L) was consistently linked to enhanced exercise tolerance, improved fatigue and quality-of-life scores. Evidence regarding the effects of supraphysiologic Hb increases or intentional Hb reduction (e.g., phlebotomy, haemodilution) was limited and heterogeneous.

Overall, we concluded that Hb modulation exerts measurable physiological and patient-perceived effects, but the strength and consistency of evidence are constrained by the quality and heterogeneity of existing studies.

Critical analysis

This umbrella review provides the first comprehensive synthesis of evidence linking Hb modulation to physiological and subjective outcomes across a spectrum of populations and interventions. We employed a transparent search strategy, adhered to PRISMA guidelines, and used a formal quality appraisal tool. By combining data from multiple disease contexts, the study successfully highlights overarching physiological patterns that transcend individual disorders.

However, several limitations temper the interpretative value of its findings. The predominance of low-quality reviews underscores the fragility of the evidence. Considerable heterogeneity–in populations, interventions, endpoints, and analytic methods–prevents reliable quantitative pooling or inference about causality.

Another limitation lies in the indirectness of umbrella-level evidence: overlapping primary studies across reviews may have inflated perceived consistency, while publication bias on expected results could favour the latter. Moreover, the review focuses on associations rather than mechanistic pathways, leaving uncertain whether observed improvements are directly mediated by Hb change or by concurrent physiological and/or behavioural/psychological changes.

Despite these limitations, the review's findings reinforce the clinical observation that raising Hb from sub-physiologic to near-normal levels can enhance both functional and subjective outcomes, whereas there is no evidence regarding Hb elevation above physiologic norms.

Future studies should emphasize standardized physiological metrics, incorporate digital or wearable monitoring for objective continuous assessment, and integrate patient-reported outcome measures to better capture the multidimensional impact of Hb modulation. Rigorous randomized trials and high-quality systematic reviews are needed to clarify optimal targets and balance benefit against risk.

Chapter 3

Clinical practice for outpatients that are chronically red cell dependent: A survey in the Netherlands

Background and context

For patients that are chronically transfusion-dependent, evidence guiding optimal transfusion triggers, unit numbers and intervals in non-acute settings is scarce. In the absence of robust data, clinical decisions regarding maintenance transfusion regimens are often empirical and institution specific. We therefore designed a survey to characterize current outpatient transfusion practices in the Netherlands, focusing on three key dimensions: pre-transfusion haemoglobin thresholds, number of RBC units per transfusion episode, and interval between transfusions. We further sought to identify patient- and haematologist-specific factors influencing these decisions.

Study summary and findings

Between June and October 2020 we administered a web-based 44-question survey to members of the Dutch Haematology Association. Fifty physicians responded (response rate ~30%) representing both academic and community hospitals. The responses revealed a very wide variation in transfusion strategies. Reported median pre-transfusion Hb threshold was 8.0 g/dL (5.0 mmol/L), but individual thresholds ranged from 6.4 to 9.6 g/dL (4.0–6.0 mmol/L). Most centres transfused 1–2 RBC units per episode (range 0–3 units) at intervals of 2–4 weeks, though reported intervals ranged from 1 to 12 weeks. Physicians reported that the clinical factors most strongly influencing transfusion strategy were the presence of angina pectoris, cardiac failure, and dyspnoea. Among subjective considerations, quality of life and patients' self-sustainability were regarded as most relevant. In contrast, fatigue, cognitive status, emotional state, and vital parameters were considered to have less influence on transfusion decisions. We concluded that while individualization may account for some variation in practice, the wide heterogeneity observed underscores the necessity for randomized controlled trials to inform evidence-based guidelines on the management of chronic transfusion-dependent patients, including the identification of key clinical parameters.

Critical analysis

This survey addresses a significant gap in transfusion medicine by providing insights into real-world practices for the management of chronically transfused outpatients. Its strength lies in providing a quantitative snapshot of the diversity of practice across Dutch haematologists and in highlighting the absence of consensus thresholds in a routine care setting. The inclusion of both unit number and interval data, along with threshold values, adds practical relevance for clinicians and guidelines.

Nevertheless, the study has several limitations. As a self-report survey, it reflects reported practice rather than verified transfusion records, opening the possibility of recall bias or social desirability bias. The relatively low response rate (30%) and possible non-response bias may reduce generalisability. Importantly, the study does not correlate transfusion strategies with clinical outcomes (such as symptom relief, quality of life improvement or iron overload). Consequently, the variation observed cannot be judged as beneficial, neutral or harmful. Differences in patient populations (diagnosis, comorbidity, transfusion burden) across centres may explain much of the heterogeneity yet cannot be delineated fully from the survey design.

Nonetheless, the findings have important implications. The documented variation hints at potential under- or over-transfusion in some patient groups and underscores the need for prospective comparative studies. From a clinical perspective, this survey invites transfusion services to reflect on their local thresholds and intervals relative to peer practice and to consider monitoring of patient outcome–both objective and subjective–and resource utilisation. For guideline developers, the work emphasises an urgent need to incorporate maintenance transfusion strategies into the broader framework of patient blood management that mostly deals with perioperative situations.

This survey of outpatient RBC transfusion practice in the Netherlands demonstrates considerable heterogeneity in thresholds, unit numbers and intervals for chronically transfused patients. While individualised care remains appropriate, the extent of variation and lack of outcome data highlight a pressing need for prospective research and evidence-based guidelines. Until such data emerge, clinicians are encouraged to monitor not only Hb levels but also patient-centred outcomes to ensure optimal practice.

Chapter 4

Remote patient monitoring in adults receiving transfusion or infusion for haematological disorders using the VitalPatch® and AccelerateIQ™ monitoring system: Quantitative feasibility study

Background and context

Patients with hematologic disorders receiving treatments such as red blood cell transfusions, chemotherapy, or immunotherapy are vulnerable to infusion-related complications, often signalled by changes in vital signs. Traditionally, symptom monitoring post-treatment is patient-reported, which can delay the detection of adverse events. Wearable biosensors–already validated and used in cardiology practice–in this line offer a solution. These devices enable continuous, real-time monitoring of physiological parameters beyond the clinic or in less supervised (such as home-) transfusion settings. This feasibility study explored whether integrating such technology into outpatient care is acceptable and practical.

Study summary and findings

In this quantitative feasibility study, twelve adult patients with hematologic conditions–including multiple myeloma, myelodysplastic syndrome, and non-Hodgkin lymphoma–were enrolled to wear the VitalPatch® biosensor for a period of 12 days around a planned infusion or transfusion. Patients received red blood cell transfusions (n = 4), intravenous proteasome inhibitors (n = 4), or immunotherapy (n = 4). The majority of participants (83%) were aged 60 years or older.

