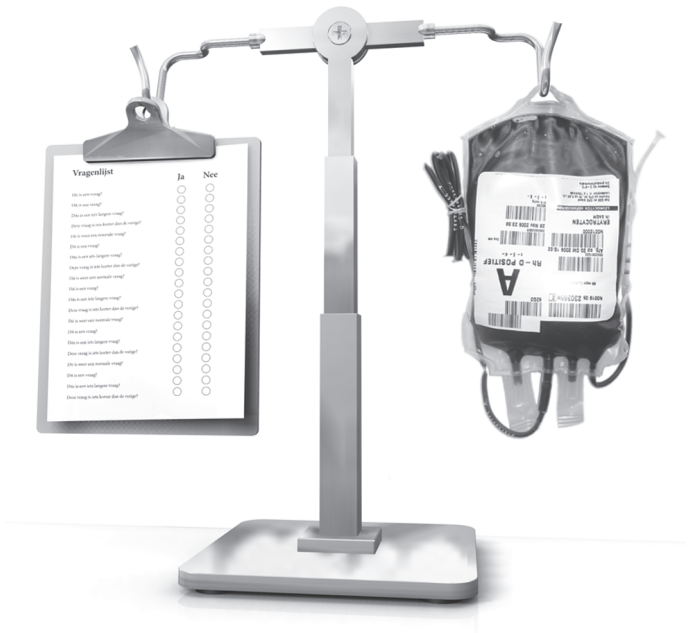
Evidence based studies in clinical transfusion medicine

GERARD JANSEN



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Aan mijn ouders

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CHAPTER 1

General introduction

INTRODUCTION

History of blood transfusion

The first blood transfusion was prescribed during the Middle Ages, in 1492, to Pope Innocent VIII. The pope, as well as the three 10-year old boys who donated the blood, died during, or shortly after the procedure.[1] Throughout this period blood transfusion was freely recommended to remedy a variety of ailments, such as ill health, insanity, depressions, manias, but not for blood loss or anemia. Inevitably, transfusion to human beings led to more and more fatal side effects, thereby leading to its outlaw in many countries. For example, Pope Innocent XI banned blood transfusion in 1679 for the Catholics. In 1825, the London obstetrician James Blundell undertook the first human-to-human transfusion to replace lost blood.[2] Two important rules of Blundell remain important in clinical transfusion medicine today: 1) a human blood donor is only suited for a human recipient, and 2) blood transfusion is only indicated to compensate blood loss.[2,3] After the discovery of the erythrocyte blood groups, like the ABO blood group and the Rhesus blood group, the results of blood transfusions improved greatly.[4-6] Despite the increasing utility of blood transfusion, it is interesting to note the relative lack of controlled clinical studies of transfusion of blood and derivatives until the last 10-15 years. Since the 1980's, focus has been set on the appropriate clinical use and application of human blood and blood preparations and on the overall safety of transfusion.

Component therapy

At one time, all blood transfusions were collected and given as whole blood. During the 1960's component therapy became possible after introduction of the centrifugation technique. Whole blood units could then be divided into buffycoats, used for the preparation of platelet concentrates, red blood cell (RBC) concentrates and plasma units. This chapter will focus on platelet and RBC transfusion.

Platelet transfusion

Platelet transfusions are indicated to control or prevent bleeding in patients with thrombocytopenia or platelet dysfunction. In particular, supportive and prophylactic platelet transfusions have reduced mortality and hemorrhagic complications in patients with acute leukemia.[7-10] The recent surge in hematologic treatment options (e.g. stem cell transplantation) has lead to an increase in the use of platelet transfusions. However, time limited storage concerns and the ongoing need to recruit donors to maintain the fresh availability of the supply remain a worldwide challenge. This had led to increased efforts in evidence based research on the collection, preservation and use of platelet concentrates to solve the logistic problems of the supply.

RBC transfusion

The generally accepted reason for transfusing RBC is to increase the circulating RBC mass as a means to improve oxygen supply to the tissues.[11] Patients with chronic and acute anemia are treated with RBC transfusions instead of whole blood to avoid the risk of circulatory overload.[12,13] Despite the development of several techniques to reduce blood loss, RBC transfusion remains the cornerstone in the treatment of chronic and acute anemia. The easy availability and the seemingly safe use of blood and blood components in developed countries have even resulted in a liberal use of blood transfusions in clinical practice.

Transfusion triggers

Platelet transfusion

The threshold for prophylactic platelet transfusions is based on the platelet count of the patient (Table 1). Serious spontaneous hemorrhage in clinically stable patients may not occur with a platelet count of $\geq 10 \times 10^9$/L.[14-19]

The efficacy of platelet transfusions is difficult to measure in routine clinical practice. Various methods have been investigated that predict in vivo survival from in vitro characteristics. These methods are of some value in the quality control of the platelet products,

Table 1. Recommended platelet count in adults[20]

$\geq 10 \times 10^9$/L	Bone marrow depression by – Leukemia – Infiltration tumor cells – Drugs – Chemotherapy
$\geq 40 \times 10^9$/L	– Before antithymocyte globulins – During treatment with heparin (therapeutic) or Low-molecular weight heparin – Gastroscopy, colonoscopy, rectumscopy, with or without biopsy – Bronchoscopy without biopsy, with or without bronchoalveolar lavage – Punction (ascites, pleural, and lumbar) – Removing central-venous catheter – Breathing – Surgical interventions other than mentioned above
$\geq 60 \times 10^9$/L	– Biopsy (liver, renal, lung biopsy and biopsy during bronchoscopy) – Tooth extraction – Placement of central venous catheter (Hickman-, subclavian catheter, etc.) – Sinus lavage in Ear-Nose-Throat area
$\geq 100 \times 10^9$/L	– Neurosurgery – Cardio-pulmonary surgery – Intracranial surgery

but cannot predict in vivo survival. This is caused by patient factors as splenomegaly, alloimmunization, sepsis and disseminated intravascular coagulation. In vivo measurement e.g. direct measurement of platelet survival with for example ^{51}Cr or ^{111}In, is not possible.[21,22] Two indirect methods have been developed to assess the effect of platelet transfusion: the one hour Corrected Count Increment (CCI) and the platelet recovery method:

$$CCI = \frac{\text{Post- pre platelet count } (\times 10^9/L) \times \text{Body surface area of the patient } (m^2)}{\text{Number of platelets transfused } (\times 10^{11})}$$

$$\text{Recovery } (\%) = 100 \times \frac{\text{Absolute platelet increment } (\times 10^9/L) \times \text{Blood volume } (L)}{\text{Number of platelets transfused } (\times 10^{11})}$$

A CCI of $>7.5 \times 10^9$/L at 1 hour and $>2.5 \times 10^9$/L at 16-24 hours is considered successful.[23] A CCI of $<7.5 \times 10^9$/L at 1 hour is likely to be due to an immunological cause. A normal 1-hour CCI followed by a worse CCI after 16-24 hours may be due to a non-immunological cause. The recovery should theoretically be about 67% in a stable patient, but the minimum recovery to define a successful transfusion is considered as >20% at 1 hour post transfusion and >10% at 20-24 hours. In clinical practice, the successfulness of a platelet transfusion is usually affected by several factors including damage to platelets in vitro and clinical variables in the patient.

RBC transfusion

As mentioned earlier, the generally accepted RBC transfusion goal is to increase the circulating RBC mass to improve oxygen delivery at the tissue level. To compensate for the reduced capacity of the blood to carry oxygen in a patient with chronic anemia the body reacts with 1) an increase in cardiac output, 2) a redistribution of blood flow and 3) an increase in the 2,3-DPG content of the red blood cells, which causes a shift to the right in the oxygen dissociation curve, so that at a given degree of oxygen saturation of Hb, oxygen is more readily given up to the tissues.[24,25] Clinically this process manifests in a variety of ways. Clinical symptoms of anemia are classified as compensated (palpitations, dizziness, tachycardia), mild (weakness, sweating, tachycardia), moderate (restlessness, pallor, oliguria) and severe (collapse, air hunger, anuria) (Table 2).[26,27]

Friedman was the first to introduce the term 'transfusion trigger', to describe the moment when blood transfusion is clinically indicated and should be prescribed.[28] Although a Consensus Conference in 1988 emphasized the folly of relying on a single hemoglobin (Hb) value as an indication for transfusion, the Hb level currently remains the most important parameter in the decision to prescribe RBC transfusions.[29-32] The most frequent

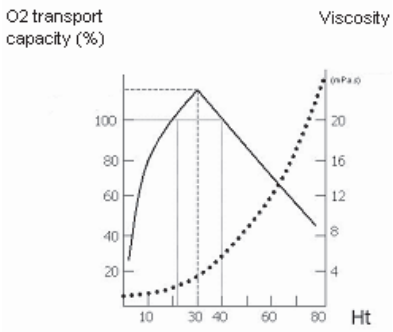
Table 2. Symptoms of blood loss[27]

Blood loss	Blood pressure	Symptoms and Signs	Degree of shock
10% - 15% (500 – 1000 mL)	Normal	Palpitations, dizziness, tachycardia	Compensated
15% - 25% (1000 – 1500 mL)	Slight fall	Weakness, sweating, tachycardia	Mild
25% - 35% (1500 – 2000 mL)	70 – 80 mm Hg	Restlessness, pallor, oliguria	Moderate
35% - 45% (2000 – 3000 mL)	50 – 70 mm Hg	Collapse, air hunger, anuria	Severe

Hb transfusion trigger used is a Hb value of 5.0 mmol/l. This value is described in figure 1. This level is generally used as the cardiac output does not substantially increase until the Hb concentration falls to about 4.4 mmol/l. In addition, some authors suggest that Hb values below 5.0 mmol/l may lead to a worse haemostasis (e.g. a lower platelet adhesion capacity and a higher velocity).[30,33-37] The possible risks of RBC transfusion, described in the next paragraph, have caused a reconsideration of transfusion policies in a number of clinical fields.[38-40] Some authors have introduced a more restrictive transfusion policy by lowering the Hb transfusion trigger. In these studies no cardiovascular events occurred in stable patients when more restrictive transfusion trigger values were used.[41-43] However, in elderly patients with acute myocardial infarction a higher Hb transfusion trigger of 6.0 mmol/l is recommended.[44]

Recently, an international working group reviewed currently used response definitions of patients with chronic anemia (Myelodysplastic Syndromes (MDS)) and developed a uniform set of guidelines for future therapy and clinical trials.[45] While RBC transfusions are the cornerstone in the treatment for MDS patients, treatment should be aimed at reduction of morbidity associated with cytopenias. The group especially emphasized the

Figure 1. Hb dissociation curve



goal of improving the health related quality of life (HRQoL) of the blood transfusion recipients.

Health-related quality of life

The term HRQoL was introduced in the literature in 1967 for patients with chronic hemodialysis.[46] Since that time, this subject has become more widely applied in clinical medicine, especially in patients with oncologic malignancies.

The HRQoL encompasses physical, psychological and social domains of health. Conceptually, HRQoL domains can be measured in terms of 'objective' functioning (what the patient is able to do) and, complementary, in the patients' subjective evaluation thereof. HRQoL is measured using questionnaires. Generally, there are three types of HRQoL measures:

1) generic measures, intended for use both in general population surveys and in studies of patients with diverse health conditions, allowing for comparison of HRQoL scores across disease stages and diagnostic groups;
2) condition-specific measures, developed for use among specific patient population (e.g. cancer, diabetes); and
3) domain-specific measures, for measurement of specific symptoms (e.g. fatigue, pain).

It is common practice to combine condition-specific and/or domain-specific measures with generic measures. The feasibility and other psychometric properties of HRQoL measures, however, may differ between populations.

HRQoL can only be partly explained by clinical variables.[47] Still, patient-reported outcomes, including HRQoL, have increasingly been incorporated in the evaluation of medical interventions. For example, many physical diseases, in particular chronic diseases such as cancer, multiple sclerosis, arthritis, renal disease, and HIV infection are associated with fatigue.[48-52] Currently evidence supports the value of anemia management as a contributor to improving patient's HRQoL by reducing fatigue in cancer patients receiving chemotherapy.[53-57] However, the relationship between fatigue and different Hb values has not yet been investigated.

Risks of blood transfusions

Since the nineties guidelines and directives from National and European health authorities have required hospitals to institute a hemovigilance system. The objective of this hemovigilance system is to collect and assess information concerning unexpected and undesirable effects arising from the therapeutic use of labile blood products, and to

prevent the recurrence of such incidents. Results of the systems in France, the Netherlands (Transfusie Reacties In Patiënten; TRIP) and the UK ('Serious Hazards Of Transfusions'; SHOT) have shown a transfusion complication rate of 0.1 – 2.3 per 1000 blood products administered.[58-60] The real incidence is probably higher because many incidents go unrecognized and/or unreported.

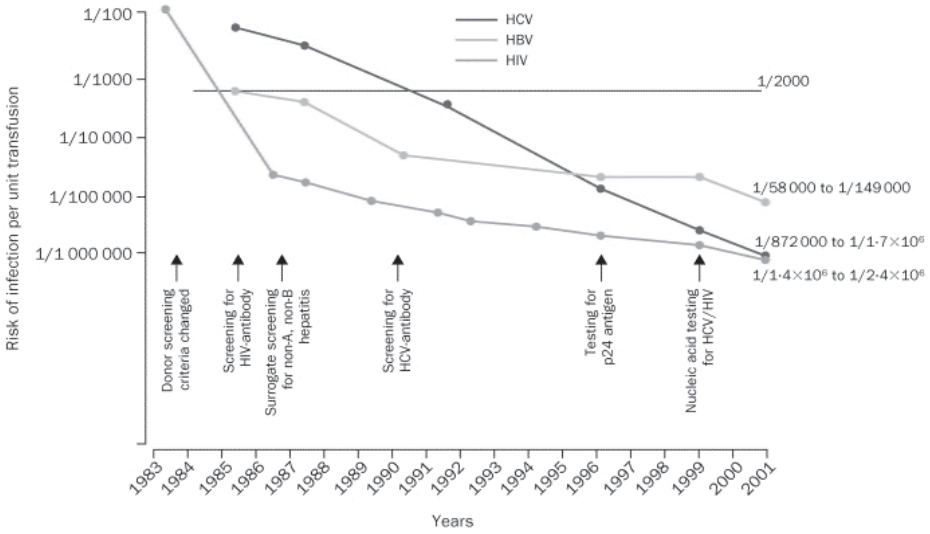
Complications of blood transfusions, however rare, can be divided into non-infectious and infectious complications. Non-infectious complications represent approximately 99% of the reported incidents. They can be divided into:

1) incorrect blood component ('wrong blood') transfused;
2) acute transfusion reaction;
3) delayed transfusion reaction;
4) transfusion-associated graft-versus-host-disease;
5) transfusion-related acute lung injury (TRALI);
6) post-transfusion purpura (thrombocytopenia arising 5-12 days following transfusion of RBC associated with the presence of antibodies directed against the HPA (Human Platelet Antigen) systems); and
7) formation of RBC alloantibodies.

Patients exposed to foreign antigens on platelets may develop alloantibodies that cause alloimmunization resulting in platelet refractoriness. Alloimmunization is most often due to patient antibodies against donor HLA class I antigens present on the leukocyte and platelet surface. Multitransfused patients have a risk varying from 12-22% to develop RBC alloantibodies.[61-64] Various studies have showed that 17-30% of primary detected RBC alloantibodies were caused by RBC transfusion.[65,66] Recently, the complication TRALI has become more prominent in clinical medicine.[67] Increased understanding of the pathology and an enhanced awareness of this complication by physicians has significantly increased the overall reporting of TRALI. Currently it is the third most reported transfusion complication.[68]

Infectious complications include transfusion-transmitted infections caused by bacterial, viral, prion, fungal, and parasitic infections. Although rare, infectious complications, especially bacteria-associated transfusion reactions, are identified as the most frequent cause of death in transfusion incidents. The onset of symptoms related to a transfusion-transmitted viral infection may occur from several weeks to years after the transfusion. The most common transfusion-associated viral infections include Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human T-cell Lymphotropic Virus (HTLV), Cytomegalo Virus (CMV), Epstein Barr Virus (EBV), Parvovirus B19, and lately in the US West Nile Virus.[69] For-

Figure 2. Risks of transfusion-related transmission of HIV, HBV and HCV in the USA[71]



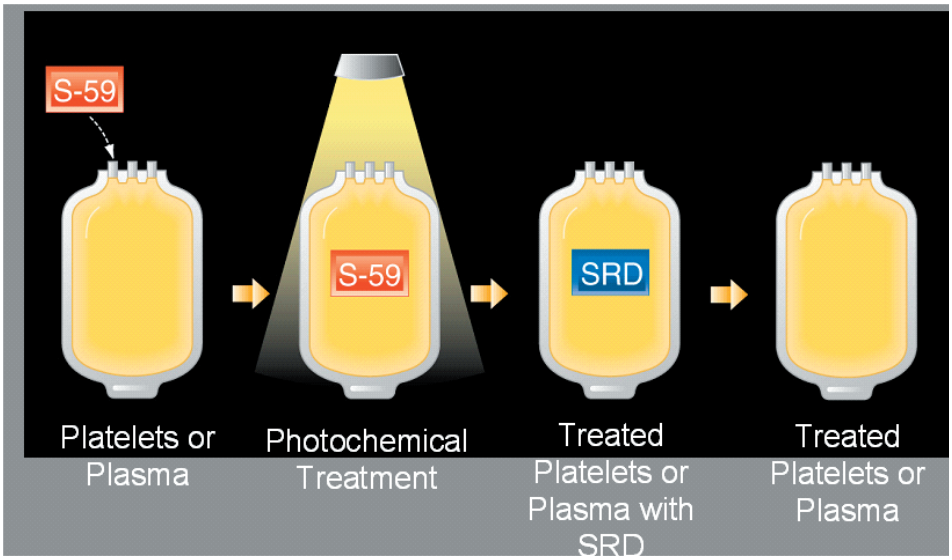
tunately, the incidence of transfusion-related transmission of HIV, HBV and HCV has decreased significantly after the introduction of several screening techniques (Figure 2). However, more recently, there has been a reported increase in parasitic infections like Trypanosoma Cruzi, especially in the southern states of the US and in Spain.[70]

Platelet transfusions and bacterial contamination

Currently the most frequent complication of platelet transfusion is bacterial contamination of the platelet products. Platelet concentrates are stored at room temperature for a maximum period of 5 to 7 days. These conditions increase the risk of bacterial contamination.[72,73] Recently a photochemical treatment (PCT) process using the psoralen compound amotosalen HCL (S59) and long wavelength ultraviolet (UVA) light was developed for inactivation of infectious pathogens and leukocytes (Figure 3).[74-76] PCT with S59 and UVA is a nucleic-acid-specific inactivation process with a broad spectrum of activity against bacteria, viruses, protozoa and leucocytes. S59 reversibly binds to DNA or RNA. By illumination, this binding becomes irreversible. Thus bacteria, viruses and protozoa are unable to replicate. The integral S59 Reduction Device (SRD) removes the residual S59 and free photoproducts.

Platelet components prepared with PCT offer the potential to further improve the safety of platelet transfusion using technology compatible with current buffy coat platelet components preparation methods.[77,78] However, for RBC transfusions pathogen inactivation techniques are not yet available for clinical use.

Figure 3. Photochemical treatment technique



Scope of this thesis

Clinical blood transfusion practice is a lengthy, interrelated chain, from donor to recipient with different links, which historically have improved at varying rates. The necessity of blood transfusion for chronically ill patients coupled with the grave potential for complication demands the introduction of more evidence-based studies in clinical transfusion medicine. This overview describes the application of evidence-based studies in clinical blood transfusion medicine. Improvement can be attained by the improvement of the actual blood and blood products as well as overall advancements in the practice of clinical blood transfusions.

In chapter 2, a new technique to increase the safety of platelet concentrates, e.g. a photochemical treatment (PCT) for inactivation of infectious pathogens and WBCs, is introduced. The effect of PCT on the functional characteristics of the platelets was evaluated in vitro. Chapter 3 compares the effects of a restrictive RBC transfusion therapy with those of a more liberal one for clinical patients treated with intensive chemotherapy for acute myeloid leukemia. This study was done retrospectively. Therefore, the effect on the health-related quality of life (HRQoL) of the patients could not be measured. A cross-sectional pilot study performed for psychometric evaluation of three internationally established HRQoL measures in patients with chronic anemia, and for investigation of the association between the severity of chronic anemia and HRQoL is described in chapter 4. Chapter 5 describes these HRQoL measures when evaluated in patients with acute anemia. Fatigue and HRQoL were investigated in women after vaginal delivery,

elective, and emergency caesarean section (CS) and their relationship with postpartum Hb levels. Characteristics of these HRQoL measures in patients after delivery are shown in chapter 6. Finally, in chapter 7, the results are discussed, summarized and suggestions for further research are made. A proposal for a new RBC transfusion model for patients with anemia is described. Special attention is given to the WOMB study. This is a prospective multicenter randomized clinical trial, which was developed to measure the role of RBC transfusion in the treatment of women with postpartum hemorrhage and the effects of RBC transfusion on HRQoL of this patient group. While this study is still ongoing, the design and some interim results are described in chapter 7.

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CHAPTER 2

Functional characteristics of photochemically treated platelets

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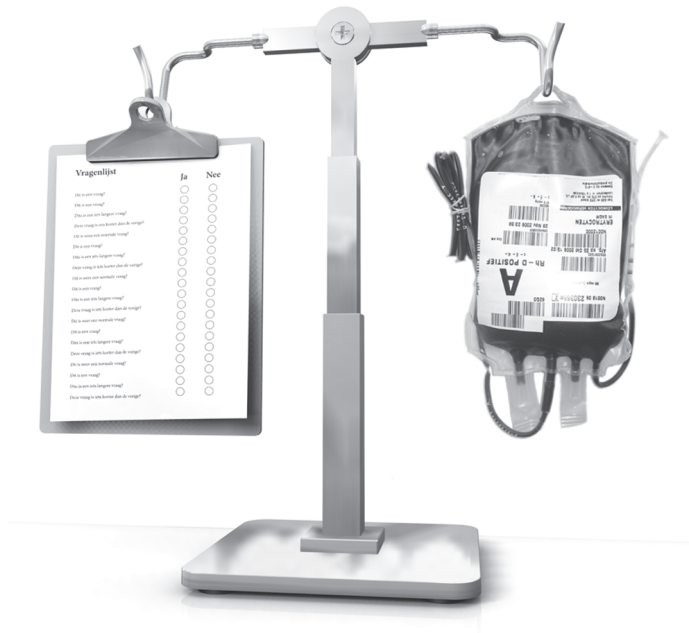

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ABSTRACT

Background: A photochemical treatment (PCT) process using the psoralen compound amotosalen HCL (S59) and long wavelength UVA light was developed for inactivation of infectious pathogens and WBCs. In this study the effect of PCT on functional characteristics of the platelets was evaluated in vitro.

Study design and methods: Platelet concentrates were treated photochemically using the experimental clinical processing system T-bag S59 Reduction Device (SRD) (n=4) or the commercially available integral processing system Wafer SRD (n=4) and compared with control platelet concentrates in plasma/PAS III alone (n=4). The evaluation included variables with respect to the overall quality of the product (e.g. HSR, pH), the function (aggregation and activation tests), apoptosis (annexin V and caspase 3), and lysis.

Results: No differences were found in the product quality variables, in P-selectin expression, and the apoptosis variables. PCT using the T-bag SRD led to a significant decrease in aggregation capacity with collagen and thrombin and a significant increase in plasma LDH, whereas no differences for the Wafer SRD were found.

Conclusion: PCT using the experimental T-bag SRD led to a significant decrease in platelet function. However the commercially available Wafer SRD had only minor in vitro effects on the quality of the platelets.

INTRODUCTION

Platelet concentrates (PCs) are predominantly used for the treatment of thrombocytopenic patients or patients with platelet dysfunction. There are many controversies that surround platelet-transfusion practices today.[1,2] Platelet transfusions are associated with a number of adverse events, like fever, bacteremia, exanthema and, rarely, GVHD.

A photochemical treatment (PCT) method, which utilizes the psoralen (S-59) and long wavelength ultraviolet light, has been developed to inactivate infectious pathogens and WBCs in PCs (Cerus Corporation, Concord, CA, and Baxter Healthcare Corporation, Deerfield, IL).[3-6] A recent study of van Rhenen et al. assessed the application of PCT, using the experimental T-bag S59 Reduction Device (SRD), to platelets prepared from pooled buffy coats.[7] The PCT process resulted in compatible in vitro overall quality variables of the PCs for up to 7 days of storage. However, PCT using the experimental T-bag SRD led to a significant increase of lysis after 5 days of storage. The effect of PCT on functional characteristics of the platelets was not investigated.

In the current study, the effects of PCT platelets using the experimental T-bag SRD and the commercially available Wafer SRD on overall quality variables, apoptosis, lysis, and functional characteristics were compared to platelets in plasma/PAS III.

MATERIALS AND METHODS

Preparation of the buffy coats

Blood units of 500 ml ± 10 percent were collected from volunteer donors in 70 mL CPD anticoagulant solution using triple Optipac (Baxter Healthcare). Selection of donors and the blood-donation procedure were based on local standard practices. The whole blood units were kept overnight (16-20 hr) at room temperature (20 ± 2°C). High-speed centrifugation was applied to separate cellular components from plasma (Sorvall RC3C/RC3bp Sorvall, Newtown, CT). Buffy coats (volume 55 ± 5 mL, Hct 0.50 ± 0.05 percent, and a rest volume of 3 mL plasma) were separated from plasma and RBCs using the Optipress II standard procedure.

Preparation of the pooled buffy coats

Using a sterile docking device SCD 312 (Terumo, Japan), 15 AB0-identical buffy coats were pooled in a 1.3-L PL 2410 plastic container. After thorough mixing, the pool was divided into three equal volumes with the size of the pool set GURX 67b. To each of the

three pooling bags 280 ml PAS III (Intersol) was added to reduce the plasma concentration to 30 to 45 percent for optimal PCT performance.

Preparation of the leukoreduced buffy-coat derived PCs

Slow speed centrifugation (655 × *g*, 5 min) was applied to separate RBCs and WBCs from the five buffy coat ABO Rh identical platelet-rich plasma-PAS III solution (Sorvall RC3). Leukoreduced PCs were prepared by manual filtration of the platelet-rich plasma-PAS III through a PLX 5 Asahi filter following standard blood-bank procedures. The control PC (Study Group 1) was stored in a final PL 2410 1.3-L platelet storage bag.

Preparation of the PCT buffy-coat derived PCs

Using a sterile docking device TSCD (Terumo, Japan) two of the three leukoreduced PCs were docked to PCT train (GURX 68b). S59 was added to the PCs in a special (pl2410) illumination container. PCs were exposed to UVA (320-400 nm, 3 J/cm^2) with constant agitation (60 cycles/min).

The S59-treated PCs were transferred to the S59 Reduction Device (SRD) to remove the excess of S59 and photo products from the PCs. Two different SRD were used: the experimental clinical processing system T-bag SRD, which is used in previous in vitro and in vivo studies, [7,8] and the commercially available integral processing system Wafer SRD.[9] The T-bag SRD contains 2.5 ± 0.1 g of absorptive beads enclosed in a polyester poach. The Wafer SRD is a solid-phase, waferlike structure with the same concentration of beads. The SRD treatment was done overnight for 16 hours at 20 ± 2°C with constant agitation (60 cycles/min) in a platelet storage climate cupboard.

Platelet storage

After SRD treatment (Study Groups 2 and 3), the PCs were transferred into a final 1.3-L PL2410 plastic bag. The PCs were stored for up to 11 days from collection, with constant agitation (60 cycles/min) at 20 ± 2°C in a platelet storage climate cupboard.

Day 0 was the day of collection, and Day 1 was the day of processing. Day 2 was the first day of testing in this study.

Study groups

Because the products were pooled, a maximum of three different pooled products was possible. The T-bag SRD was used experimentally and the new Wafer SRD is now commercially available. PCT was only available in a PAS III/plasma solution. Therefore, PC in PAS III/plasma functioned as control. The three study groups were 1) PC in plasma/PAS III; 2) PC in plasma/PAS III, PCT, 16-hour SRD using the experimental T-bag; and 3) PC in plasma/PAS III, PCT, 16-hour SRD using the commercially available Wafer.

Overall quality variables

Platelet aliquots were drawn under sterile conditions on storage Day 2, 4, 7, 9 and 11. Haematological variables were measured electronically (Cell Dyn 3500, Abbott Laboratories, Chicago, IL). Hct level, pH, pool volume, plasma volume, and volume of RBCs were measured starting on Day 2. Blood gases and bicarbonate were analyzed with a blood gas system (238 pH Blood Gas System, Ciba, Corning, UK).
Glucose concentration and lactate concentration were measured in a commercial analyzer (Dimension Chemistry Analyzer, Dupont, Wilmington, DE).

Functional characteristics

For estimation of platelet activation, P-selectin expression was measured by two-color labeling by flow cytometry (FACScan, Becton & Dickinson, San Jose, CA). FITC labeling of platelets was performed with anti-CD42a (Becton & Dickinson). P-selectin expression was determined using PE-labeled anti-CD62P (Becton & Dickinson).
Hypotonic shock response (HSR) was measured as described by Holme et al.[9] Measurements were performed on a spectrophotometer (LKB, Ultrospect II, Cambridge, UK).

Platelet aggregation was studied by aggregometry (Chrono-Log Whole Blood Aggregometer 540 VS, Chrono-Log, Havertown, PA). Aggregation tests were performed on Day 2, 4, 7, and 9. Platelet samples were diluted with Group 0 positive plasma to a platelet count of 200×10^9/L and incubated at room temperature for 2 hours before testing. Agonists were added to the samples to achieve final concentrations as follows: ADP, 10 μM; epinephrine, 0.1 μM; collagen 5 μg per mL; thrombin, 1 U per mL. ATP secretion was also measured according to the instructions of the manufacturer (Chrono-Log, Havertown, PA).

Apoptosis and lysis

The externalization of phosphatidylserine, which is a late result of apoptosis, was measured with Annexin V (BioVision, Kordia Life Sciences, Leiden, The Netherlands).[11-13] Caspase 3, a cysteinyl protease, plays a central role in the early apoptosis pathway. Its activity was measured with D_2R (Alexis Biochemicals, Kordia Life Sciences, Leiden, The Netherlands).[14] Apoptosis was measured on Day 2, 4, 7, 9, and 11. Diluted platelet suspension (50 μL) were incubated with 5 μL of fluorescein-labeled Annexin V or 1 μL D_2R in the dark at room temperature.

Lysis was determined by measurement of the LDH concentration in the supernatant of the platelet suspension, using enzyme assay (Roche Diagnostics GmbH, Mannheim, Germany), following the standard procedure on Day 2, 4, 7, 9, and 11.

Statistical analysis

All tests were performed in quadruplicate. In vitro data were expressed as the arithmetic mean ± SD. All data were analyzed paired T-test to determine significant differences between the three groups of PC treatments. An alpha of 0.017 and a beta of 0.80 were used. Differences were considered significant when p was less than 0.017. Because of the small sample size of four, detectable differences were 3 SDs or more. Analysis was performed in SPSS 10.0 for Windows.

RESULTS

Overall quality variables

No significant differences were found for pool volume, Hct level, plasma volume and volume of RBCs (Table 1) between the three study arms. Platelet concentration was significantly higher after PCT treatment using Wafer SRD compared to control platelets in plasma/PAS III, due to the higher plasma concentration after PCT treatment using Wafer SRD. No significant difference in platelet concentration or loss over time was found when using PCT with the experimental T-bag SRD or the commercially available Wafer SRD (Table 2). All platelet products met the PCT target range requirements.[7]

After PCT, platelets were compared to untreated control platelets during 7 days of storage. No differences were found for pO_2 or pCO_2 between the three study arms. Although well maintained, pH and HCO_3^- were significantly lower after PCT. At Day 7, the pH in all groups was higher than 6.8, and the HCO_3^- was higher than 4 mmol/L, providing adequate buffering of the PCs. No significant differences were found for glucose, lactate, ATP concentration, and HSR between the three study arms. A significant but small increase in mean platelet volume was found after PCT with the experimental T-bag SRD and the commercially available Wafer SRD (Table 2).