The VitalPatch® system–capable of measuring heart rate, respiration rate, skin temperature, activity, heart rate variability and position–was generally well tolerated, with minimal interference in daily activities. Patient-reported outcomes were collected at baseline, day 1, day 5, and day 8 after application of the patch. Data indicated that wearing the device had minimal impact on the patient's life. Ease of use, influence on sleep, impact on follow-up of health, or discomfort with continuous monitoring did not change between baseline and day 8. Patients reported low levels of discomfort, although a 20% increase in skin irritation was reported, particularly when applying a second patch. Both patients and nurses rated the wearability and usability of the device positively. Nurses also reported that the sensor was easy to apply and provided reliable measurements.

In this study we concluded that remote physiological monitoring using wearable biosensors is feasible and acceptable among adult patients receiving outpatient transfusions or infusions. These findings support the potential for broader implementation of such technologies to improve patient safety and data collection in haematology care.

Critical analysis

While this feasibility study highlights the potential of wearable biosensors like the VitalPatch® to enhance outpatient monitoring in haematology, its limitations constrain the broader implications of its findings. The small sample size (n = 12), short duration of monitoring (12 days), and observational design restrict generalizability and preclude conclusions about clinical efficacy or long-term outcomes.

The study shows that continuous monitoring is technically feasible and generally well accepted by patients and healthcare staff. However, the absence of a control group or direct linkage between recorded physiological changes and clinical actions limits its ability to demonstrate tangible clinical benefit. Although not a goal of the study, no adverse events or treatment modifications were reported in response to biosensor data. Therefore, impact on clinical decision-making has yet to be formally evaluated.

Furthermore, while usability ratings were favourable, participant recruitment from a single centre introduces potential selection bias. A more practical challenge is the battery life of 4 days, while mild skin irritation in some patients also raises concerns about long-term tolerability, especially in older adults with sensitive skin.

Broader implementation challenges–such as data interpretation, workflow integration, and costs–remain unexplored. Nevertheless, the study does support continued use and development of remote biosensor monitoring as part of a shift toward personalized, proactive care in haematology.

Unpublished exploratory observations beyond the study scope

Although not part of the study's predefined objectives, we conducted exploratory analyses of the physiological data collected via the VitalPatch®. Notably, post-transfusion measurements revealed patterns that appeared physiologically relevant and clinically intriguing (Fig. 1). These preliminary findings prompted further interest in the potential role of wearable biosensors in monitoring transfusion responses, ultimately serving as the impetus for the subsequent pilot study.

Chapter 5

Remote monitoring of vital and activity parameters in chronic transfusion-dependent patients: A feasibility pilot using wearable biosensors

Background and context

This study aimed to assess the feasibility of using wearable biosensors and web-based assessments to monitor vital signs, activity levels, and cognitive function in transfusion-dependent patients with myelodysplastic syndrome or thalassemia.

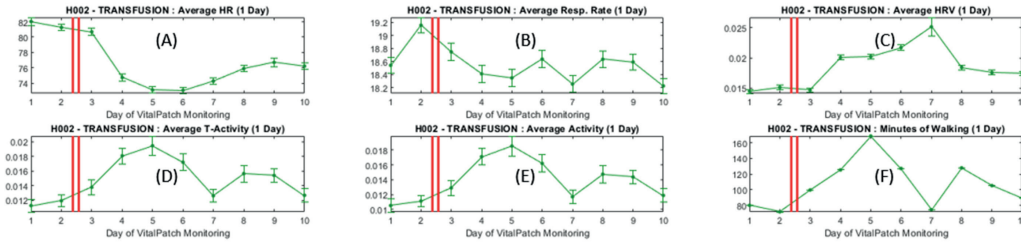

Figure 1. Example of daily parameter courses derived by the physIQ cloud analytics platform of one patient receiving a transfusion. Double red line: Time of transfusion; (A) mean heart rate per day, (B) mean respiratory rate per day, (C) mean heart rate variability per day, (D) mean smoothed activity level per day, (E) mean gross activity level per day, (F) mean minutes of walking per day.

Study summary and findings

In this follow-up pilot study, five patients who regularly receive transfusions were monitored starting 7 days before transfusion up until the following transfusion. The monitoring tools included the AccelerateIQ™ platform leveraging the VitalPatch® biosensor, the Withings Steel HR smartwatch, and web-based cognitive and quality of life assessments. Data collection was successful, with the AccelerateIQ™ platform yielding 97.8% high-quality usable data and the Withings Steel HR providing 98.9% high-quality usable data. Post-transfusion assessments indicated a significant decrease in heart rate and an improvement in sustained attention, suggesting a positive physiological and cognitive response to transfusion. However, measures of physical activity and self-reported quality of life did not show significant changes following transfusion.

Critical analysis

This feasibility study demonstrates the potential of integrating wearable biosensors and digital assessments into the care of transfusion-dependent patients. The high quality and usability of the collected data indicate that such technologies can be effectively employed in this patient population. The observed improvements in heart rate and cognitive function post-transfusion provide preliminary evidence that objective physiological and cognitive metrics may serve as valuable indicators of transfusion efficacy.

Besides the small sample size, the lack of significant changes in physical activity and quality of life measures may be due to the short–one single transfusion cycle–monitoring period. Moreover, patient-related factors such as age, frailty, comorbidities, and individual circumstances substantially affect these parameters.

Moreover, reliance on heart rate alone is likely insufficient to support algorithm-driven decision-making in transfusion care. More nuanced physiological markers such as heart rate variability, or yet-to-be-identified proxies of transfusion need–like a gradually declining condition–will likely be necessary to develop robust, clinically relevant algorithms.

Future research should explore the integration of wearable biosensor data into clinical decision-making processes. Such studies could assess whether continuous monitoring can lead to more personalized transfusion schedules, improved patient outcomes, and enhanced quality of life. Furthermore, evaluating the cost-effectiveness and patient adherence to long-term use of wearable devices will be essential for widespread implementation.

Chapter 6

Heart rate changes after phlebotomy in polycythaemia vera and healthy donors: An observational case-crossover pilot study

Background and context

While low Hb is linked to fatigue and reduced quality of life, excessive levels–as seen in polycythaemia vera (PV)–can increase blood viscosity, potentially also compromising oxygen delivery. Despite this, the physiological effects of modest Hb reduction in non-anaemic individuals or in PV patients undergoing phlebotomy remain poorly studied. This pilot aimed to explore whether small decreases in Hb levels elicit measurable physiological responses, and whether consumer-grade biosensors can detect them.

Study summary and findings

The study involved six healthy blood donors and five PV patients who were regularly monitored via smartwatches for one week before and after phlebotomy. Among healthy donors, a significant increase in heart rate post-phlebotomy was observed, particularly during daytime hours, with gradual normalization. PV patients showed no consistent change in heart rate. Activity levels rose briefly in healthy donors but declined post-phlebotomy in PV patients, with modest recovery. Quality-of-life scores showed minimal change in both groups.

Critical analysis

The study effectively illustrates that even small Hb reductions can provoke measurable physiological changes in healthy individuals, notably increased heart rate. However, the small, homogeneous sample–especially the all-female healthy donor group–limits generalizability. The short follow-up period may not capture long-term changes, and the observed variations in step count and quality-of-life scores may reflect natural

fluctuations more than true physiological shifts. The consistently high (100%) quality of life score in the healthy donor group indicates a limitation of the EQ-5D-5L questionnaire, where the ceiling effect prevents variation in responses.

Notably, PV patients exhibited greater physiological stability, suggesting that either a slightly higher baseline Hb might reduce the impact of phlebotomy, or possibly adaptation to chronic phlebotomy–no newly diagnosed PV patients with much higher Hb values were investigated. The study underscores the potential of wearable devices for passive physiological monitoring in diverse clinical settings. The findings suggest that even subtle changes in normal haemoglobin levels can be detected by a smartwatch, making it an intriguing technique. However, given the very small sample size, this pilot study should be viewed as an initial signal pointing toward the potential for larger-scale investigations.

Chapter 7

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

Background and context

As a follow-up to earlier pilot studies, we are currently conducting the REMOTE-2 study–a multicentre, randomized, within-subject crossover trial in outpatient clinics. The study investigates the physiological and patient-reported effects of varying red blood cell transfusion strategies in adults with chronic transfusion dependence due to myelodysplastic syndromes, myeloproliferative neoplasms, or overlap conditions. Each participant receives their standard-of-care transfusion regimen, followed by two intensified regimens: one with one additional red blood cell unit (SoC+1), and one with two additional units (SoC+2). The primary objective is to assess the effect of increasing transfusion-modulated Hb on heart rate using wearable biosensors. Secondary objectives include evaluating changes in physical activity, quality of life, and cognitive function. Heart rate and activity were continuously monitored with a wrist-worn biosensor; QoL, fatigue, and cognition were assessed at predefined time points before and after transfusion. Due to slow enrolment, an interim analysis of the first 12 participants was undertaken to provide early insights and determine whether continuation of the study remained justified.

Summary and results

An increase in haemoglobin level was followed by a dose-dependent reduction in heart rate. SoC transfusions yielded a small non-significant decrease, whereas SoC+1 and SoC+2 resulted in progressively larger reductions. Heart rate reductions persisted into the late post-transfusion phase following SoC+1 and SoC+2. Daily step count showed

wide inter- and intra-individual variability with no consistent differences between regimens, and no temporal pattern suggestive of transfusion-related improvement.

Nor were any statistically significant cognitive effects of transfusion volume observed. However, descriptive patterns suggested small, inconsistent improvements in planning, working memory strategy, and sustained attention–most apparent in the SoC+2 regimen. Whether these reflect transfusion effects or practice/familiarity effects is uncertain.

QoL and fatigue scores did not show statistically significant improvements. Nevertheless, trends were compatible with short-term benefit: reduced physical burden and fatigue at the early post-transfusion visit following SoC+1 and SoC+2, with some persistence of improvement in the SoC+2 regimen. These findings mirror earlier small trials suggesting better symptom control under more liberal transfusion strategies.[1,2]

Overall, the interim data suggest that higher transfusion volumes reduce heart rate in a dose-dependent manner, with non-significant but clinically plausible trends toward improved patient-reported outcomes.

Critical analysis

This interim analysis provides an early contribution to a field with limited empirical evidence, addressing the clinically relevant question of whether higher haemoglobin targets in chronically transfusion-dependent patients yield measurable physiological or patient-reported benefits.

The most compelling finding is a dose-dependent reduction in heart rate with higher transfusion volumes, supporting the hypothesis that increased haemoglobin decreases cardiopulmonary compensation and enhances physiological reserve. This effect remained significant after conservative statistical correction, reinforcing its validity and demonstrating the sensitivity of wearable biosensors to detect subtle, clinically meaningful changes.

Interpretation is constrained by the small sample size, which limits power for secondary outcomes and may obscure effects on quality of life, cognition, or activity. High variability in step counts and self-reported measures further reduces sensitivity, while cognitive results may be confounded by practice effects, and remote CANTAB testing may be less reliable in older populations.[3] Additionally, adjustments to SoC transfusion volumes to avoid excessive unit numbers introduce complexity in interpreting comparisons. For patients with a three-unit SoC–where a SoC + 2 strategy would result in five units and increase the risk of transfusion-associated circulatory overload–the SoC dose was reduced to two units, yielding SoC, SoC + 1, and

SoC + 2 regimens of two, three, and four units. This also shifts the SoC comparator in this crossover design, as it no longer matches patients' usual baseline dose.

The absence so far of clear improvements in activity or QoL does not preclude clinical benefit, as chronic anaemia may require sustained haemoglobin elevation for functional gains on physical or mental fitness to emerge, and current instruments may lack sensitivity to short-term changes. Minimizing haemoglobin fluctuations, rather than achieving transient post-transfusion peaks–may ultimately prove more relevant to patient well-being. More frequent transfusions preferably at home in this respect should be investigated with wearables additionally monitoring potential transfusion reactions/side effects.

Overall, this interim analysis provides preliminary evidence supporting the biological plausibility of benefit from more liberal transfusion strategies in chronic anaemia. Higher transfusion volumes consistently reduced heart rate in chronically anaemic, transfusion-dependent patients, suggesting heart rate may serve as a useful intermediate marker of transfusion effect, with early signals also hinting at potential improvements in symptoms and cognitive function. The study further demonstrates the feasibility of integrating wearable technology into transfusion trials. While these findings require confirmation in larger, fully powered cohorts, they support continued investigation of individualized, outcome-oriented transfusion strategies beyond traditional restrictive thresholds, including evaluation of whether sustained Hb elevation translates into meaningful gains in function, cognition, or quality of life and how such benefits balance against risks such as iron overload.