Table 1. Buffy-coat pool characteristics (mean ± SD)

Study arm	Pool volume (mL)	Hct (L/L)	Volume of RBCs (mL)	Platelet concentration (10^9/L)	Plasma volume (mL)
PAS III	563.7 (6.7)	0.57 (0.03)	147.4 (13.0)	304.3 (20.7)	136.3 (6.6)
PAS III, PCT, T-bag SRD	562.0 (7.0)	0.57 (0.04)	139.8 (3.3)	315.1 (10.0)	142.4 (9.9)
PAS III, PCT, Wafer SRD	559.9 (3.7)	0.60 (0.01)	132.8 (2.3)	336.9 (4.2)*	147.1 (1.4)

*p<0.017 compared to PAS III, PCT, T-bag SRD

Table 2. Overall quality variables

	Number	Day 2 (mean ± SD)	Day 4 (mean ± SD)	Day 7 (mean ± SD)
Platelet concentration (x10^9/L)				
PAS III	4	1302.3 ± 230.2	1260.5 ± 203.2	1258.3 ± 223.0
PAS III, PCT, T-bag SRD	4	1254.5 ± 84.8	1223.5 ± 79.8**	1218.3 ± 80.7
PAS III, PCT, Wafer SRD	4	1330.5 ± 120.7	1323.8 ± 101.0	1292.3 ± 87.7
PO_2 (mm Hg)				
PAS III	4	101.5 ± 15.0	69.3 ± 27.8	77.3 ± 26.4
PAS III, PCT, T-bag SRD	4	98.5 ± 18.7	76.5 ± 3.9	88.0 ± 5.1
PAS III, PCT, Wafer SRD	4	95.5 ± 22.0	63.5 ±7.9	75.8 ± 9.7
pCO_2 (mm Hg)				
PAS III	4	35.3 ± 5.7	26.7 ± 4.0	23.5 ± 4.5
PAS III, PCT, T-bag SRD	4	35.3 ± 2.4**	25.8 ± 0.5	23.3 ± 0.5
PAS III, PCT, Wafer SRD	4	39.8 ± 3.0	28.3 ± 1.7	26.0 ± 1.8
pH				
PAS III (N=4)	4	7.06 ± 0.03	7.06 ± 0.05	7.0 ± 0.02
PAS III, PCT, T-bag SRD	4	7.03 ± 0.01**	7.06 ± 0.02**	7.0 ± 0.01**
PAS III, PCT, Wafer SRD	4	6.94 ± 0.06*	6.97 ± 0.01*	6.9 ± 0.01*
HCO_3^- (mmol/L)				
PAS III	4	10.1 ± 0.5	9.1 ± 1.0	7.1 ± 0.4
PAS III, PCT, T-bag SRD	4	9.4 ± 0.3**	8.9 ± 0.3**	7.1 ± 0.2
PAS III, PCT, Wafer SRD	4	7.8 ± 0.1*	7.3 ± 0.2	5.5 ± 0.2*
Glucose (mmol/L)				
PAS III	4	8.0 ± 0.4	6.3± 0.4	2.7 ± 0.2
PAS III, PCT, T-bag SRD	4	8.0 ± 0.3	6.4 ± 0.3	3.2 ± 0.4**
PAS III, PCT, Wafer SRD	4	7.8 ± 0.2	6.2 ± 0.2	2.6 ± 0.3
Lactate (mmol/L)				
PAS III	4	6.5 ± 0.8	9.9 ± 0.7	16.1 ± 0.6
PAS III, PCT, T-bag SRD	4	5.9 ± 0.5	8.8 ± 0.6	14.3 ± 0.6*
PAS III, PCT, Wafer SRD	4	6.0 ± 0.6	8.9 ± 0.6*	14.6 ± 0.5*
ATP (µmol/10^{11} platelets)				
PAS III	4	3.1 ± 0.5	3.7 ± 0.6	2.8 ± 0.5
PAS III, PCT, T-bag SRD	4	3.3 ± 0.8	3.3 ± 0.5	2.9 ± 0.3**
PAS III, PCT, Wafer SRD	4	3.5 ± 0.5	3.6 ± 0.4	3.4 ± 0.5*
Hypotonic shock response (%)				
PAS III	4	66.8 ± 4.0	61.5 ± 4.2	62.8 ± 3.3
PAS III, PCT, T-bag SRD	4	65.0 ± 2.7	65.0 ± 1.4	66.3 ± 5.6
PAS III, PCT, Wafer SRD	4	61.3 ± 4.9	63.3 ± 5.4	63.0 ± 2.9
Mean platelet volume (fL)				
PAS III	4	7.4 ± 0.3	7.3 ± 0.3	7.5 ± 0.5
PAS III, PCT, T-bag SRD	4	7.9 ± 0.4	7.9 ± 0.3	8.0 ± 0.2**
PAS III, PCT, Wafer SRD	4	7.8 ± 0.4	8.0 ± 0.1*	8.3 ± 0.3*

*$p<0.017$ compared to PAS III

**$p<0.017$ compared to PAS III, PCT, Wafer SRD

Functional characteristics

PCT platelets using the experimental T-bag SRD demonstrated significantly less aggregation on Day 2 than control platelets with collagen as agonist. With thrombin as agonist, significantly less aggregation was found on Day 4. Although not significant, a decrease in aggregation was also seen for PCT platelets using the Wafer SRD. A significant decrease of aggregation in time was seen in the three study groups for collagen and thrombin during storage. The ADP aggregation was strongly reduced for all groups starting from Day 2 (Fig. 1A-C), which is according to earlier studies.[10] No decrease was seen in ADP aggregation during storage of platelets, and no differences were seen between the three study groups.

Figure 1a. Collagen aggregation

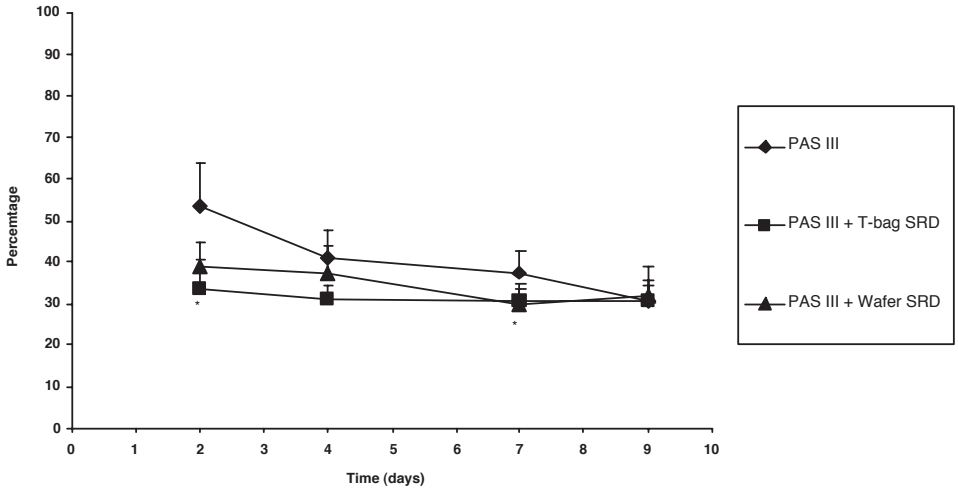


Figure 1b. Thrombin aggregation

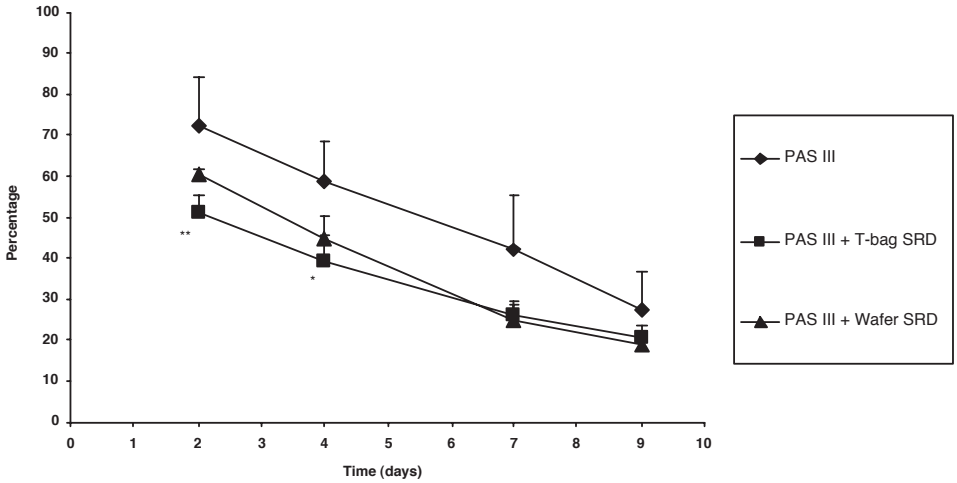
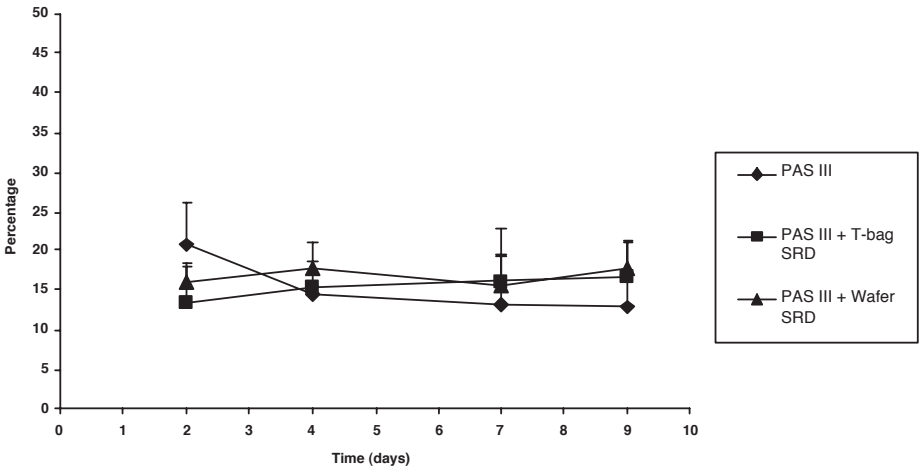


Figure 1c. ADP aggregation



*p<0.017 PCT platelets using T-bag SRD compared to control platelets in plasma/PAS III. **p<0.017 PCT platelets using Wafer SRD compared to PCT platelets using T-bag SRD. Aggregation percentages from fresh platelet rich plasma platelets isolated from venous blood above 50 percent considered normal.

Activation

The P-selectin level started at 70 percent on Day 2 for the three study arms. There was an increase of about 20 percent to a final level of 90 percent on Day 11. PCT did not lead to a higher expression of the activation marker P-selectin. No differences were found between the three study groups (Table 3).

Apoptosis and lysis

No differences were found for annexin V expression between the three groups. On Day 2 about 20 percent of the platelets were positive for annexin V. There was a small increase in

Table 3. Activation and apoptosis (mean percentage (SD))

	Number	Day 2	Day 4	Day 7	Day 9	Day 11
CD62 expression						
PAS III	4	69.4 (10.6)	75.2 (8.5)	81.4 (2.1)	88.6 (2.3)	90.3 (4.0)
PAS III + T-bag SRD	4	66.9 (8.4)	70.8 (5.2)	81.4 (1.2)	86.9 (2.4)	86.0 (4.0)*
PAS III + Wafer SRD	4	71.9 (5.9)	81.0 (2.1)	84.0 (4.3)	91.1 (1.9)	91.3 (2.3)
Annexin V expression						
PAS III	4	18.2 (7.2)	29.0 (4.0)	19.5 (4.8)	29.6 (1.3)	30.9 (15.0)
PAS III + T-bag SRD	4	27.2 (11.7)	28.0 (13.9)	22.2 (11.8)	30.6 (6.9)	36.6 (0.14)
PAS III + Wafer SRD	4	14.4 (2.5)	25.9 (5.9)	26.4 (3.1)	28.6 (11.8)	30.6 (3.0)
Caspase 3 expression						
PAS III	4	1.15 (0.44)	2.18 (1.26)	3.67 (3.33)	3.73 (2.14)	3.13 (2.31)
PAS III + T-bag SRD	4	1.28 (1.21)	2.20 (2.09)	2.18 (1.54)	2.43 (1.08)	1.48 (0.54)
PAS III + Wafer SRD	4	0.78 (0.28)	1.78 (1.03)	3.63 (2.00)	2.83 (1.16)	1.53 (0.69)

*p<0.017 compared to PAS III, PCT, Wafer SRD

Table 4. LDH concentration (U/L, mean (SD))

	Number	Day 2	Day 4	Day 7	Day 9	Day 11
PAS III	4	200.8 (37.4)	270.5 (65.8)	318.8 (78.5)	508.3 (302.3)	413.8 (183.1)
PAS III, PCT, T-bag SRD	4	739.8 (87.6)*	807.8 (68.8)*	901.0 (89.0)*	878.8 (163.6)	970.8 (282.9)*
PAS III, PCT, Wafer SRD	4	276.3 (61.6)**	411.0 (208.1)	509.0 (391.7)	316.0 (36.6)**	330.3 (47.8)**

*p<0.017 compared to PAS III

**p<0.017 compared to PAS III, PCT, T-bag SRD

time in all groups. A maximum of 4 percent of the platelets showed a possible caspase 3 activity. There might be a small increase during storage time. No significant differences were found between the study arms. PCT did not lead to an increase in apoptosis (Table 3).

The LDH concentration was increasing over time. There was a significant difference between LDH concentration after PCT using the experimental T-bag SRD compared to control platelets. No differences were found between PCT platelets using the Wafer SRD and control platelets (Table 4).

DISCUSSION

In this in vitro study, functional characteristics of PCT platelets using the experimental T-bag SRD and the commercially available Wafer SRD were compared to control platelets in plasma/PAS III. No published data from platelets treated with PCT using the commercially available Wafer SRD are yet available.

Control platelets in plasma/PAS III were characterized at the start (Day 2) by a better in vitro aggregation capacity than platelets treated with PCT using Wafer SRD and T-bag SRD, as shown by aggregation experiments with collagen and thrombin. Platelets treated with PCT using the commercially available Wafer SRD showed a slightly better in vitro aggregation capacity than platelets treated with PCT using the experimental T-bag SRD. In all three study groups, platelet function, as shown by aggregation experiments with collagen and thrombin, decreased over storage time. On average, PCT resulted in a loss of thrombin aggregation function of about 20 percent, compared to control platelets in plasma/PAS III. Several factors may account for this loss. To establish the cause of loss of function, we studied several variables that could contribute, such as overall quality variables, platelet activation, apoptosis, or lysis.

All three platelet products met the PCT target range requirements for the overall quality variables. PCT seems to have only a minor effect on overall quality variables.

For platelet activation, the expression of P-selectin, which is a marker of release of α-granules, was measured. The expression of P-selectin was comparable for these study groups. PCT had no additional effect on activation of platelets as shown with CD62 expression. Expression of CD62 is influenced by magnesium and potassium and is higher in PCs with PAS/plasma solution than PCs in plasma only (unpublished results).[14] Because in an earlier clinical study no differences in count increment after platelet transfusion were observed, P-selectin expression might be a reversible characteristic of PC in a PAS solution.[9] However, there have been conflicting data regarding the role of P-selectin in in-vivo outcomes.[15-18]

Apoptosis is a major form of cell death, characterized initially by a subset of stereotypic morphological changes.[19] Caspases, which are cysteinyl proteases that cleave after aspartic acid, are key effectors of apoptosis. Caspase 3 plays a central role in the early apoptosis pathway, [13,20,21] which leads to the externalization of phosphatidylserine to the surface of the platelet membrane, detectable with annexin V.[10-12] In this study, no additional effect on caspase 3 activity and annexin V expression was found. Annexin V is also detectable when platelets are activated. Therefore, the role of apoptosis (markers) in platelets remains unclear.

The increased lysis of platelets, as measured by plasma LDH, using the T-bag SRD compared to the commercially available Wafer SRD, suggests that the T-bag SRD is more harmful to platelets than the Wafer SRD, probably due to mechanical cause. The decrease in platelet function after PCT, shown by the aggregation experiments, was more pronounced for T-bag SRD than for Wafer SRD, which might be explained by the significant higher percentage of lysis.

In two recently performed clinical studies, platelets treated with PCT using T-bag SRD showed different results on the 1-hour and 24-hour CCI compared to control platelets treated in plasma/PAS II.[8,22] The sample size of our in vitro study was small, which increases the risk of Type II errors. However, even if beta-type errors were inadvertently made due to the small sample size, the results of our in vitro study are in agreement with the clinical performance of the PCT platelets in the in vivo study and suggest that PCs after PCT using Wafer SRD are less harmful to platelets than T-bag SRD.

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CHAPTER 3

Feasibility of a restrictive red-cell transfusion policy for patients treated with intensive chemotherapy for acute myeloid leukemia

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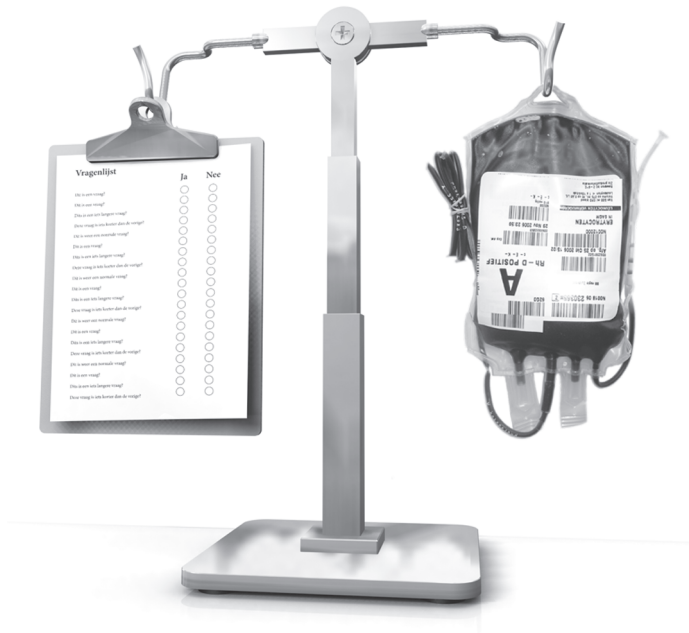

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ABSTRACT

Background: Red-cell transfusions are required for symptomatic treatment of severe anemia caused by intensive chemotherapy. Concerns about the transfusion-related complications, such as infections (e.g. the very low risk of human immunodeficiency virus (HIV)/hepatitis C (HCV) transmission and the risk of postoperative infections), hemolytic transfusion reaction, immunological effects and the costs, prompt a reevaluation of the transfusion practice.

Study design and methods: Retrospective analysis of prospectively collected data on 84 patients with acute myeloid leukemia (AML), who were treated with combination chemotherapy between June 1, 1997 and December 7, 2001, was performed. The use of red-cell transfusions with a restrictive transfusion policy (hemoglobin = 7.2-8.8 g dL^{-1}, dependent on age and symptoms, n=38) was compared with a more liberal transfusion trigger (hemoglobin = 9.6 g dL^{-1}, n=46). The number of units transfused was recorded. Signs and symptoms of anemia, chemotherapy-related effects and complications were investigated for both transfusion policies.

Results: The more restrictive transfusion policy led to a significant decrease of 11% of red blood cell transfusions in patients with AML. No significant differences were found in the incidence of infections, number of platelet units transfused, bleeding complications, cardiac symptoms or response to chemotherapy.

Conclusion: The more restrictive transfusion policy was feasible in this clinical setting and it might be concluded that a restrictive transfusion policy is safe in supporting clinical patients treated with intensive chemotherapy for AML.