Other currently running trials

Another transfusion study incorporating biosensor technology is REDDS: Study 2.[4] This investigation compares patients' standard transfusion regimens with a fixed weekly transfusion schedule to investigate the effect of reduced Hb fluctuations. In addition to assessing health-related quality of life (HRQoL), the study employs accelerometry to objectively measure patient activity levels throughout the study period. Lastly, the OURA feasibility pilot study, using a finger ring based biosensor, will assess whether patients with myelodysplastic syndromes (MDS) can maintain Oura ring use for more than 70% of the time over a three-month period. Secondary exploratory analyses will examine correlations between wearable-derived physiological parameters and transfusion dates and self-rated physical functioning.[5]

Current applications of biosensors in other fields

While a focused approach is essential to advancing transfusion-related biosensor development, insights from other fields can inform and accelerate progress. A leading example is the use of hybrid closed-loop systems in diabetes management,[6] which integrate continuous glucose monitoring with algorithm-driven insulin delivery and remote data sharing, exemplifying the potential of biosensor-guided therapy.

This model has also spurred interest in wearable biosensors for neuropsychiatric applications, including the detection of stress-related biochemical markers. [7] In wound care, biosensors are employed to monitor parameters such as pH, temperature, moisture, and inflammatory biomarkers, enabling timely intervention and improved healing outcomes.[8] Similarly, cardiovascular research utilizes biosensors in flexible comfortable formats (patches textiles, contact lenses, tattoos) to continuously track vital heart-related signals, moving beyond simple measurements such as heart rate, toward integrated cardiovascular health tools–an approach that may also inform transfusion monitoring strategies.[9]

General discussion

Transfusion research has traditionally focused on broad clinical outcomes such as survival and hospital length of stay–primarily in patient groups with acute anaemia–leading to the conclusion that a restrictive transfusion strategy is generally preferable–an approach informed by the scarcity and cost of blood products as well as the undeniable, sometimes severe, adverse effects associated with transfusion. Yet for patients with chronic, transfusion-dependent anaemia, quality of life and objective measures of functional well-being should be integral considerations. These patients' physical and psychological states are shaped by highly individual and timing-specific factors, and emerging technologies such as wearable devices may offer continuous, patient-centred assessment that could support more personalized transfusion care.

Despite decades of research, uncertainty remains regarding how Hb modulation translates into measurable physiological and patient-reported outcomes. In Chapter 2, where we evaluated all available evidence from reviews, we concluded that Hb modulation exerts measurable physiological and patient-perceived effects, but the strength and consistency of evidence are constrained by the quality and heterogeneity of existing studies.[10]

In clinical practice, this uncertainty is reflected in the substantial variation in transfusion thresholds, unit numbers, and intervals reported in the Netherlands, underscoring the need for prospective evidence to guide more standardized and outcome-driven transfusion policies.[11]

Despite the well-documented impact of anaemia on functional and cognitive decline, mobility, and overall physical performance,[12–15] especially in elderly populations, a causality behind these associations is not proven; possibly, lower haemoglobin concentrations may simply indicate a more advanced disease, with consequently poorer QoL scores independent of the anaemia.

These unresolved uncertainties underscore the need for alternative markers to evaluate transfusion effects and support more individualized decisions. One approach explored in the present work involved the use of wearable biosensors and web-based assessments.

The feasibility studies we performed indicate that biosensors are well tolerated and technically viable in outpatient settings, including among older adults.[16,17] Building on this foundation, our interim analysis showed that transfusing more RBC units was associated with a dose-dependent reduction in heart rate with the suggestion of a sustained effect up until the next transfusion.[18] The observed heart rate reductions likely reflect an alleviation of the compensatory tachycardia characteristic of chronic anaemia, thereby improving physiological reserves.

These physiological changes have not yet been shown to translate into significant improvements in secondary outcomes such as quality of life, fatigue, activity or cognitive function; an expected limitation given the sample size, though several trends were suggestive. Trends towards improved cognitive performance may reflect either subtle transfusion-related effects or practice-related improvement, especially given the challenges older adults may face with web-based assessments. Similarly, trends toward reduced fatigue and improved physical quality-of-life domains align with the hypothesis that higher Hb levels enhance oxygen delivery and reduce compensatory strain, consistent with findings from liberal versus restrictive transfusion trials.[1,2] These findings, however, should be considered as hypothesis-generating and should be interpreted cautiously given the small sample size and variability in patient responses.

In contrast, daily step counts did not reflect transfusion effects and appear driven more by individual lifestyle patterns than by Hb levels, indicating that step counts are unlikely to serve as reliable functional markers. More structured assessments, such as the 6-minute walk test, and long-term monitoring periods may more accurately capture transfusion-related changes in functional capacity and a gradually changing lifestyle.

Given the multifactorial determinants of quality of life, it remains uncertain to what extent the increase in haemoglobin level alone produces clinically meaningful improvements. It is plausible that reducing the amplitude of haemoglobin fluctuations, rather than simply increasing Hb peaks, may yield greater benefits, a hypothesis warranting further investigation. The latter is the subject of the presently running REDDS2 study.

While these early findings are encouraging, they require cautious interpretation. Key uncertainties persist regarding the reliability and interpretation of biosensor signals, recommended clinical responses to alerts, and the downstream impact of

biosensor-guided transfusion strategies on mobility, QoL, healthcare use, and survival. Artificial intelligence may enhance signal fidelity by distinguishing anaemia-related physiological changes from day-to-day variability in patients' activities and comorbidities. Ultimately, large randomized trials with longer observation periods comparing biosensor-guided strategies with current Hb-threshold-based practice are needed to determine their true clinical value, incorporating both short-term physiological outcomes and long-term patient-centred endpoints.

Before biosensor-supported transfusion management can be implemented at scale, several practical and methodological challenges must be addressed. A key priority is establishing validated cut-off points and alert thresholds, as the current analyses demonstrate that biosensors can reliably detect transfusion-related physiological changes but do not yet define when these changes should trigger clinical action. Without such criteria, alerts may accumulate unnecessarily, increasing the likelihood of false positives and contributing to alert fatigue, with the risk that clinically relevant signals are overlooked. Additional considerations include integration with electronic health records, workflow implications for clinicians, and cost-effectiveness. Nevertheless, in an aging population with increasing healthcare demands, biosensor-guided transfusion approaches hold considerable promise for personalizing care, optimizing resource use, and ultimately improving patient-centred outcomes.

Future applications of biosensors in transfusion medicine

We anticipate that wearable biosensors will become increasingly integrated into transfusion medicine, particularly in the context of the ongoing shift toward decentralized and patient-centred models of care. The convergence of continuous remote monitoring via cloud-connected wearable devices with personalized, machine-learning–driven analytics holds considerable promise for the early detection of anaemia-related physiological deterioration. The anticipated development of multimodal biosensors that can combine electric signals from the heart with biomarkers from blood or tears could substantially reduce the reliance on frequent, routine outpatient visits for haemoglobin monitoring, thereby alleviating the workload of healthcare professionals.

In parallel, the development of patient-facing smartphone applications may provide opportunities for disease education, therapy guidance, and even advanced care planning, further supporting patient autonomy while decreasing the time and resources required from clinical staff. Importantly, however, attention must also be given to equitable access. Without deliberate safeguards, these technologies may disproportionately benefit patients with greater resources, digital literacy, or access to robust healthcare systems, thereby widening existing disparities; considerations of affordability, usability, and inclusivity in algorithm design will therefore be essential.

Despite promising advances, substantial challenges remain before biosensor-guided transfusion strategies can be fully realized in clinical practice. Robust evidence from large, diverse patient cohorts is needed to determine which biosensor-derived parameters–or combinations thereof–are most clinically informative, alongside rigorous validation studies to establish their accuracy, reproducibility, and clinical utility. Artificial intelligence may play a key role in distinguishing anaemia-related physiological changes from the substantial variability introduced by patients' daily lives.

By enabling individualized baselines and the detection of clinically meaningful anaemia-related deviations, biosensor-based approaches hold significant potential to personalize transfusion care, optimize resource use, and enhance patient-centred outcomes in an aging population with increasing healthcare demands. At the same time, wearable technologies may help overcome the vigilance requirements that currently hinder home-based transfusions for chronically transfusion-dependent patients, while also providing long-term physiological data to further support individualized decision-making.

Considerations for future trials

Definitive evaluation of biosensor-guided transfusion strategies will ultimately require a large international, multicentre trial. A pragmatic design could compare current standard-of-care transfusion practices with an intervention arm in which transfusion decisions are supported by biosensor-derived algorithms enhanced by machine-learning techniques. Key outcomes should include total transfusion requirements, healthcare utilization and associated costs, physiological responses captured by biosensors (for example, whether algorithm-guided patients achieve more sustained reductions in heart rate), patient-reported quality-of-life measures, and longer-term functional outcomes such as the 6-minute walk test, grip strength, and acute-care presentations.

However, the feasibility of such a trial is constrained by the limited pool of eligible patients. As demonstrated by the slow recruitment in our own study, achieving adequate sample sizes would require substantial resources and extended timelines. Exploring analogous populations–such as athletes or patients with heart failure–may offer insights into which physiological parameters best reflect functional status and could help refine outcome selection for future transfusion trials.

Careful consideration must also be given to the choice of biosensor. With rapid technological turnover, devices selected at trial initiation risk becoming obsolete by completion. Ideally, the biosensor should be wireless, capable of autonomous cloud-based data transfer, and require minimal patient involvement to ensure consistent data capture. Questionnaires and cognitive assessments, if included, should be concise and selected with care, as anaemia-related fatigue in this frail population may influence performance unless this effect forms part of the research question.

Conclusion

Taken together, the work presented in this thesis underscores the longstanding uncertainty surrounding how haemoglobin modulation translates into meaningful physiological and patient-reported outcomes, and how this uncertainty continues to shape the wide variation observed in current transfusion practice. Across our studies, we found that haemoglobin augmentation consistently reduces compensatory tachycardia, suggesting a tangible improvement in physiological reserve. However, effects on broader functional outcomes, cognition, activity, and quality of life remain less clear, limited both by small sample sizes and the inherent complexity of these multidimensional endpoints.

Our feasibility studies demonstrate that wearable biosensors and web-based assessments are well tolerated, technically robust, and capable of capturing subtle physiological changes in chronically transfused patients. Yet their ultimate clinical value–the extent to which biosensor-derived signals can guide transfusion decisions, predict deterioration, or improve patient-centred outcomes–remains to be established. Addressing these questions will require larger, rigorously designed trials that evaluate not only short-term physiological responses but also long-term impacts on functional capacity, quality of life, iron overload, healthcare utilization, and survival.

Despite the challenges that lie ahead, the integration of continuous monitoring with advanced analytics offers a promising path toward more individualized, responsive, and outcome-driven transfusion care. As healthcare systems adapt to an aging and increasingly complex patient population, the development of physiologically informed, patient-centred transfusion strategies has the potential to substantially enhance both clinical outcomes and quality of life for those living with chronic anaemia.

To borrow once more from Bram Stoker – "The blood is the life": The challenge ahead is to ensure that every unit transfused not only sustains life, but meaningfully enriches it.

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Appendices

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Nederlandse samenvatting

Bloed speelt een cruciale rol in het menselijk lichaam. Hemoglobine in rode bloedcellen zorgt voor het transport van zuurstof naar alle organen en weefsels. Wanneer het hemoglobinegehalte te laag is, zoals bij bloedarmoede, kan dit leiden tot klachten zoals vermoeidheid, kortademigheid en een verminderde kwaliteit van leven. Een veelgebruikte behandeling is het geven van bloedtransfusies. Tegelijkertijd brengen transfusies ook risico's en kosten met zich mee, wat het belangrijk maakt om zorgvuldig af te wegen wanneer en hoeveel bloedtransfusies gegeven worden.

In de afgelopen decennia is een terughoudend transfusiebeleid de standaard geworden. Dit beleid is grotendeels gebaseerd op onderzoek bij acuut zieke patiënten, waarin is aangetoond dat lagere hemoglobinegrenzen veilig zijn als gekeken wordt naar harde uitkomsten zoals overleving en complicaties. Voor patiënten met chronische bloedarmoede is echter minder duidelijk wat de optimale strategie is. Bij deze groep spelen klachten en kwaliteit van leven een grote rol, wat de vraag oproept of streven naar een hoger hemoglobinegehalte mogelijk meer voordelen dan nadelen geeft.

Het doel van dit proefschrift is om beter te begrijpen hoe veranderingen in hemoglobine het lichaam en de kwaliteit van leven beïnvloeden, en hoe deze kennis kan bijdragen aan een meer gepersonaliseerde benadering in de transfusiegeneeskunde.

In hoofdstuk 2 vatten we eerder verrichte onderzoeken samen, waarmee we laten zien dat veranderingen in het hemoglobinegehalte invloed hebben op zowel lichamelijke functies als door patiënten gerapporteerde uitkomsten, zoals vermoeidheid en kwaliteit van leven. Op basis van bestaande studies blijkt dat een stijging van het hemoglobine doorgaans leidt tot verbetering van deze uitkomsten, vooral bij lagere uitgangswaarden. Tegelijkertijd wordt duidelijk dat er grote kennislacunes bestaan en dat veel studies van beperkte kwaliteit zijn.