INTRODUCTION

Pancytopenia is a common complication of myelosuppressive chemotherapy. Allogeneic red blood cell (RBC) transfusions are required for symptomatic treatment of the severe anemia caused by intensive chemotherapy.[1] The transfusion requirement is influenced by different clinical factors, of which the kind of chemotherapy is the most important one.[2] Other clinical events include tumor burden, fever, bacteriaemia, systemic fungal infection, mucosal bleeding, melaena/haematemesis and diarrhea. The efficacy of transfusional support seems to decrease gradually during the cytopenic period.[2-4]

Most clinical practice guidelines recommend a restrictive allogeneic RBC transfusion practice in patients without cardiac complications in the surgical and medical intensive care unit.[5-8] However, the optimal transfusion trigger in the hematological intensive care unit has not been defined and often differs between hospitals.[4] A hemoglobin (Hb) concentration of below 9.6 g dL^{-1} is generally taken as a trigger for RBC transfusion in hematological patients with a pancytopenia.[9] Concerns about transfusion-related complications, such as the risk of human immunodeficiency virus (HIV)/hepatitis C (HCV) transmission or postoperative infections, tumor behavior and immunological complications, as well as rising costs, led us to reconsider the transfusion policy. To assess a restrictive transfusion policy in hematological patients treated with intensive chemotherapy, new guidelines for the administration of red cells were introduced. The objective of this study was to investigate to what extent a restrictive transfusion policy decreases the total number of RBC transfusions and the number of units given per transfusion. In addition, clinical events associated with pancytopenia in both the restrictive transfusion policy and the liberal transfusion policy were compared. The University Hospital, Rotterdam, has a Hematology department split between two sites in Rotterdam. In both sites, the same prospective HOVON 29 study was going on. The only difference between the two sites was the transfusion trigger for RBC transfusion. The site determined whether the patient was allocated to the restrictive or the liberal transfusion group.

MATERIAL AND METHODS

Patients

In this retrospective study, data were analyzed which were collected prospectively according to the Good Clinical Practice directives of HOVON leukemia protocols at the intensive care unit of the department of Hematology, Erasmus Medical Center Rotterdam. Patients in the Erasmus Medical Center (central location) were transfused according the restrictive policy, whereas the liberal transfusion strategy was applied in

the other location (Daniel den Hoed Kliniek). From June 1, 1997 to December 7, 2001 84 patients with newly diagnosed acute myeloid leukemia (AML), who were between 15 and 60 years of age, were treated with combination chemotherapy (ARA-C 200 mg m^{-2} on days 0-6 and Idarubicin 12 mg m^{-2} on days 1-3). The AML was classified according the French-American-British (FAB) classification. A poor, good, or intermediate risk classification as defined by the HOVON leukemia protocol was used: Good risk = AML with t(8;21)(q22;q22) or AML1/ETO fusion gene and white blood cell (WBC) ≤ $20x10^9$/l at diagnosis and no additional unfavorable cytogenetic abnormalities or inv/del(16)(p13;q22) or MYH11/CBFβ fusion gene and no additional unfavorable cytogenetic abnormalities (more than three distinct clonal abnormalities; monosomes of chromosomes 5 or 7; del 5q or del 7q; abnormalities of the long arm of chromosome 3; t(6;9)(q23;q34) or DEK-CAN fusion gene; abnormalities of the long arm of chromosome 11). Intermediate risk = AML patients not assigned to Good risk or Poor risk. Poor risk = AML with unfavorable cytogenetic abnormalities, except those with simultaneous favorable cytogenetic abnormalities. In this study the transfusion requirements of these patients were studied under the two transfusion policies during the first induction cycle of chemotherapy.

Transfusion regimens

All patients received leukocyte-depleted RBC concentrates with a leukocyte count of less than $1x10^6$ L^{-1}. RBCs were suspended in a 110 ml SAG-M solution, with a haematocrit of 0.60 to a total volume of 265 mL.

Restrictive transfusion policy

In the revised restrictive transfusion protocol, age dependent lower limits were applied for prophylactic transfusion (Table 1). Patients younger than 25 years of age received a RBC transfusion when their Hb level dropped below 7.2 g dL^{-1}. In patients between 25 and 50 years of age, a transfusion trigger of below 8.0 g dL^{-1} was used. In patients between 50 and 70 years of age, the hemoglobin threshold was below 8.8 g dL^{-1}. RBC transfusions were administered on a unit-by-unit basis.

Liberal transfusion policy

The liberal transfusion policy was the standard practice at the start of the study. According to the liberal protocol, RBC transfusions were given when the hemoglobin level dropped below 9.6 g dL^{-1} (Table 1). Two units were given per transfusion in the liberal transfusion policy.

RBC transfusions were always given regardless of the hemoglobin concentration, if signs and symptoms of a decreased oxygen transportation capacity such as dyspnoea, syncope, postural hypotension, tachycardia (>100 bpm), angina pectoris or transient ischemic attack (TIA) occurred.

Table 1. Transfusion policies.

Age (Years)	Restrictive group		Liberal group	
	Hb transfusion trigger (g dL^{-1})	Mean Hb (g dL^{-1})	Hb transfusion trigger (g dL^{-1})	Mean Hb (g dL^{-1})
<25	7.2	7.5 (n=3)	9.6	8.8 (n=3)
25-50	8.0	8.0 (n=22)	9.6	9.3 (n=32)
50-70	8.8	8.3 (n=13)	9.6	9.5 (n=11)
Total	8.2	8.0 (n=38)	9.6	9.3 (n=46)

The Hb transfusion triggers for the restrictive group and the liberal transfusion group. The Hb column is the Hb guideline for both policies and the mean Hb column shows the mean Hb values during the follow-up period. There is a significant difference between the transfusion groups in the mean Hb value ($p<0.05$).

Clinical outcomes

Clinical outcomes like mortality, hemorrhages, infections, cardiac dysrhythmias and cardiac dysfunction (WHO-CTC grade 2 or higher), response to chemotherapy and myeloid: erythroid (M:E) ratio of the bone marrow smears were recorded.

Statistical methods

Statistical analysis was performed in SPSS for Windows 8.0. Frequencies were described as mean, median, range, standard error of the mean and SDs. Differences between the groups in the number of RBC transfusions and the total number of units of RBC given per transfusion were analyzed with the nonparametric Mann-Whitney test. To allow for potential confounding factors (sex, age and AML type) multiple regression was used after logarithmic transformation of the total number of RBC transfusions (e.g. the primary outcome). Differences between the total number of platelet transfusions and the number of units of platelets given per transfusion were also analyzed with the nonparametric Mann-Whitney test. Differences between complication rates were tested using the χ^2 test. P values < 0.05 were considered statistically significant.

RESULTS

The restrictive group consisted of 38 patients and the liberal group of 46 patients. There were no significant differences between these two groups in sex distribution, age, FAB classification, or risk classification. The mean follow-up period was 30 days for the restrictive group and 32 days for the liberal group (all $P > 0.05$). Characteristics of the two patient groups are shown in Table 2.

Table 2. Patient characteristics

Variables	Restrictive group (n=38)	Liberal group (n=46)	Total (n=84)
Sex			
Male	18	21	39
Female	20	25	45
Age (Years) + SD	43.2 (11.7)	42.5 (10.5)	42.8 (11.0)
FAB-classification			
M0	2	2	4
M1	11	11	22
M2	9	11	20
M3	3	5	8
M4	9	4	13
M5	2	13	15
M6	1	0	1
Risk classification*			
Good risk	7	6	13
Intermediate risk	19	28	47
Poor risk	11	10	21
Unknown	1	2	3

Social demographic variables and French-American-British (FAB) classification of the acute myeloid leukemia (AML) patients. There are no significant differences between the restrictive group and the liberal group ($p>0.05$) for sex, age, FAB classification and risk classification.

Table 3. Overview of erythrocyte and platelet transfusions

	Total number of RBC transfusions	Number of RBC units given per transfusion	Total number of platelet transfusions	Number of platelet units given per transfusion
Restrictive group				
Mean	9.6	1.3	7.5	1.1
Median	9.0	1.0	7.0	1.0
SD	3.9	0.5	3.8	0.4
St. error of the mean	0.6	0.03	0.6	0.03
Range	3.0 – 21.0	1.0 – 4.0	2.0 – 18.0	1.0 – 4.0
Liberal group				
Mean	10.8	1.8	8.5	1.2
Median	11.0	2.0	7.0	1.0
Std. deviation	2.9	0.4	4.9	0.5
St. error of the mean	0.4	0.03	0.7	0.03
Range	6.0 – 21.0	1.0 – 5.0	2.0 - 30.0	1.0 - 4.0

Overview of the number of RBC transfusions and the number of units of RBC given per transfusion in the first 31 days after starting chemotherapy. There are significant differences ($p<0.05$) between both groups in the total number of red blood cell (RBC) transfusions and in the total number of units of RBC given per transfusion in favor of the restrictive transfusion policy. In the total number of platelet transfusions and the number of units of platelets given per transfusion, there were no differences between the two transfusion groups.

Mean hemoglobin values during the follow-up period are shown in Table 1. Guidelines of both the restrictive and the liberal transfusion policy were followed correctly. A significant difference was found between the groups of 1.3 gdL^{-1} in the mean Hb value ($P < 0.05$) during the follow-up period. The total number of RBC transfusions and the average number of RBC units given per transfusion are shown for both groups in Table 3. The restrictive group received on average 9.6 (± 3.9) RBC transfusions, the liberal group received 10.8 (± 2.9) RBC transfusions, a significant difference of 11 percent ($P = 0.05$). The unadjusted ratio of geometric means was 1.17 and the 95% confidence interval (CI) ranged from 1.01 to 1.37. Adjusted for age, sex and AML type, the difference remained significant (1.25, $P = 0.007$) and the 95% CI for the ratio of adjusted geometric means ranged from 1.07 to 1.47. Per transfusion a mean of 1.32 (± 0.5) units of RBC were given in the restrictive group as compared to 1.82 (± 0.4) units in the liberal group ($P < 0.05$). The mean interval between RBC transfusions was 3.1 days in the restrictive group and 3.0 days in the liberal group.

There were no significant differences in the total number of platelet transfusions and the number of platelet units given per transfusion (Table 3). The mean interval between platelet transfusions in the restrictive group was 4.0 days and 3.8 days in the liberal group. The incidence of bleeding complications (CTC grade 2 or more) was not different (3/38 patients in the restrictive group, 8/46 patients in the liberal group with 1 or more bleeding complications, $P = 0.24$).

Table 4. Cardiac events

	Cardiac Rhythm dysfunction	95% Confidence Interval	Cardiac Function	95% Confidence Interval
Restrictive Group (N=38)	1/38	0.1% - 14%	3/38	0.6% - 18%
Liberal Group (N=46)	1/46	0.1% - 12%	5/46	4% - 24%

Overview of the cardiac events WHO-CTC grade 2 or more. No differences were found for cardiac dysrhythmias and cardiac dysfunction ($p>0.05$).

Table 5. Therapy response

	Restrictive group n (%)	Liberal group n (%)
Complete Remission	22 (58)	27 (59)
Partial Remission	7 (18)	11 (24)
No Response	7 (18)	7 (15)
Mortality	1 (3)	1 (2)
Relapse extramedullary leukemia	1 (3)	0
Total	38 (100)	46 (100)

Overview of the therapy response in the restrictive transfusion group and the liberal transfusion group. No significant differences were found in therapy response.

Differences between both groups for cardiac complications, e.g. episodes of cardiac arrhythmia and cardiac dysfunction, were not significant (Table 4). No differences were found in incidence of infections and type of infective agents.

The measured bone marrow M:E ratios were similar between the groups. Also, no significant differences were found in therapy response, e.g. complete remission, partial remission, no remission or death, between the restrictive group and the liberal group (Table 5).

DISCUSSION

Allogeneic RBC transfusions will always carry some inherent risks in terms of infections and immunomodulatory effects. The limited published evidence supports the use of restrictive transfusion triggers in patients without cardiac risk factors and symptoms.[5,7] In the hematological intensive care, a liberal transfusion trigger of 9.6 g dL^{-1} is common practice. This trigger is mostly based on literature of systematic reviews and often differs between hospitals.[4] It is the question whether this literature is relevant for AML patients, who are sick but not very old. In this retrospective analysis of prospectively collected data, a newly developed restrictive transfusion trigger protocol was studied. This new restrictive transfusion policy appeared to be feasible in this clinical setting as the guidelines were followed correctly (Table 1).

The new policy led to a significant decrease in the use of allogeneic RBC transfusions for patients treated with chemotherapy for AML. No differences were found in the incidence of cardiac complications, so it may be concluded that the restrictive transfusion trigger is also safe in hematological intensive care.

Anemia might induce prolonged bleeding time (BT), especially in thrombocytopenic patients.[10] It has been suggested that RBC transfusion might decrease the activated partial thromboplastin time and the BT in some anemic patients, which would reduce the risk of hemorrhage complications.[11,12] However, in this study, a reduction of bleeding complications was found in the patient group with the restrictive transfusion trigger. This result is supported by a decreased use of platelet transfusions in this group. Further clinical trials are needed to investigate this effect of RBC transfusions on bleeding complications in patients with a hematological malignancy.

Decreased hemoglobin levels in anemic cancer patients usually lead to a reduction of physical fitness and impaired Health Related Quality of Life (HRQoL). Consideration of

treatment of mild-to-moderate anemia will probably become more important as greater emphasis is placed on HRQoL in the management of hemato-oncological patients. For the development of more effective therapeutic interventions based on outcomes such as HRQoL as well as hemoglobin levels, further research into the relationships between hemoglobin levels, patients' well-being and safety and symptoms is needed. A restrictive transfusion policy, of which the feasibility has been demonstrated in this study, is the first step in this development.

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CHAPTER 4

Quality of life measurement in patients with transfusion-dependent myelodysplastic syndromes

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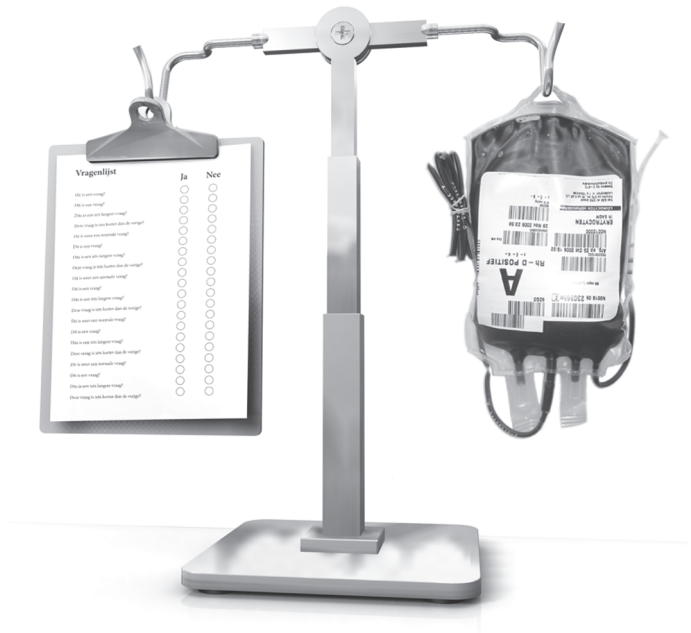

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ABSTRACT

Background: The myelodysplastic syndromes (MDS) are clonal disorders characterized by dysplasia in at least two myeloid cell lines. Fatigue is one of the most significant symptoms. MDS patients are treated with blood transfusions to improve their health-related quality of life (HRQoL).

Study design and methods: A cross-sectional pilot study was performed for psychometric evaluation of three internationally established HRQoL measures in MDS patients, and for investigation of the association between the severity of chronic anemia and HRQoL. Fifty consecutive MDS patients completed the Short Form 36, the Multidimensional Fatigue Inventory and the EuroQoL-5D Visual Analogue Scale. Hb level was measured during the same visit. Psychometric analysis focused on feasibility, construct validity and reliability.

Results: The questionnaires showed a high feasibility, reliability and validity. MDS patients had worse HRQoL scores than the age- and sex-matched general population. We found a positive correlation between hemoglobin (Hb) level and HRQoL.

Conclusion: This study provides insights into the suitability of established HRQoL measures for the evaluation of interventions in MDS patients. Hb value and HRQoL are complementary variables for evaluation of the severity of chronic anemia in patients with MDS.

INTRODUCTION

The myelodysplastic syndromes (MDS) are characterized by peripheral blood cytopenia with hypercellular bone marrow and dysplasia of the cellular elements.[1] Patients with MDS make up a heterogeneous population, with clinical features ranging from mild, stable cytopenia to severe pancytopenia with life-threatening symptoms and a high risk of progression to acute myeloid leukemia (AML). The most important clinical feature is chronic anemia, with fatigue as the most important symptom.[2] This fatigue is not an isolated physical symptom but rather involves lethargy, decreased mental alertness, physical weakness and poor concentration.

Recently, an international working group reviewed currently used response definitions of MDS, and developed a uniform set of guidelines for future therapy and clinical trials.[3] Treatment should aim to reduce the morbidity associated with cytopenias and, especially, to improve the health-related quality of life (HRQoL). Red cell transfusions are the cornerstone of the treatment for MDS patients. Although improving HRQoL is the major goal of blood transfusion, the HRQoL of MDS patients has not been investigated empirically.

In general, fatigue has the most important impact on the HRQoL of the individual in cancer patients before, during and after treatment.[4,5] The impact of MDS on HRQoL can be far reaching: in addition to the physical symptoms (e.g. bleeding and infection), fatigue, uncertainty, lack of understanding of the disease process, fear of conversion to acute myeloid leukemia and lack of communication with clinicians may influence the HRQoL.[6] HRQoL is subject to change over time in response to the course of the illness and/or treatment. A pilotstudy was conducted in MDS patients, which included the psychometric evaluation of three internationally established HRQoL methods, and investigation of the association between the severity of chronic anemia and the HRQoL.

MATERIAL AND METHODS

HRQoL covers physical, psychological and social issues (domains). Conceptually, HRQoL domains can be measured in terms of 'objective' functioning (what the patient is able to do) and the complementary subjective evaluation by the patient. The present study included both objective and subjective elements. It is common practice to combine generic measures, allowing for comparison of HRQoL scores across disease stages and diagnostic groups, with condition-specific and/or domain-specific measures.

Fifty consecutive MDS patients from three general hospitals and one university hospital completed a questionnaire consisting of the Short Form 36 (SF-36, generic HRQoL measure), the domain-specific Multidimensional Fatigue Inventory (MFI) and the EuroQoL-5D Visual Analogue Scale (VAS) for self-related health within 24 h of a regular visit to the outpatient clinic. The hemoglobin (Hb) level was measured at the outpatient visit and no blood transfusions were given for 24 h after this appointment. The patients were classified following the French-American-British (FAB) classification for MDS.

Based on the results of a psychometric analysis of four generic health measures in migraine patients, the SF-36 appeared to be the most suitable generic measure for describing HRQoL in that group of patients.[7] The SF-36, developed in the USA, is derived from the larger battery of health status instruments employed in the Medical Outcomes Study.[8-11] It consists of 36 items, organized into eight scales: mental health, physical functioning, role physical, role emotional, social functioning, bodily pain, general health perceptions and vitality. The number of response choices per item ranges from two to six. The SF-36 yields an eight-dimensional profile, with each scale having a range from 0 to 100 (100=optimal).

The SF-36 furthermore provides a physical sum score (PCS; predominantly based on the scales physical functioning, role physical, bodily pain and general health perceptions) and a mental sum score (MCS; e.g. scales mental health, role emotional, social functioning and vitality) (range 0-100, 100 = optimal).[12] PCS and MCS are constructed so that the general US population had a mean score of 50 and a standard deviation of 10. The Dutch version of the SF-36 employed in the current study was developed as a part of the International Quality of Life Assessment (IQOLA) Project, the objective of which is to translate, validate and norm the SF-36 in a wide range of languages and cultural settings.

The EuroQoL VAS, the sixth item of the generic EQ-5D measure, is a global evaluation of "own health today" using a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[13]

The Multidimensional Fatigue Inventory (MFI) was chosen to measure fatigue, the most important complaint of MDS patients. It was developed as a tool to assess fatigue in a comprehensive way, with a special interest in fatigue as experienced by patients. The MFI is a 20-item self-report instrument designed to measure fatigue in cancer and non-cancer patients.[14,15] The questionnaire covers five different dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. There are four response choices per item. Each scale has a range from 4 to 20 (4=optimal).

STATISTICS

Feasibility

The number of missing cases per item was employed as an empirical indicator of feasibility. Missing values were defined as those cases where no answer was provided and those where multiple responses were given, when only one was required. For VAS and MFI no constructed values for missing values were imputed. For the SF-36, constructed values for missing values were imputed following guidelines in the manual. Completion time was defined as the time required for the patients to complete the questionnaire.

Score distribution

Mean scores, standard deviations, and the percentages of respondents with the maximum possible score and the minimum possible score, respectively, were computed per scale.[14,16] For SF-36, mental and physical sum scores were calculated.[12]

Reliability

The internal consistency of the SF-36 and the MFI multi-item scales was determined with Cronbach's alpha-coefficient. An alpha-coefficient of 0.70 or higher was considered as sufficient for the purpose of group comparisons. Owing to the cross-sectional nature of the study, data on test-retest reliability were not available.

Correlation HRQoL and hemoglobin level

The effects of various factors on HRQoL (MDS subtype, hospital, sex and age), in addition to Hb level, were investigated using multiple regression analysis. The correlation between Hb level and HRQoL was analyzed using the Spearman's correlation coefficient.

Effect size

Effect size (ES) is a name given to a family of indices that measure the magnitude of a treatment effect. To measure the effect of Hb level on HRQoL, patients were divided into two groups by median Hb level (e.g. lower or higher than 9.5 g/dL). Cohen's d is defined as the difference between the means, divided by standard deviation, sigma, of either group. Following Cohen's suggested guidelines, d=0.2 was taken to indicate a small effect size, d=0.5 a moderate effect size and d=0.8 a large effect size.[17]

P-values < 0.05 were considered significant. All statistical analyses were performed the SPSS package, version 10.0, for Windows.

RESULTS

Between July 2001 and December 2001, 50 patients were enrolled; their characteristics are summarized in Table 1. There were no differences in Hb level and age between the hospitals, sex and MDS subtype respectively ($P > 0.05$).

Feasibility

The median completion time of the questionnaire was 15 min (range: 8-60 min). Fifteen patients needed help with completing the forms. One patient filled in only VAS and SF-36 (no MFI). One patient did not complete all MFI items, one patient did not fill in MFI subscale general fatigue and two patients did not complete MFI subscale reduced activity. Two patients did not complete the SF-36 subscales role physical and role emotional.

Score distribution

The scores of VAS, SF-36 and MFI were well distributed within the recorded ranges. The median scores of VAS, SF-36 and MFI of the MDS patients were lower than the median scores of subjects from the Dutch general population of similar age and sex.[4,14,18] In particular, the scores on the physical domain of the HRQoL were worse, e.g. physical functioning, role physical and physical sum score (SF-36) and physical fatigue (MFI).

Reliability

The internal consistency coefficients for the MFI and the SF-36 are shown in Table 2. All MFI had alpha-coefficients greater than 0.80. Six of the eight SF-36 had alpha-coefficients greater than 0.80.

Table 1. Characteristics of the 50 patients

Characteristics	Value
Sex (M/F)	31 / 19
Age (years)	
Median	73
Range	49 – 93
Hb (g/dL)	
Mean	9.7
Range	6.6 – 16.6
MDS subtype (N)	
RA	14
RARS	13
RAEB	15
RAEB-t	1
CMMoL	5

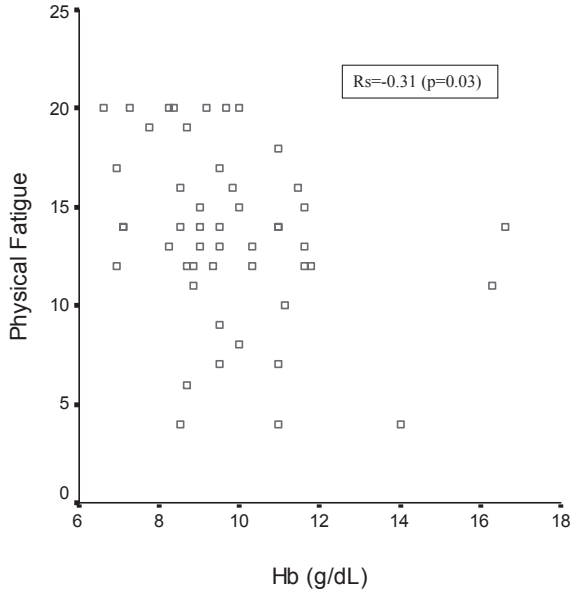
RA, refractory anemia; RARS, RA with ringed sideroblaststs; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; CMMoL, chronic myelomonocytic leukemia.

Table 2. Descriptive statistics of VAS, SF-36 and MFI: Spearman's correlation coefficient (Rs) p values and effect size (d) for a relationship with Hb

	Worst (%)[d]	Best (%)[d]	Mean (SD)	Cronbach's alpha	R_s[e]	p	d[f]
VAS[a] (score 0-100)	2	2	61.2 (18.4)		0.29	0.05	0.47**
MFI[b] (score 4-20)							
General Fatigue	17	4	13.2 (4.9)	0.94	-0.11	0.46	0.10*
Physical Fatigue	14	6	13.6 (4.4)	0.88	-0.31	0.03	0.48**
Mental Fatigue	2	25	8.4 (4.2)	0.82	-0.26	0.07	0.43**
Reduced Activity	15	4	13.1 (4.5)	0.83	-0.34	0.02	0.77**
Reduced Motivation	6	6	12.0 (4.7)	0.81	-0.27	0.06	0.43**
SF-36[c] (score 0-100)							
Bodily Pain	2	42	66.6 (31.2)	0.83	0.08	0.58	0.20*
General Health	2	2	41.5 (21.3)	0.75	0.15	0.29	0.14*
Mental Health	2	8	72.3 (20.9)	0.84	0.09	0.52	0.18*
Physical Functioning	4	2	48.1 (30.6)	0.94	0.50	0.00	0.73**
Role Emotional	23	44	59.0 (41.4)	0.79	0.22	0.13	0.14*
Role Physical	44	27	39.2 (42.5)	0.89	0.35	0.02	0.35**
Social Functioning	6	20	67.0 (29.6)	0.80	0.18	0.22	0.08*
Vitality	2	2	50.6 (25.3)	0.86	0.33	0.02	0.51**
Physical sum score	2	2	35.7 (11.7)		0.35	0.01	0.48**
Mental sum score	2	2	48.9 (12.6)		0.09	0.54	0.07*

[a]VAS scores ranged from 0 to 100 (100= best). The mean score of healthy age- and sex-matched control subjects was 80; [b]MFI subscales ranged form 4 to 20 (4=best, 20=worst); [c]Subscales of SF-36 scores ranged from 0 to 100 (100= best); [d]Percentage of patients who scored the worst or best possible score; [e]Spearman's correlation coefficient (R_s) for correlation of Hb level and VAS, SF-36 and MFI- subscales; [f]d= Cohen's d. Patients with Hb level < 9.5 g/dL (e.g. median Hb level) were compared with patients with Hb level > 9.5 g/dL. *d<0.20 is small effect , **0.2<d<0.8 is medium effect and ***d>0.8 is large effect.

Figure 1. Correlation Hb level and physical fatigue



Correlation between physical fatigue, measured with MFI, and Hb level. MFI scores range form 4 to 20 (4=best, 20=worst). Spearman's correlation coefficient is significant.

Correlation HRQoL and hemoglobin value

Table 2 also shows the correlation between Hb value and scores of the HRQoL questionnaires. A correlation of 0.29 (P = 0.05) was found for VAS. For SF-36, correlations between Hb and subscales physical functioning, role physical, vitality and physical sum score were statistically significant. Other subscales were not significantly correlated. Correlation between the MFI subscales physical fatigue and reduced activity, and Hb level were significant. There was a trend towards significance for mental fatigue and reduced motivation. Figure 1 shows the correlation between MFI subscale physical fatigue and Hb level.

There was a medium effect of the Hb level on VAS score (0.23). In particular, the Hb level showed medium-to-large effects on the physical domain of fatigue. This was also shown by the medium to large effects of the Hb level on the physical domain of the SF-36 scores.

No relationship between any outcome parameters (e.g. Hb, age, HRQoL scores) was found with MDS subtype.

DISCUSSION

In the present study, three internationally established HRQoL measures SF-36, VAS and MFI, were evaluated in MDS patients. These measures proved to be useful in describing HRQoL in MDS patients. Additionally, an association between Hb level and HRQoL was found.

Data collection with the three measures was feasible in this population. One patient filled in the SF-36 and VAS but not the MFI, maybe as a result of problems with turning the pages. Completing the questionnaires was thus not difficult for these patients.

MDS patients appeared to have a consistently reduced HRQoL, measured with SF-36 and MFI, than persons of similar age, especially on the physical dimensions. No differences for MDS subtype were found, which may be because of the small group size. All alpha-coefficients of SF-36 and MFI were greater than 0.70, making them potentially suitable for group comparisons. These HRQoL scores may also be influenced by co-morbidity factors, which would be expected in this elderly patient group.

The physical domain of HRQoL was considered the primary outcome variable in this study. A correlation between Hb value and the physical domain of HRQoL was found. This correlation, although significant, was lower than 1. This suggests that the HRQoL is affected by influences other than Hb level, which is in agreement with the literature.[19] Thus, HRQoL can only be partly explained by the Hb level.

In daily practice, evaluation of success of red cell transfusion and the clinical decision to transfuse has been measured only by effect on Hb levels.[6,20,21] The association between Hb value and HRQoL found in this study indicates the need to evaluate both the Hb value and HRQoL when deciding whether or not to give red cell transfusions.

Further longitudinal research is needed to assess the effect of red cell transfusion on HRQoL and to confirm the role of HRQoL in deciding whether red cell transfusion(s) is necessary. The measures tested in this pilot study are complementary and seem to be useful tools in future clinical trials.

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CHAPTER 5

New insights into fatigue and health-related quality of life after delivery

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Submitted

ABSTRACT

Background: A delivery may have a major impact on the health-related quality of life (HRQoL) of the new mother, especially on fatigue. A common complication during delivery that might have a relationship with maternal morbidity is blood loss. The objectives were to investigate fatigue and HRQoL in women after vaginal delivery (VD), elective caesarean section (CS) and emergency CS and its relationship with postpartum hemoglobin (Hb) levels during the first six weeks postpartum.

Study design and methods: 141 patients (71 after VD, 36 after elective CS and 34 after emergency CS) completed the HRQoL questionnaires MFI and EQ-5D between 12-24 hours after VD and 24-48 hours after CS (T=0). One, three and six weeks postpartum these questionnaires were repeated, together with the SF36.

Results: Patients after VD had higher mean physical HRQoL scores than after CS. The average period to reach full physical recovery was three weeks after VD, six weeks after elective CS and more than six weeks after emergency CS. Mean mental HRQoL scores of the study groups were similar or even better compared to reference values. The significant correlation between Hb level and mean physical HRQoL scores, found at T=0, had disappeared at one week postpartum.

Conclusion: Results of this study provided insights into the natural course of fatigue and HRQoL postpartum. Important differences in fatigue and HRQoL scores were observed between the three modes of delivery. These HRQoL measures can be used in future clinical trials to assess the effects of interventions postpartum.

INTRODUCTION

The birth of a child may have a major impact on the health-related quality of life (HRQoL) of the new mother. Traditionally the postpartum period is considered to be six weeks, the period the reproductive organs need to recover.[1] Longitudinal studies measuring HRQoL during the first year postpartum are available, describing serious physical and emotional problems (e.g. breast discomfort, urine incontinence, back pain, fatigue, depression and sexual problems postpartum).[2,3] Some of these symptoms are still present more than 12 months postpartum.[4] With an incidence of 60- 70% fatigue is a common symptom one year postpartum.[2,4] Furthermore, HRQoL in patients after vaginal deliveries was found to be different compared to patients with cesarean deliveries.[3] The fatigue is not an isolated physical symptom but rather involves lethargy, decreased mental alertness, physical weakness, and poor concentration. HRQoL is a multidimensional concept with physical, psychological and social domains. It can be measured in terms of 'objective' functioning (what the patient is able to do) and, complementary, in terms of the patient's subjective evaluation thereof. To date, studies about fatigue and HRQoL in the immediate postpartum period are lacking.

One of the most prevalent delivery related complications that might have consequences on maternal HRQoL, and especially fatigue, is blood loss. The circulating blood volume increases during pregnancy to 100 mL/kg constituting to an average total blood volume of six-seven liters. The several blood components contribute differently to this increase: plasma increases with 40% whereas erythrocyte volume increases with 15-20%. Consequently, hemoglobin (Hb) level decreases with a maximum of approximately 10%.[5] This natural process of hemodilution improves the placental circulation. In addition, the blood coagulation system will be activated which reduces the risk of extensive blood loss during parturition and thus postpartum anemia. During the first three days after delivery the redistribution of extracellular fluid induces a further decrease in Hb level. From the third day postpartum Hb levels start to increase and return to normal values six weeks postpartum. Forty percent of the patients suffer from more than 500 mL blood loss after vaginal delivery (VD).[6] Blood loss of more than 1000 mL complicates 30% of the patients undergoing a caesarean section (CS) and 70% of the patients undergoing a CS in combination with a hysterectomy.[6] The most important consequence of obstetric hemorrhage is anemia, with severe fatigue as a common symptom.[7]

The goals of this study were to establish the natural course of fatigue and HRQoL during the first six weeks postpartum. Internationally established HRQoL measures were used to measure fatigue and generic HRQoL in patients after different modes of delivery during the first six weeks postpartum. In addition, the relationship between Hb values and fatigue was assessed.

MATERIALS AND METHODS

The Ethics Committees of the three participating hospitals approved the study protocol. Because patients were only asked to fill in HRQoL questionnaires, patients did not have to give informed consent.

Patients

In the period of June 2003 till March 2004, 71 consecutively patients after VD and 70 consecutively patients after CS were included in two university hospitals and in one general hospital in the Netherlands. This prospective cohort study was performed in the three participating hospitals, coordinated by one researcher (AJGJ). The inclusion was performed consecutively: the first 61 patients (31 after VD and 30 after CS) entered the study in the first hospital, followed by 60 patients (30 after VD and 30 after CS) in the second hospital and finally 20 patients (10 after VD and 10 after CS) in the third hospital. So we recruited for 10 months: on average three months in the first hospital, three months in the second hospital and one month in the third hospital. Patients undergoing CS were grouped into those undergoing an elective CS (N= 36) and those undergoing an emergency CS (N=34). Indications for elective CS were breech and transverse presentation, two or more previous caesarean sections, previous anorectal surgery, maternal condition and a previously complicated VD.
Emergency CS was defined as a CS performed during labor. Recruitment of the patients took place 12-24 hours after VD and 24-48 hours after CS (time point T=0). The larger delivery-study interval in the CS group was chosen to reduce possible short-term effects of the surgery procedure itself. All patients who underwent CS received spinal anesthesia. Other inclusion criteria were maternal age older than 18 years and working knowledge of the Dutch language.