In hoofdstuk 3 onderzoeken we hoe artsen in de praktijk omgaan met transfusies bij patiënten die langdurig afhankelijk zijn van rode bloedcellen. We laten zien dat er aanzienlijke variatie bestaat in de gekozen transfusiegrenzen en behandeldoelen, en op basis van welke patiëntkenmerken deze beslissingen worden genomen. Dit wijst mogelijk op een gebrek aan eenduidige richtlijnen voor deze patiëntengroep, maar kan ook een uiting zijn van de heterogeniteit van de patiëntengroep.

In hoofdstukken 4 en 5 richten we ons op nieuwe manieren om het effect van bloedarmoede en transfusies te meten. We onderzoeken de haalbaarheid van het gebruik van draagbare sensoren (wearables) om patiënten op afstand te monitoren. Deze technologie maakt het mogelijk om continu gegevens te verzamelen over bijvoorbeeld hartslag, ademhaling en lichamelijke activiteit. De resultaten laten zien dat deze vorm van monitoring uitvoerbaar is en potentieel waardevolle inzichten kan geven

in de fysiologische effecten van transfusies.

In hoofdstuk 6 bestuderen we het omgekeerde van transfusie: het verwijderen van bloed door middel van een aderlating – bij zowel gezonde bloeddonoren als patiënten met polycythaemia vera, een ziekte die een te hoog hemoglobinegehalte geeft. We laten zien dat een aderlating leidt tot meetbare veranderingen in hartslag – vooral bij een normaal hemoglobinegehalte – wat inzicht geeft in hoe het lichaam reageert op veranderingen in zuurstoftransportcapaciteit.

In hoofdstuk 7 onderzoeken we of het effect van een bloedtransfusie afhankelijk is van de hoeveelheid toegediende rode bloedcellen. In een gerandomiseerde studie laten we zien dat er aanwijzingen zijn voor een dosis-effectrelatie, waarbij grotere hoeveelheden bloed mogelijk leiden tot grotere verbeteringen in fysiologische en door patiënten gerapporteerde uitkomsten. Dit ondersteunt onze hypothese dat transfusies beter afgestemd kunnen worden op de individuele behoefte van de patiënt.

In hoofdstuk 8 bespreken we de belangrijkste bevindingen van dit proefschrift en plaatsen we deze in een breder perspectief. Het uiteindelijke doel van een transfusie is het verbeteren van zuurstofvoorziening in weefsels en het daarmee verhogen van de kwaliteit van leven, maar deze effecten worden slechts gedeeltelijk weerspiegeld door het hemoglobinegehalte. Dit proefschrift laat zien dat een meer gepersonaliseerde benadering van transfusiegeneeskunde tot betere zorg kan leiden. Hierbij moeten niet alleen laboratoriumwaarden, maar ook fysiologische metingen en de ervaringen van de patiënt worden meegenomen. Nieuwe technologieën, zoals wearables en eHealth-toepassingen, bieden mogelijkheden om deze gegevens continu op een objectieve manier te verzamelen.

Deze ontwikkelingen kunnen er in de toekomst voor zorgen dat beter bepaald kan worden wanneer een transfusie nodig is en wat de optimale hoeveelheid is voor een individuele patiënt. Dit kan leiden tot zorg die niet alleen veiliger en efficiënter is, maar vooral beter aansluit bij de behoeften en kwaliteit van leven van de patiënt.



PhD portfolio

The PhD trajectory - an overview
CRediT table of this thesis
Dissemination table
Completed courses and training

The PhD trajectory – an overview

In October 2018, Rik Tonino started his PhD trajectory within TRIP at the hematology department of the Haga Teaching Hospital, under the supervision of dr. M.R. Schipperus and prof. dr. J.J. Zwaginga. During the initial phase, he worked with a dataset collected by a previous PhD candidate, M. Wilson, to conduct a retrospective study on preoperative iron status and perioperative transfusion requirements. In parallel, he analyzed data from a recently completed pilot study using biosensors, which resulted in the publication presented in Chapter 4.

This early phase also involved exploring several potential research directions, including chronic graft-versus-host disease after transfusion. Following an assessment of their scientific relevance, feasibility and potential, these topics were not pursued further. Instead, the research focus gradually developed towards the measurable effects of red blood cell transfusion in patients with chronic anaemia. Rik contributed to the conceptualization of a subsequent biosensor pilot study, based on the hypothesis that red blood cell transfusion could produce measurable changes in physiological parameters, quality of life and cognition.

The use of biosensors was relatively novel within transfusion medicine and offered the possibility of collecting repeated, objective measurements in addition to patient-reported outcomes. This methodological development became an important component of the PhD project. Its clinical relevance was linked to the limited evidence regarding the benefits of transfusion for chronically anaemic patients and the possibility that current transfusion policies may be overly restrictive for some patients.

Building on these initial studies, the research program broadened into an evaluation of transfusion practice and outcomes. It included a national survey of transfusion policies in the Netherlands, an umbrella review of the available evidence on the physiological and quality-of-life effects of transfusion, and several pilot and multicenter studies investigating the effects of red blood cell transfusions and phlebotomies. Together, these projects reflect the development of Rik's scientific perspective from analyzing existing datasets to formulating research questions, selecting appropriate methodologies and coordinating prospective clinical studies.