HRQoL questionnaires

The HRQoL questionnaires used in the present study included both objective and subjective elements. The Multidimensional Fatigue Inventory (MFI) was chosen to measure fatigue. The MFI was originally developed to assess fatigue comprehensively in cancer patients during radiotherapy.[8,9] The measure covers five dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Each dimension is addressed by five items, with 4 response choices per item. Each scale has a score, which ranges from 4 to 20 (4=optimal).

It is common practice to combine condition-specific and/or domain-specific measures with generic measures, allowing for comparison of HRQoL scores across disease stages and diagnostic groups. The generic measures EuroQoL 5D (EQ-5D)[10], including the

Visual Analogue Scale (VAS) for self-related health, and the Short-Form 36 (SF36) were used.[11-13] These measures have a high feasibility, reliability and validity and are internationally standardized and widely used.

The EQ-5D instrument was developed by the international EuroQoL Group as a standardized generic measure for description of health status.[10] The descriptive part of the 5D-version consists of five items (Mobility; Self-Care; Usual Activities; Pain/Discomfort; Anxiety/Depression), each following the general form: 1 = no problems, 2 = some problems, 3 = extreme problems. The sixth item, the VAS, is a global evaluation of own health with a range from 0 (worst imaginable health state) to 100 (best imaginable health state).

The generic measure SF36, developed in the United States, was derived from the larger battery of health status instruments employed in the Medical Outcomes Study.[11-13] It consists of 36 items, organized into eight scales: Mental Health, Physical Functioning, Role Physical, Role Emotional, Social Functioning, Bodily Pain, General Health Perceptions, and Vitality. The number of response choices per item ranges from two to six. The SF36 yields an eight-dimensional profile, with each scale having a range from 0 to 100 (100=optimal). The SF36 furthermore provides a physical sum score (PCS) (predominantly based on the scales Physical Functioning, Role Physical, Bodily Pain and General Health Perceptions) and a Mental sum score (MCS) (e.g. scales Mental Health, Role Emotional, Social Functioning, and Vitality) were computed (range 0 to 100, 100 = optimal).[13] Physical and Mental sum scores were constructed so that the general US population had a mean score of 50 and a standard deviation of 10. The Dutch version of the SF36 employed in the current study was developed as a part of the International Quality of Life Assessment (IQOLA) Project, whose objective is to translate, validate, and norm the SF36 in a wide range of languages and cultural settings.[14]

The first set of questionnaires was completed within 12 - 24 hours after VD and within 24 – 48 hours after CS (T=0). Simultaneously, the Hb levels were measured according to routine hematological examination. Three patients (one with VD and two with emergency CS) received RBC transfusions between delivery and the moment of recruitment. Patients were treated postpartum, if necessary, with oral iron and folic acid therapy. One, three and six weeks after delivery (time points T=one, three and six) again the EQ-5D and MFI together with the SF36 questionnaires were completed at home. The SF36 questionnaire refers to HRQoL during the preceding week. Therefore this questionnaire was not used at T=0.

Statistics

Patients undergoing VD or CS were analyzed separately. Patients undergoing CS were posthoc grouped into elective CS (N=36) and emergency CS (N=34). P-values < 0.05 were considered significant.

HRQoL questionnaires

In SF36 constructed values for missing values were imputed following guidelines in the manual. Feasibility (completion time) and reliability (Cronbach's alpha) were measured. A Cronbach's alpha of more than 0.7 was considered reliable.[15] For EQ-5D VAS, SF36 and MFI mean scores and standard errors were computed per scale.[8,13] Differences between the three modes of delivery were analyzed using repeated measurement ANOVA, using an unstructured covariance matrix. The hypothesis was if the overall mean levels of fatigue and HRQoL were different for the three study groups. It was verified, using appropriate interaction terms, that the factor center did not affect the results. Scores of SF36 en EQ-5D VAS were compared with reference scores of the age-matched female Dutch population ("references"). For MFI, no reference scores are available.

The relationship between fatigue and Hb values

The relationship between the Hb values at time point T=0 and the scores of the different MFI subscales at the different time points was investigated using Spearman correlation coefficients.

RESULTS

All patients met the inclusion criteria in the period of enrollment and all eligible women accepted to participate. The included patients were comparable with the total population of women given birth in our region. Baseline demographics of the patients after VD, after elective CS and after emergency CS are shown in Table 1. No differences were found for Hb values of the three study groups between the three hospitals (data not shown). From the 71 patients after VD, 18 patients had an instrumental VD. No baseline differences in EQ-5D including VAS, SF36 and MFI scores and recovery time were found between patients after spontaneous VD and instrumental delivery. Only a small difference between patients after spontaneous VD and instrumental VD in recovery time was measured with SF36 subscale SF (P=0.03) (data not shown).

Validation of HRQoL questionnaires

At six weeks postpartum 62% of the patients after VD, 53% of the patients after elective CS and 65% of the patients after emergency CS returned the HRQoL questionnaires. The

Table 1. Patient characteristics

	Vaginal Delivery (N=71)	Elective Caesarean Section (N=36)	Emergency Caesarean Section (N=34)
Age (Years), mean ± sd	30.5 ± 5.7	30.5 ± 5.4	32.4 ± 5.4
Gestational age at delivery (weeks, mean ± sd)	38.9 ± 2.6	37.3 ± 3.1	39.7 ± 1.8
Hemoglobin value (g/dL)*	11.1 (7.0 – 15.0)	10.6 (7.5 - 13.7)	10.3 (7.2 - 13.3)
Singleton	68 (96%)	35 (97%)	33 (97%)
Primiparous	23 (32%)	11 (31%)	15 (44%)

* Hemoglobin values were measured 12-24 hours after vaginal delivery or 24-48 hours after cesarean section. Median (minimum-maximum) is shown.

refusals did not differ between the study groups. At the various time points, the scores of VAS, SF-36 and MFI spread well within ranges. The HRQoL questionnaires showed a high feasibility with a mean completion time of 10 minutes and a low amount of missing values: the mean amount of missing values (range) of the returned HRQoL measures for the time points combined was 1.8 for the MFI, 1.1 for EQ-5D classification, including VAS, and 0.3 for SF-36. With Crohnbach's alphas > 0.7 for all HRQoL subscales, except SF36 BP (> 0.5), the HRQoL measures showed a high reliability.

Fatigue scores

Scores of the MFI questionnaire are shown in Table 2. The maximum difference at the different time points between mean MFI Physical Fatigue scores of patients with a physiological VD and patients with an instrumental VD was 1.6 (P=0.25, data not shown). No differences were found between patients after VD with and without instrumental delivery for other fatigue subscales. Repeated measurements ANOVA showed that patients who underwent an elective CS had significantly higher overall mean fatigue scores than patients after a VD for fatigue subscales General Fatigue (P<0.001), Physical Fatigue (P<0.001) and Role Physical (P = 0.026). Patients after emergency CS had higher overall fatigue scores (i.e. more fatigue) for the subscales General Fatigue (P=0.01), Physical Fatigue (P<0.001), Reduced Activity (P<0.001) and Mental Fatigue (P=0.032) than patients after VD. Results of MFI subscale Physical Fatigue are shown in Figure 1. No differences were found in changes over time between the three study groups. For Mental Fatigue scores, no differences were found between the three study groups (P>0.05).

Generic HRQoL scores

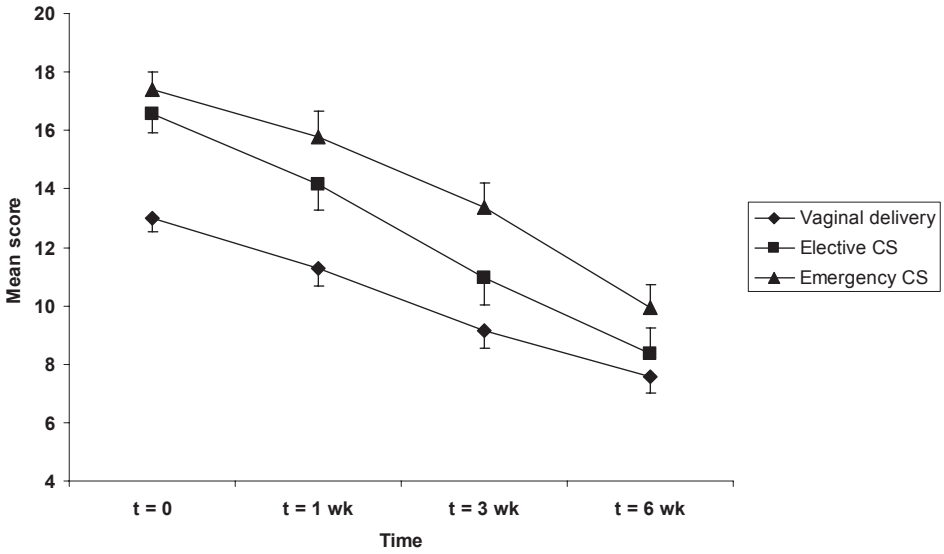
Scores of SF36 using Repeated measurement ANOVA are shown in Table 3. Patients after VD had significantly higher (i.e. better) mean HRQoL scores measured with the generic questionnaires than patients after elective CS. Patients after emergency CS had lower SF36 scores than patients after elective CS and VD. Patients after VD needed on

Table 2. Results of MFI scores at 4 different time points in women after 3 modes of delivery

	Vaginal Delivery (N=71)				Elective Caesarean Section (N=36)				Emergency Caesarean Section (N=34)			
	12-24 hours	**1 week**	**3 weeks**	**6 weeks**	**24-48 hours**	**1 week**	**3 weeks**	**6 weeks**	**24-48 hours**	**1 week**	**3 weeks**	**6 weeks**
General Fatigue	13.8 ± 0.5	13.3 ± 0.6	11.1 ± 0.6	9.9 ± 0.6	16.0 ± 0.7	13.5 ± 0.8	12.7 ± 0.9	10.5 ± 0.9	16.1 ± 0.7	16.6 ± 0.8	14.2 ± 0.8	12.1 ± 0.9
Physical Fatigue	13.0 ± 0.4	11.3 ± 0.6	9.1 ± 0.6	7.6 ± 0.6	16.6 ± 0.6	14.2 ± 0.9	11.0 ± 1.0	8.4 ± 0.9	17.4 ± 0.6	15.8 ± 0.9	13.4 ± 0.9	9.9 ± 0.8
Reduced Activity	13.1 ± 0.4	12.0 ± 0.5	10.6 ± 0.6	8.1 ± 0.5	16.6 ± 0.6	14.5 ± 0.8	11.8 ± 0.9	9.5 ± 0.8	16.6 ± 0.6	15.0 ± 0.8	12.6 ± 0.8	9.8 ± 0.8
Reduced Motivation	11.1 ± 0.5	8.7 ± 0.5	8.1 ± 0.5	6.5 ± 0.5	11.7 ± 0.7	8.2 ± 0.8	7.4 ± 0.8	7.2 ± 0.8	12.7 ± 0.7	10.0 ± 0.7	8.4 ± 0.7	7.6 ± 0.7
Mental Fatigue	10.3 ± 0.6	9.6 ± 0.6	8.9 ± 0.6	8.0 ± 0.6	12.1 ± 0.8	10.2 ± 0.9	9.8 ± 1.0	8.8 ± 0.9	12.3 ± 0.8	11.3 ± 0.9	10.9 ± 0.9	9.9 ± 0.9

MFI subscales range from 4 to 20 (4 = best, 20 = worst). Mean scores ± s.e.m. according to repeated measurements ANOVA are shown. Age matched Dutch female reference values are not available.

Figure 1. Scores of MFI subscale Physical Fatigue at four different time points in women after three modes of delivery.



MFI Physical Fatigue subscale range from 4 to 20 (4 = best, 20 = worst). Mean ± s e.m, using repeated measurement ANOVA model, are shown.

average three weeks to reach mean normal HRQoL scores of the physical subscales Physical Functioning and Role Physical whereas patients after elective CS needed six weeks. Patients after emergency CS needed more than six weeks to reach mean scores of the normal population of the physical HRQoL scales Physical Functioning ($P<0.001$) and Role Physical ($P<0.001$). No differences were found in changes over time between the three study groups. No differences were found between patients with and without instrumental delivery.

The differences in general HRQoL scores between the three study groups may be explained by differences in physical HRQoL e.g. Role Physical (Figure 2) and Physical Functioning (Table 3). No significant differences were found for mental HRQoL between the three study groups ($P>0.05$). Mean mental HRQoL scores were even slightly higher than mean scores of age and sex matched Dutch reference values. Results of EQ-5D and VAS are comparable with the results of the SF36 questionnaire and are shown in Table 4.

The relationship between fatigue and Hb values

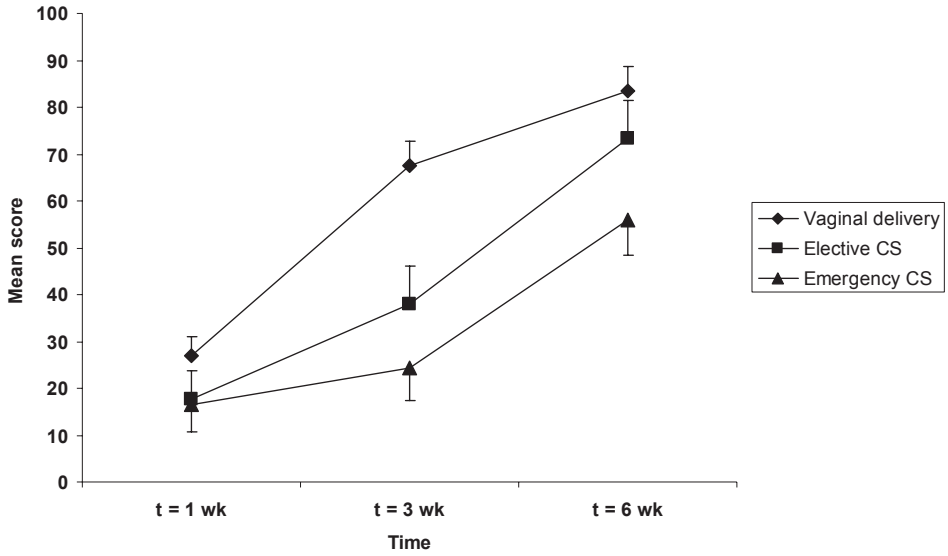
A significant, but weak, correlation between Hb values and fatigue scores at 12-24 hours after VD and 24-48 hours after CS (time point T=0) was found for MFI subscales General Fatigue ($P=0.002$), Physical Fatigue ($P=0.001$), Reduced Activity ($P=0.013$) and Reduced

Table 3. Results of SF36 scores at 3 different time points in women after 3 modes of delivery

	Vaginal Delivery (N=71)				Elective Caesarean Section (N=36)				Emergency Caesarean Section (N=34)			
	1 week	3 weeks	6 weeks	Reference value	1 week	3 weeks	6 weeks	Reference value	1 week	3 weeks	6 weeks	Reference value
Physical Functioning	58.6 ± 3.0	82.6 ± 2.7	90.1 ± 2.7	91.9	44.8 ± 4.4	68.1 ± 4.3	85.8 ± 4.1	91.9	32.8 ± 4.1	52.5 ± 3.8	77.0 ± 3.7	91.9
Role Physical	26.9 ± 4.1	67.7 ± 5.0	83.5 ± 5.3	83.1	17.7 ± 6.0	37.9 ± 8.1	73.3 ± 8.0	83.1	16.4 ± 5.6	24.4 ± 7.0	56.0 ± 7.5	83.1
Bodily Pain	44.7 ± 2.4	72.0 ± 3.3	83.6 ± 4.0	78.9	38.7 ± 3.5	56.6 ± 5.4	75.1 ± 6.1	78.9	35.6 ± 3.3	55.4 ± 4.5	68.1 ± 5.7	78.9
General Health	76.5 ± 2.4	74.2 ± 2.3	76.8 ± 2.5	78.3	75.9 ± 3.6	78.4 ± 3.5	77.5 ± 3.8	78.3	72.2 ± 3.4	73.6 ± 3.2	76.6 ± 3.5	78.3
Vitality	55.3 ± 2.3	64.9 ± 2.4	71.4 ± 2.6	67.4	53.6 ± 3.4	60.9 ± 3.7	65.9 ± 4.0	67.4	42.4 ± 3.2	52.1 ± 3.3	63.2 ± 3.6	67.4
Social Functioning	64.0 ± 3.4	83.9 ± 2.8	89.2 ± 2.7	85.9	53.1 ± 5.0	73.8 ± 4.4	84.0 ± 4.1	85.9	47.0 ± 4.6	61.3 ± 3.8	80.6 ± 3.8	85.9
Role Emotional	69.7 ± 5.3	85.4 ± 4.7	88.8 ± 4.8	81.1	75.0 ± 7.8	85.8 ± 7.6	83.6 ± 7.3	81.1	54.0 ± 7.3	70.6 ± 6.6	68.7 ± 6.7	81.1
Mental Health	80.9 ± 2.2	83.2 ± 2.0	87.0 ± 2.0	76.4	79.1 ± 3.2	84.9 ± 3.2	83.5 ± 3.1	76.4	73.8 ± 3.0	79.2 ± 2.8	86.1 ± 2.9	76.4
Physical Sumscore	35.5 ± 1.0	46.8 ± 1.1	51.2 ± 1.2	53.8	31.4 ± 1.5	39.1 ± 1.7	48.6 ± 1.9	53.8	29.9 ± 1.4	35.8 ± 1.5	44.9 ± 1.7	53.8
Mental Sumscore	53.3 ± 1.4	54.1 ± 1.3	55.1 ± 1.3	48.2	53.6 ± 2.0	56.3 ± 2.0	53.1 ± 2.0	48.2	48.8 ± 1.9	51.9 ± 1.8	53.3 ± 1.8	48.2

SF36 subscales range from 0 to 100 (0=worst; 100=best). Mean scores ± s.e.m according to repeated measurements ANOVA are shown. Reference values are female and age matched Dutch subjects.[14]

Figure 2. Scores of SF-36 subscale Role Physical at three different time points in women after three modes of delivery.



SF36 Role Physical was assessed at three different time points. The scale ranges from 0 to 100 (0 = worst, 100 = best). Mean ± s.e.m are shown (repeated measurement ANOVA model). A significant difference between mean scores of patients after vaginal delivery and mean scores of patients after emergency CS was found. No differences were found after six weeks for mean scores of patients after vaginal delivery and elective CS.

Motivation (P=0.047). However, Hb values at time point T=0 were not significantly related to fatigue and generic HRQoL scores one, three and six weeks postpartum (except for MFI Reduced Activity at three weeks postpartum, P=0.02). No correlation between Hb values at time point t=0 and mental fatigue scores was found. Using ANOVA, taking into account the type of delivery groups, correlations between Hb and HRQoL outcomes were not significant at one, three and six weeks postpartum.

DISCUSSION

Fatigue is an important symptom after delivery. So far, different prospective health surveys of pregnant women have been published, which showed decreased physical HRQoL scores during pregnancy with lower scores in the third trimester.[16,17] In the present study, a set of internationally established methods for HRQoL measurement, measuring fatigue in all its domains, appeared to be feasible in clinical patients after delivery. At six weeks postpartum our data from the SF-36 were comparable with previously published data.[18]

Table 4. EQ-5D scores (% patients who answered "no problem") and VAS scores (mean (s.e.m.))

	Vaginal Delivery	Elective CS	Emergency CS
Mobility			
T = 0	35.2	13.9	0
T = 1 week	63.0	48.0	24.1
T = 3 weeks	88.5	73.7	60.7
T = 6 weeks	95.5	94.7	95.5
Controls*	90.0		
Self-care			
T = 0	63.4	22.2	8.8
T = 1 week	85.2	80.0	72.4
T = 3 weeks	96.2	94.7	89.3
T = 6 weeks	97.7	100.0	100.0
Controls*	97.9		
Usual Activities			
T = 0	19.7	8.3	2.9
T = 1 week	38.9	12.0	13.8
T = 3 weeks	63.5	31.6	17.9
T = 6 weeks	93.2	73.7	59.1
Controls*	85.3		
Pain/ discomfort			
T = 0	15.5	2.8	2.9
T = 1 week	24.1	16.0	6.9
T = 3 weeks	67.3	42.1	35.7
T = 6 weeks	84.1	89.5	59.1
Controls*	67.3		
Anxiety/ depression			
T = 0	90.1	83.3	76.5
T = 1 week	85.2	84.0	62.1
T = 3 weeks	90.4	94.7	82.1
T = 6 weeks	97.7	89.5	86.4
Controls*	87.2		
VAS			
T = 0	67.8 (2.0)	63.3 (2.8)	55.1 (2.9)
T = 1 week	74.7 (2.0)	69.1 (2.9)	61.6 (2.8)
T = 3 weeks	80.8 (1.9)	76.1 (2.9)	69.5 (2.6)
T = 6 weeks	86.4 (1.6)	83.3 (2.4)	77.1 (2.2)

*Controls are female and age matched Dutch subjects.[33]

One of the most interesting findings was the difference in recovery time between the three study groups, which was consistently observed with all three HRQoL measures. After VD the time to complete recovery was three weeks, whereas after elective CS patients needed six weeks to reach normal non-pregnant values. Patients after emergency CS were not fully recovered even after six weeks. The differences at six weeks between types of delivery are according to the literature.[3] Postpartum patients had higher, but not significant, mental HRQoL scores than the scores during pregnancy from the studies

previous mentioned.[16,17] This was independently of the type of delivery. Conflicting data are published about these findings in the literature. The latter finding corresponds to the general idea of the "happy young mother being on a pink cloud". Another possibility might be that these questionnaires were not sensitive enough to discriminate between type of delivery for mental health.

VD is the most physiological route of delivery, which may well explain the differences in physical HRQoL scores between VD and CS. Patients undergoing an emergency CS experienced both labor and an operative procedure, which may explain the worse HRQoL scores. Patients undergoing an elective CS experienced the effect of an operation. The effects of surgery and anesthesia might be of more influence on the HRQoL scores than a VD. From an HRQoL point of view, it might be concluded that emergency CS should be prevented as much as possible. Patients at high risk of undergoing emergency CS should be closely monitored to offer timely elective CS. Early recognition of such patients might be achieved by using for example a recently published risk-scoring system.[19] Also, greater support and care for women who underwent CS seems necessary.

Several variables may influence HRQoL of patients after delivery e.g. duration of gestation at delivery and condition of the child. We choose only to investigate the role of anemia, a common problem after delivery, which also may influence HRQoL. In this study a correlation between Hb levels and physical HRQoL scores was found 12-24 hours after VD and 24-48 hours after CS. However, this correlation had disappeared one week postpartum. Red blood cell (RBC) transfusion is one of the principle treatments for postpartum anemia. The incidence of RBC transfusion after primary postpartum hemorrhage varies between <1% and 4% for VD (20-26), and between 1% and 7% for CS.[20-30] The attitude of physicians toward RBC transfusion in patients undergoing CS has lately been evaluated.[31] This study showed large differences in criteria for postpartum transfusion between physicians and consequently recommended unification of the protocols. In general, the indication for a RBC transfusion is based on Hb thresholds.[32] The aim however, of RBC transfusions postpartum is not to increase Hb values, but to treat severe fatigue and to prevent the consequences of hypoxia, severe hypovolemia and shock. The results of this study may indicate a short-term effect of postpartum Hb levels on fatigue and HRQoL scores. Although RBC transfusions should be aimed at improving fatigue and HRQoL, HRQoL questionnaires are not applied in the clinical decision involving blood transfusions yet. Currently, a multicenter trial, the WOMB study (Well being of Obstetric Patients on Minimal Blood transfusions) (ClinicalTrials.gov identifier: NCT00335023) is ongoing. The questionnaires used in the WOMB study were validated in the present study.

The limitations of this study include the small sample size, the low response rate and the lack of information about the HRQoL of the patients before delivery. The sample size of 141 patients is large enough to obtain reference values for fatigue and health related quality of life postpartum. Although there is lack of information about the HRQoL scores of patients before delivery, the patients of our study might be comparable with the general population who give birth in our region. This is because half of the patients were included in university hospitals and the other half in a general hospital; the patients were included consecutively and no differences were found in patient characteristics. However, this sample size is too small to measure the influence of possible confounders on fatigue and health related quality of life e.g. age, nulli,/multipara, comorbidity, socioeconomic status and previous complications. There was a low response rate of the questionnaires of 53-65% at T = six weeks, despite the recall by telephone. However, because no differences were found between the mode of delivery and all three measures showed a low percentage of missing values and completing the questionnaires was not difficult for these patients, these questionnaires were considered reliable.

In conclusion, the data from this study provide detailed insights in the natural course of fatigue and HRQoL after VD and after CS. They can be used as reference in clinical trials to assess the effects of obstetrical interventions, such as blood transfusion after obstetric hemorrhage, on postpartum HRQoL. The ultimate goal would be to develop an alternative transfusion policy, not solely based on Hb levels but in which HRQoL values are also taken in to account.

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CHAPTER 6

Psychometric evaluation of health related quality of life measures in women after different types of delivery

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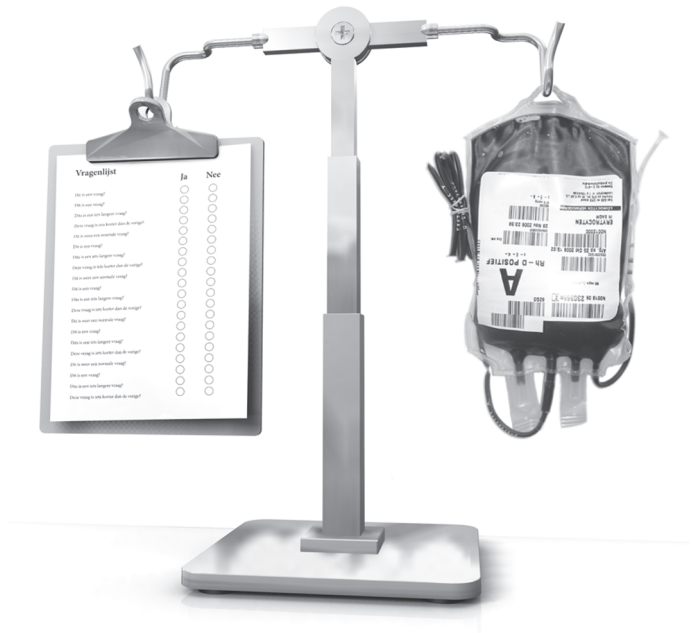

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ABSTRACT

Background: We examined the psychometric properties of three internationally established measures for Health Related Quality of Life (HRQoL) in women after vaginal delivery (VD), elective caesarean section (CS) and emergency CS.

Study design and methods: Prospective longitudinal study. 141 consecutive patients (71 after VD, 36 after elective CS and 34 after emergency CS) were enrolled in 2 university hospitals and 1 general hospital in the period June 2003 till March 2004. Women completed the Multi-dimensional Fatigue Inventory (MFI) and the EQ-5D classification of own health between 12-24 hours after VD or 24-48 hours after CS (t=0). Subsequent assessments, additionally including the Short Form 36 (SF-36), were made at 1, 3 and 6 weeks after delivery. We analyzed feasibility (response, completion time, reported difficulties, item non response), reliability (Cronbach's alpha), discriminative validity between groups by type of delivery, and responsiveness over time. (Wilcoxon's signed rank tests and effect sizes).

Results: The MFI, SF-36 and EQ-5D proved to be highly feasible and reliable (alpha >0.7 for all scales of MFI and SF-36) in this group of respondents. The measures were able to discriminate between groups by mode of delivery, and to detect moderate recovery in physical and small recovery in mental status over time in the first 6 weeks after delivery. The suboptimal total questionnaire response of 60% after 6 weeks was attributable to low response among women of non-Dutch ethnic origin.

Conclusion: The combination of MFI, SF-36 and EQ-5D showed good psychometric performance and is a good choice to measure HRQoL after delivery. Additional efforts need to be made to increase response rates among immigrants.

INTRODUCTION

Patient-reported outcomes, including health-related quality of life (HRQoL), have increasingly been incorporated in the evaluation of medical interventions. HRQoL is often defined as patient-reported functioning and well being in the physical, psychological and social domains. Generally, there are three types of HRQoL measures:

1) generic measures, intended for use both in general population surveys and in studies of patients with diverse health conditions, allowing for comparison of HRQoL scores across disease stages and diagnostic groups
2) condition-specific measures, developed for use among specific patient population (e.g. cancer, diabetes)
3) domain-specific measures, for measurement of specific symptoms (e.g. fatigue, pain)

It is common practice to combine condition-specific and/or domain-specific measures with generic measures. The feasibility and other psychometric properties of HRQoL measures, however, may differ between populations.

Blood loss during delivery is one of the most frequently occurring delivery related complications that may have consequences for maternal HRQoL, e.g. because of excessive fatigue. Red blood cell (RBC) transfusion is one of the primary treatments for the resulting postpartum anemia. In general, the medical indication to give a RBC transfusion postpartum is based on Hb thresholds.[1] The main purpose however, of RBC transfusions postpartum is not to increase Hb values, but to improve HRQoL. HRQoL data are not applied in clinical decision-making process regarding blood transfusions yet. When planning a study on the HRQoL effects of a novel RBC transfusion policy after delivery, we tested the appropriateness of HRQoL measures including the domain-specific Multidimensional Fatigue Inventory (MFI) for fatigue and two generic measures (Short Form 36 (SF-36) and the EQ-5D classification of own health) among women after vaginal delivery (VD), elective caesarean section (CS) and emergency CS. The objectives of this study were to assess, in a clinical obstetrical setting:

1. the feasibility of the MFI, SF-36 and EQ-5D (indicators: response rate, missing/non-unique answers, reported difficulties, and completion time)
2. the score distribution of the MFI, SF-36 and EQ-5D (mean scores, standard deviations, presence of floor and ceiling effects)
3. the reliability of the scales of MFI and SF-36 (internal consistency)
4. the discriminative ability of the MFI, SF-36 and EQ-5D rating of own health between groups of women by type of delivery 1 week after delivery

5. the responsiveness over time of the MFI, SF-36 and EQ-5D rating of own health (differences between mean scores at T=0 and T=6 weeks, and effect sizes)

MATERIAL AND METHODS

Patients

In the period June 2003 till March 2004, 71 consecutive patients after VD and 70 patients after CS were included in two university hospitals and in one general hospital in the Netherlands. Patients undergoing CS were posthoc divided into those undergoing an elective CS (N= 36) and those undergoing an emergency CS (N=34). Inclusion criteria were: maternal age older than 18 years and proper knowledge of the Dutch language. Details of the study have been published previously.[2] Ethnic origin was defined according to the criteria of Statistics Netherlands.[3] If a woman herself and at least one of her parents were born abroad, or if a woman was born in the Netherlands but at least one of the parents were born abroad, she was classified as being of non-Dutch ethnic origin.

HRQoL measures

MFI

The originally Dutch Multidimensional Fatigue Inventory (MFI) was developed as a tool to comprehensively assess fatigue in cancer patients.[4,5] Nowadays the English translation is available. The questionnaire covers five dimensions: General Fatigue (GF), Physical Fatigue (PF), Mental Fatigue (MF), Reduced Motivation (RM) and Reduced Activity (RA). Each dimension is covered by a five-item scale. The number of response choices per item is four. Each scale has ranges from 4 to 20 (4=optimal). Reference scores are available for MFI, but not by age and sex, so that we could not use these.[6]

SF-36

The generic SF-36 version 1 was developed in the United States from the larger battery of health status instruments employed in the Medical Outcomes Study.[7-10] It consists of 36 items, organized into eight scales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH). The number of response choices per item ranges from two to six. The SF-36 yields an eight-dimensional profile, with each scale having a range from 0 to 100 (100=optimal). The SF-36 furthermore provides a physical summary score (PCS; predominantly based on the scales PF, RP, BP and GH) and a mental summary score (MCS relating to VT, SF, RE and MH).[11] PCS and MCS were constructed so that the general US population had a mean score of 50 and a standard deviation of 10. The

Dutch version of the SF-36 employed in the current study was developed as a part of the International Quality of Life Assessment (IQOLA) Project, whose objective is to translate, validate, and norm the SF-36 in a wide range of languages and cultural settings.[12,13] Reference scores by age and sex were available from Aaronson et al.[12]

EQ-5D

The EQ-5D classification of own health was developed by the international EuroQoL Group.[14] It consists of five items (Mobility; Self-Care; Usual Activities; Pain/Discomfort; Anxiety/Depression), each following the general form: 1 = no problems, 2 = some problems, 3 = extreme problems. The sixth item is a global evaluation of own health on a visual analogue scale (EQ-VAS) with a range from 0 (worst imaginable health state) to 100 (best imaginable health state). Reference scores by age and sex were available from Hoeymans et al.[15]

Timing of assessments

Women completed the MFI and EQ-5D 12-24 hours after vaginal delivery (VD) and 24-48 after caesarean section (CS), respectively (T = 0). One, three and six weeks after delivery (time points T = 1, 3 and 6 weeks) the EQ-5D and MFI were filled in at home. The SF-36 was added to the latter three questionnaires. The questionnaires were returned by mail to the investigators and patients were reminded by telephone in order to increase the response.

Statistics

Patients

Frequencies were described as number, mean, and SDs. Differences in type of delivery were analyzed using the χ^2 test.

Feasibility

Total questionnaire response, missing/non-unique answers, and the completion time were used as feasibility indicators. At the end of the questionnaires women could report their experienced difficulties while filling in the questionnaires. Missing values were defined as those cases, where no answer was given, and those where more than one response was given when only one was required. Completion time was defined as the time as reported by the patient required to complete the questionnaire. In addition the number of patients who needed help filling in the HRQoL questionnaire was recorded.

Score distribution

For EQ-VAS and MFI, no constructed values for missing values were imputed. For SF-36, constructed values for missing values were imputed following guidelines in the manual after the item non-response analysis.[16] Mean scores, standard deviations, and the percentages of respondents with the maximum possible score and the minimum possible score were calculated per scale. For SF-36, mental and physical summary scores were calculated.[11] For the EQ-5D classification we computed the percentages of subjects reporting 'no problems'.

Reliability

The internal consistency of the SF-36 subscales and the MFI subscales was determined with Cronbach's alpha coefficient. An alpha-coefficient of 0.70 or higher was considered as sufficient for the purpose of group comparisons.[17] Internal consistency could not be measured for EQ-5D classification, as it consists of one item with ordered response options per scale.

Discriminative validity

Discriminative validity was defined as the ability of the MFI, SF-36 and EQ-VAS to discriminate between groups of women by type of delivery at T=1 week. Discriminative validity was measured with effect sizes defined as d= [(Mean(a) – Mean(b)]/SD(pooled). a= scores of patients after VD, b= scores of patients after elective CS or emergency CS and SD(pooled)= $\sqrt{[(SD(a)^2 + SD(b)^2)/2]}$. The effect size (d) gives an indication of the clinical relevance of the statistically significant differences. $0.20 \leq d < 0.50$ indicates a small effect, $0.50 \leq d < 0.80$ a moderate effect, and $d \geq 0.80$ a large effect.[17] Scores of MFI, SF-36 and EQ-5D classification, including VAS, were compared with reference scores of the age-matched female Dutch population ("references").

Responsiveness over time

Differences between mean scores of MFI, SF-36, and EQ-VAS at T = 0 and T = 6 weeks were analyzed using two-sided Wilcoxon's signed rank tests. When scores differed with p-values < 0.05 in the expected direction (e.g. improvement) this was viewed as a sign of sensitivity to change of the studied measures. Moreover, an effect size estimation (d) was calculated which related the difference in mean scores to the dispersion in scores. The d was defined as = [(Mean score (a) – Mean (b)]/SD (pooled). a= scores at T=0, b= scores of patients at T=6 weeks and SD(pooled)= $\sqrt{[(SD(a)^2 + SD(b)^2)/2]}$, with interpretation as above.

P-values <0.05 were considered significant. All statistical analyses were performed using the SPSS package, version 11.5, for WINDOWS. The medical ethical review board of Erasmus MC, University Medical Center Rotterdam, approved this study.

RESULTS

Patient characteristics

The characteristics of the patients are shown in table 1. Mean age was 30.5-32.4 years for the three study groups, with a gestational age at delivery of 37.3-39.7 weeks. Almost all women had singleton births and approximately one third were primiparous. Thirty-four percent of the patients in the study group were of non-Dutch ethnic origin. Of the patients from Dutch ethnic origin, 46% had a VD, 28% an elective CS and 26% an emergency CS, where the percentages of patients from non-Dutch ethnic origin were 60%, 19% and 21% respectively (p>0.05).

Feasibility

A total of 55% of the patients returned all HRQoL measures, 16% returned three questionnaires, 9% returned two questionnaires and 20% returned only the first questionnaire. Of the ethnic Dutch patients 70% returned all questionnaires, whereas only 44% of the ethnic non-Dutch patients returned all questionnaires. For all different time points combined, the mean amount of missing values (range) of the returned HRQoL measures was 1.8 (0-4) for the MFI, 1.1 (0-3) for EQ-5D classification, including VAS, and 0.3 (0-1) for SF-36.

Table 1. Patient characteristics

	Vaginal Delivery (N=71)	**Elective Caesarean Section (N=36)**	**Emergency Caesarean Section (N=34)**
Age (Years), mean ± sd	30.5 ± 5.7	30.5 ± 5.4	32.4 ± 5.4
Gestational age at delivery (weeks, mean ± sd)	38.9 ± 2.6	37.3 ± 3.1	39.7 ± 1.8
Singleton	68 (96%)	35 (97%)	33 (97%)
Primiparous	23 (32%)	11 (31%)	15 (44%)
Ethnic origin (N)*			
Dutch	42	26	24
Non-Dutch	29	9	10
Unknown		1	

Patient characteristics. *Ethnic origin was defined according to the criteria of Statistics Netherlands (CBS 2000). If a woman herself and one of her parents were born abroad, or if a woman was born in the Netherlands but one of the parents was born abroad, she was classified as non-Dutch ethnic origin.

Table 2. Mean (SD), minimum score (%) and maximum score (%), Crohnbach's alpha and effect size at different time points

	Time point	Mean (SD)	Minimum score (%)	Maximum score (%)	Cronbach's alpha	Time point	Mean (SD)	Minimum score (%)	Maximum score (%)	Cronbach's alpha	Effect size (Cohen's d)
EQ-VAS	0	63.5 (17.6)	0.0	4.3		6 weeks	82.8 (12.0)	0	15.3		1.28
SF36 PF	1 week	48.8 (24.1)	0.0	0.9	0.91	6 weeks	85.4 (19.1)	1.2	25.9	0.91	1.68
SF36 RP	1 week	22.0 (30.3)	50.0	8.3	0.77	6 weeks	73.8 (36.8)	12.9	57.6	0.85	1.54
SF36 BP	1 week	40.9 (17.9)	3.7	0.9	0.48	6 weeks	78.2 (27.7)	0.0	60.0	0.66	1.60
SF36 GH	1 week	75.2 (18.3)	0.0	2.8	0.76	6 weeks	78.0 (18.0)	0.0	10.6	0.79	0.15
SF 36VI	1 week	51.7 (17.9)	0.0	0.0	0.70	6 weeks	68.2 (18.3)	0.0	6.0	0.79	0.91
SF36 SF	1 week	57.2 (25.9)	3.7	10.2	0.66	6 weeks	86.2 (18.5)	0.0	55.3	0.70	1.29
SF36 RE	1 week	67.0 (39.9)	19.4	51.9	0.81	6 weeks	82.7 (34.4)	10.6	77.6	0.89	0.42
SF36 MH	1 week	79.0 (16.2)	0	12.1	0.81	6 weeks	86.3 (14.4)	0.0	19.0	0.82	0.48
MFI GF	0	14.9 (4.2)	18.7	2.2	0.83	6 weeks	10.5 (4.6)	2.4	13.1	0.89	1.00
MFI PF	0	15.0 (4.2)	17.0	0.7	0.85	6 weeks	8.5 (4.2)	0.0	24.1	0.89	1.55
MFI RA	0	14.9 (3.9)	13.9	0	0.75	6 weeks	9.0 (3.9)	0.0	16.9	0.82	1.51
MFI RM	0	11.6 (4.1)	1.4	4.3	0.74	6 weeks	7.1 (3.6)	0.0	38.6	0.85	1.17
MFI MF	0	11.3 (4.9)	8.0	11.6	0.89	6 weeks	8.8 (4.6)	1.2	35.7	0.93	0.53

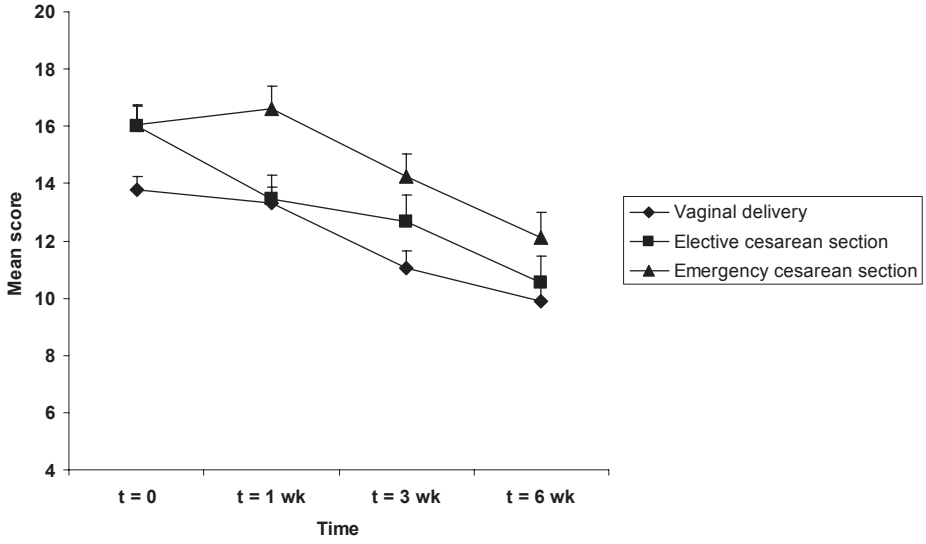
Mean scores (SD), percentage of patients with minimum/maximum score, Crohnbach's alpha and effect size of MFI, SF-36 and EQ VAS at different timepoints. Scores at T=6 weeks were significant compared at T=0 ($p<0.01$, with two-sided Wilcoxon's signed rank tests). $0.20 \leq d < 0.50$ indicates a small effect, $0.50 \leq d < 0.80$ a moderate effect, and $d \geq 0.80$ a large effect.

Mean reported completion time of the set of HRQoL measures at T=0 was 8.5 minutes, at T=1 week 11.9 minutes, at T=3 weeks 10.7 minutes, and at T=6 weeks 9.2 minutes (ranges 2-30 minutes). Seventeen out of the 141 patients at T=0 needed help filling in the questionnaires, 11 patients out of 141 at T=1 week, 5 patients out of 141 at T=3 weeks and 5 patients out of 141 at T=6 weeks.

Score distribution

Mean scores, standard deviations, and the percentage of respondents showing the maximum and the minimum possible scores of the MFI, EQ-VAS at T=0 and T=6 weeks, and of SF-36 at T=1 week and T=6 weeks, are shown in table 2. At T=1 week the SF-36 subscale RP showed a floor effect (>25% of the respondents having the lowest possible score), and the SF-36 scale RE showed a ceiling effect (>25% of the respondents having the highest possible score). At T=6 weeks no floor effects were seen, but the SF-36 scales PF, RP, BP, SF, RE, and the MFI scales RM and MF showed a ceiling effect. The distributions of most MFI scales were skewed towards the worst possible score range at T=0. This was also evidenced by the substantial percentage of respondents scoring at the lowest possible scale level, particularly for the functional limitations scales. At T=6 weeks the distributions were skewed toward the best possible score range. Figure 1 shows the MFI scores over time for the three study groups. In all three study-samples a wide range of scores was observed for all scales of SF-36 subscales. The results of the EQ-5D at the different time points, e.g. the percentage of patients after VD, elective CS, and emergency CS who scored "no problem", are shown in table 3.

Figure 1A. MFI subscale General Fatigue (mean and se)



MFI subscales range from 4 to 20 (4 = best, 20 = worst). Mean ± s.e.m. are shown.

Figure 1B. MFI subscale Physical Fatigue (mean and se)

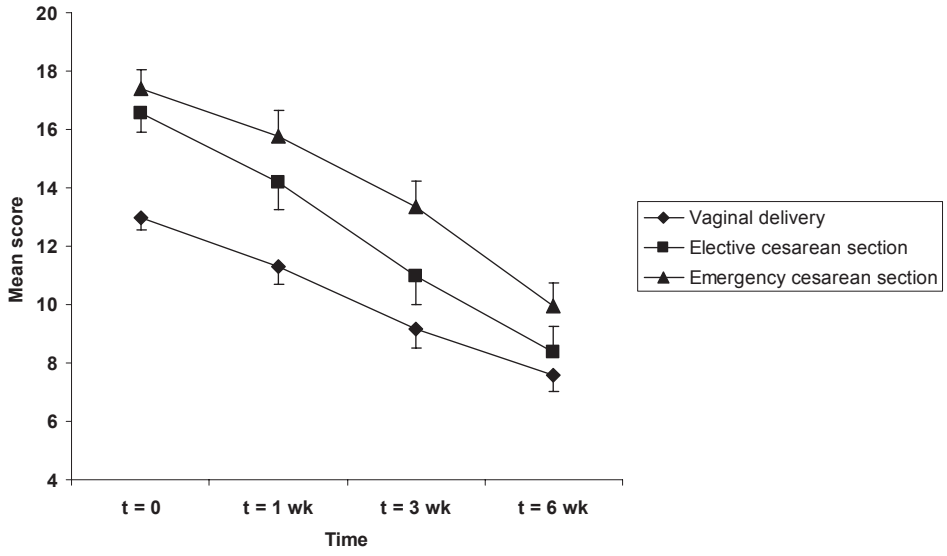
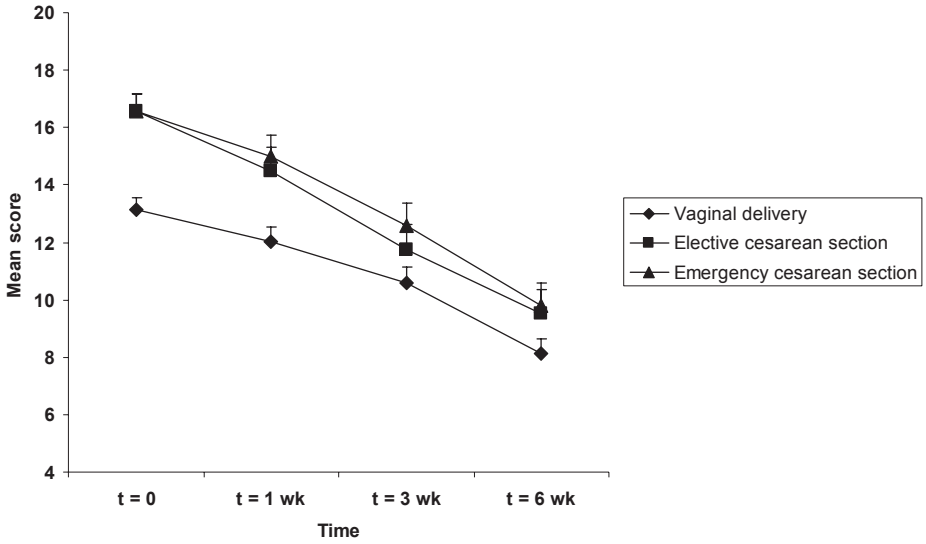


Figure 1C. MFI subscale Reduced Activity (mean and se)



MFI subscales range from 4 to 20 (4 = best, 20 = worst). Mean ± s.e.m. are shown.

Reliability

Cronbach's alphas of SF-36 scales at T = 1 week and T = 6 weeks, and MFI scales at T = 0 and T= 6 weeks are shown in table 2. All alphas were higher than 0.70, except SF-36 scale BP at T = 1 week (0.48) and at T = 6 weeks (0.66).

Figure 1D. MFI subscale Reduced Motivation (mean and se)

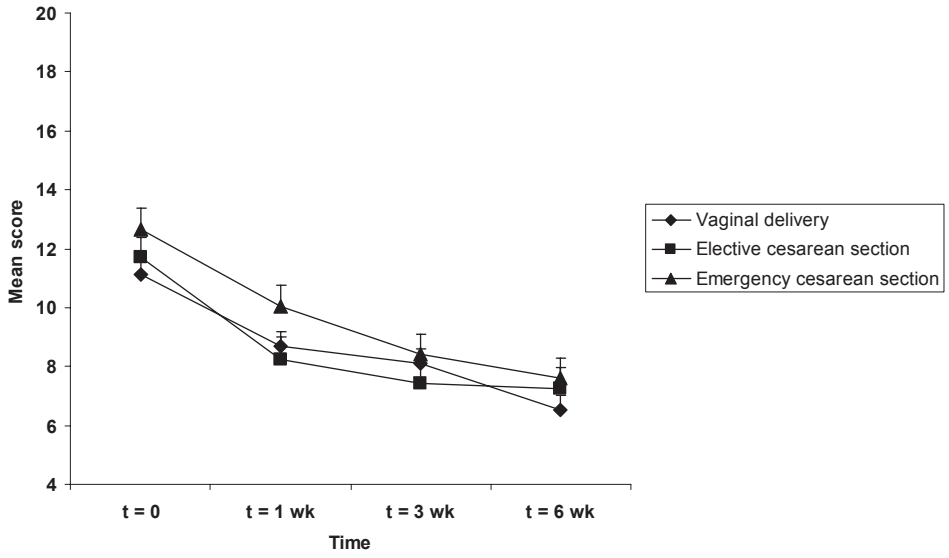
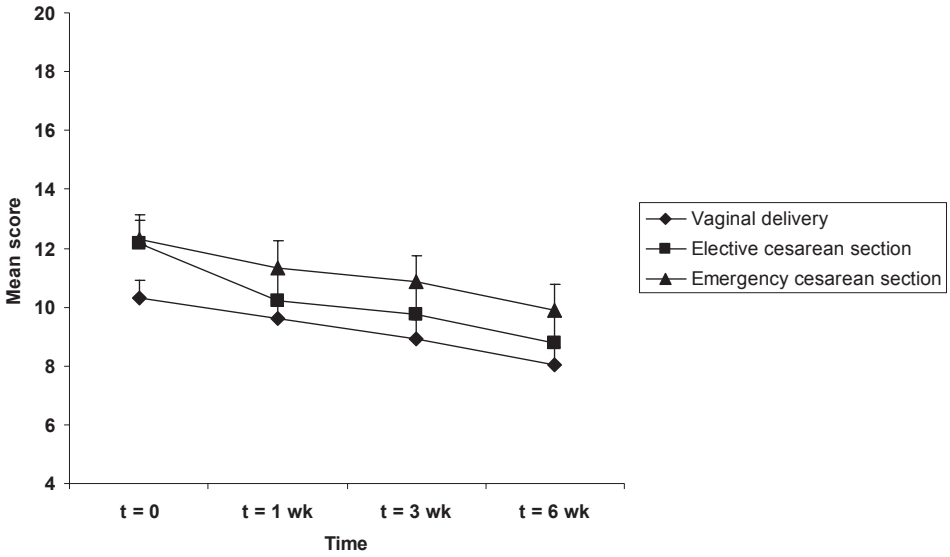


Figure 1E. MFI subscale Mental Fatigue (mean and se)



MFI subscales range from 4 to 20 (4 = best, 20 = worst). Mean ± s.e.m. are shown.

Discriminative validity

Mean scores and standard deviations of MFI, EQ-VAS, and SF-36 at T = 1 week are shown in table 4. All mean scores were lower after emergency CS. Especially the physical HRQoL scores were on average significantly lower compared to patients after VD, as ex-

Table 3. Scores of EQ-VAS, MFI, SF-36 (mean ± SD) and effect sizes at T=1 week compared to patients after VD

	Vaginal Delivery (N=71)	Elective Caesarean Section (N=36)	Effect size (