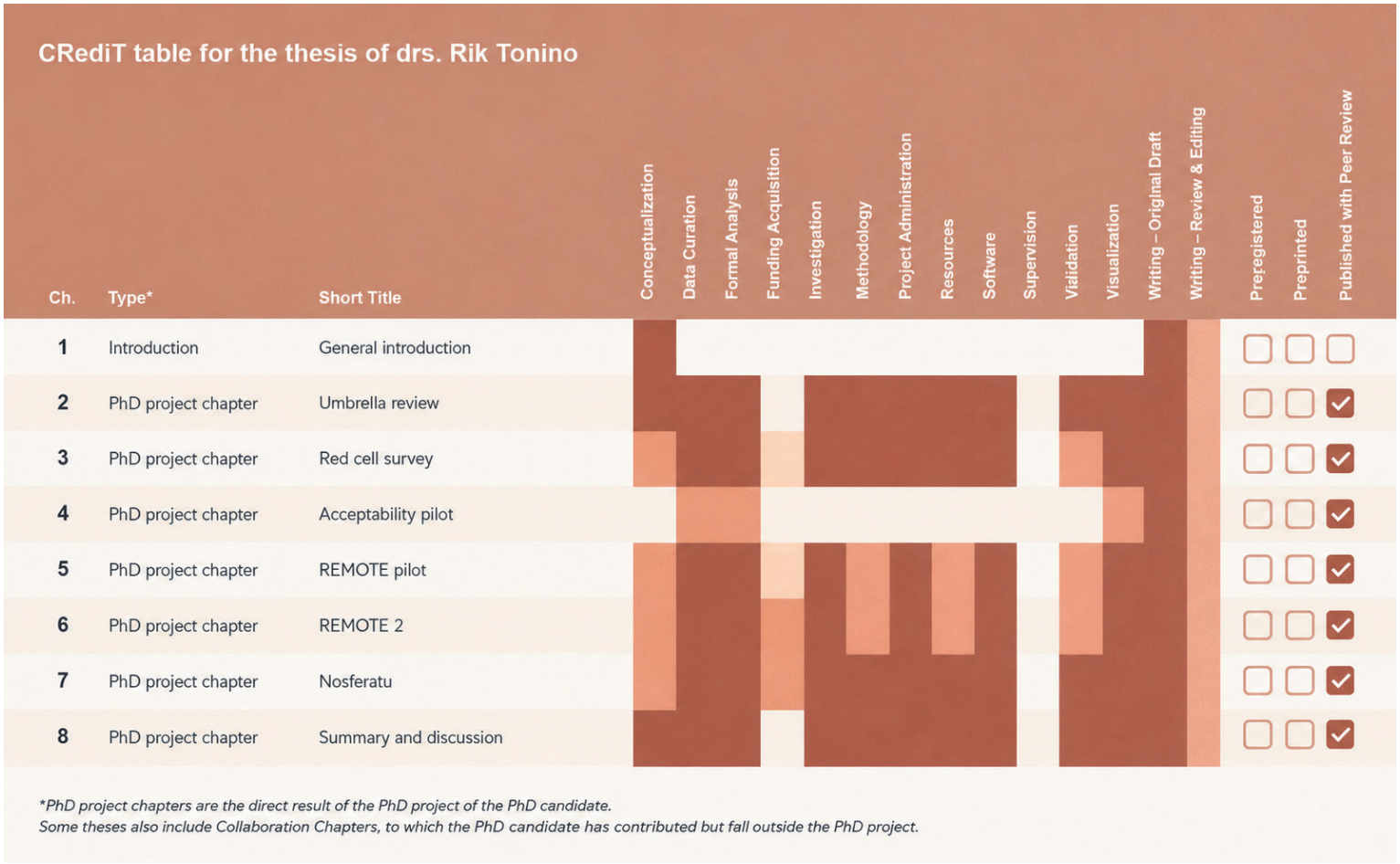
Rik increasingly assumed responsibility for the full research cycle. He took the lead in drafting study protocols and methodological plans, preparing applications for ethical approval, applying for research funding and obtaining a PPOX grant from Sanquin. He was also responsible for data management, formal statistical analysis, data visualization, manuscript preparation and the publication process in peer-reviewed journals. Whereas these activities were initially conducted with close guidance from his supervisors and co-supervisors, he required progressively less supervision as the trajectory advanced.

Team science was particularly important in the multicenter studies. Rik collaborated with methodological experts, haematologists and researchers from several hospitals to optimize the study designs and establish the practical infrastructure required for participant recruitment and data collection. During the COVID-19 pandemic, lockdowns and changing clinical priorities created substantial challenges for patient inclusion. Rik and the collaborating teams therefore used remote and digital procedures to maintain contact with participants and support study participation, while taking into account that some older patients with chronic anaemia experienced difficulties with these methods. Sustained coordination across centres ultimately enabled completion and publication of the studies included in this thesis.

Rik also contributed to education and scientific communication. He supervised a student who participated in the umbrella review and guided the student through the review process. He presented his research orally at meetings including International Society of Blood Transfusion (ISBT), Dutch Hematology Congress (DHC) and the Nederlandse Vereniging Voor Bloedtransfusie – TransfusieReacties In Patiënten (NVB-TRIP) symposium, and presented posters at EHA, ASH and NVB-TRIP – the latter at which Rik received the scientific poster prize. In addition, he participated in online meetings with transfusion experts to discuss emerging evidence, methodological developments and opportunities for collaboration in future international trials.

Overall, the trajectory shows a progression from working with existing data to independently developing and leading a clinically oriented research program. It also demonstrates increasing scientific independence, methodological expertise, collaborative capacity and responsibility for the organization and dissemination of multicenter research.

CRediT table for the thesis of drs. Rik Tonino



Ch.	Type*	Short Title	Conceptualization	Data Curation	Formal Analysis	Funding Acquisition	Investigation	Methodology	Project Administration	Resources	Software	Supervision	Validation	Visualization	Writing – Original Draft	Writing – Review & Editing	Preregistered	Preprinted	Published with Peer Review
1	Introduction	General introduction	■												■	■	☐	☐	☐
2	PhD project chapter	Umbrella review	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑
3	PhD project chapter	Red cell survey	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑
4	PhD project chapter	Acceptability pilot		■	■									■	■	■	☐	☐	☑
5	PhD project chapter	REMOTE pilot	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑
6	PhD project chapter	REMOTE 2	■	■	■	■	■	■	■	■	■		■	■	■	■	☐	☐	☑
7	PhD project chapter	Nosferatu	■	■	■	■	■	■	■	■	■		■	■	■	■	☐	☐	☑
8	PhD project chapter	Summary and discussion	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑

**PhD project chapters are the direct result of the PhD project of the PhD candidate.*
Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

Dissemination table - list of publications

Tonino RPB, Larimer K, Eissen O, Schipperus MR. Remote Patient Monitoring in Adults Receiving Transfusion or Infusion for Hematological Disorders Using the VitalPatch® and AccelerateIQ™ Monitoring System: Quantitative Feasibility Study.	
Chapter in this thesis	4
Conference contributions	• NVB-TRIP symposium 2019 – poster presentation awarded with scientific award. [*https://nvbtransfusie.nl/terugblik-op-het-symposium-2019/*] • NVB Consortium 2019 – Oral presentation [*https://nvbtransfusie.nl/cto-verslagen/*]
Preprint	https://preprints.jmir.org/preprint/15103/submitted
Publication in peer-reviewed journal	doi:10.2196/15103

Tonino RPB, Wilson M, Zwaginga JJ, Schipperus MR. Prevalence of iron deficiency and red blood cell transfusions in surgical patients.	
Chapter in this thesis	*Not included*
Publication in peer-reviewed journal	doi: 10.1111/vox.13194

Tonino RPB, Schipperus MR, Zwaginga JJ. Clinical practice for outpatients that are chronically red cell dependent: A survey in the Netherlands.	
Chapter in this thesis	3
Conference contributions	• NVB–TRIP Symposium 2021 – oral and poster presentation *[https://www.tripnet.nl/wp-content/uploads/2021/06/Poster-NVB-TRIP-Red-Survey.pdf* and *https://nvbtransfusie.nl/wp-content/uploads/NVB-TRIP2021-def-programma-voor-website-20210426.pdf]*
Publication in peer-reviewed journal	doi: 10.1111/vox.13220

Mateo E, Tonino RPB, Canto A, Monroy Noyola A, Miranda M, Soria JM, Garcia Esparza MA. The neurotoxic effect of ochratoxin-A on the hippocampal neurogenic niche of the adult mouse brain.	
Chapter in this thesis	*Not included*
Publication in peer-reviewed journal	doi: 10.3390/toxins14090624

Tonino RPB, Tweardy M, Wegerich S, Brouwer R, Zwaginga JJ, Schipperus MR. Remote monitoring of vital and activity parameters in chronic transfusion-dependent patients: A feasibility pilot using wearable biosensors.

Chapter in this thesis	5
Open study materials	Openbare onderzoeksregistratie, Nederlands register Onderzoek met Mensen: ReMoT, ID NL-OMON50160
Conference contributions	• ISBT 2023 – oral presentation [*https://www.isbtweb.org/static/e23245b0-7dbe-4bba-8da2251141bec83b/ISBT-Gothenburg-Programme-PDF-version-3.pdf*] • EHA 2021 – poster presentation [*https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325068/*]; • NVB-TRIP 2021 – oral presentation and poster presentation [*https://www.tripnet.nl/wp-content/uploads/2021/06/Poster-NVB-TRIP-Remote-Pilot*.pdf and *https://nvbtransfusie.nl/wp-content/uploads/NVB-TRIP2021-def-programma-voor-website-20210426.pdf*]
Preprint	preprints.jmir.org [ref: 30895]
Publication in peer-reviewed journal	doi: 10.1159/000526438

Tonino RPB, Zwaginga LM, Schipperus MR, Zwaginga JJ. Hemoglobin modulation affects physiology and patient-reported outcomes in anaemic and non-anaemic subjects: An umbrella review.

Chapter in this thesis	2
Open study materials	PROSPERO protocol registration: CRD42022299392
Conference contributions	ASH 2022 – poster presentation
Publication in peer-reviewed journal	doi: 10.3389/fphys.2023.1086839

Tonino RPB, Schipperus MR, Zwaginga JJ. Toward personalized transfusion strategies: The emerging role of wearable biosensors in chronic anaemia management.

Chapter in this thesis	8
Conference contributions	• EHA 2022 – Poster presentation [*https://library.ehaweb.org/eha/2022/eha2022-congress/358487/*] • NVB consortium 2022 – oral presentation [*https://nvbtransfusie.nl/cto-verslagen/*]
Publication in peer-reviewed journal	doi: 10.1016/j.tmrv.2025.150927

Tonino RPB, Schipperus MR, Hardi L, Tiren-Verbeet NL, Brouwer RE, Zwaginga JJ. Heart rate changes in chronically red cell transfusion-dependent patients - A dose-dependent effect of red cell transfusion: A randomized crossover trial, interim analysis.

Chapter in this thesis	7
Open study materials	Openbare onderzoeksregistratie, Nederlands register Onderzoek met Mensen ID NL-OMON52859 / NL9289 [*https://onderzoekmetmensen.nl/nl/node/52859/pdf*]
Conference contributions	• ISBT 2023 – oral presentation [*https://www.isbtweb.org/static/e23245b0-7dbe-4bba-8da2251141bec83b/ISBT-Gothenburg-Programme-PDF-version-3.pdf*] • NVB consortium 2022 – oral presentation [*https://nvbtransfusie.nl/cto-verslagen/*]
Publication in peer-reviewed journal	doi: 10.1111/trf.70023

Tonino RPB, Huis in 't Veld EMJ, Schipperus MR, Zwaginga JJ. Heart rate changes after phlebotomy in polycythaemia vera and healthy donors: An observational case-crossover pilot study.

Chapter in this thesis	6
Open study materials	ClinicalTrials.gov: NCT05396170
Publication in peer-reviewed journal	doi: 10.1111/tme.70038

Completed courses and other training

Mandatory activities		
Month/year	*Title*	*Hours*
05/2019	Leiden University Onboarding Programme Inform & Connect (2 activities)	5
04/2019	Responsible Research (2 activities)	42
09/2019	Basic Methods and Reasoning in Biostatistics	42
Scientific courses, workshops and other training activities		
06/2019	Analysis of repeated measurements	42
09-12/2020	Rothman Course	72
11/2020	Using R for data analysis	28
03-06/2021	Causal inference	84
04/2021	Meta-analysis	24
06/2021	Regression analysis	42
11/2021	Klinische epidemiologie op Schiermonnikoog	56
Transferable skill courses, workshops and other training activities		
10/2020	Speedreading	14
11/2021	Academic Writing for PhDs	56
11/2021	Effective communication: How to build effective work relationships	6
11/2020	Presenting skills	14
11-12/2021	Qualitative interviewing	30

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Curriculum Vitae

Rik Tonino was born on 2 October 1990 in Breda, the Netherlands. He completed bilingual (Dutch–English) VWO at Mencia de Mendoza Lyceum in Breda. He subsequently moved to Leiden to study medicine at Leiden University Medical Center. During his medical studies, he also spent one year studying at the conservatoire in The Hague.

After obtaining his medical degree, Rik worked as a physician in internal medicine at Alrijne Hospital in Leiderdorp followed by the Department of Hematology at Haga Teaching Hospital. During this period, he met dr. Martin Schipperus, under whose supervision he began the PhD research presented in this thesis.

During his PhD trajectory, he completed a broad doctoral training programme. This included mandatory training in responsible research conduct and biostatistics, as well as advanced courses in repeated-measures analysis, causal inference, meta-analysis and regression analysis. He also undertook training in academic writing, scientific presentation, effective communication and qualitative interviewing.

In 2023, Rik started his residency in internal medicine at Groene Hart Hospital in Gouda and Leiden University Medical Center. He currently lives in Rijswijk with his partner, Carlijn, and their two daughters, Linde and Filou.

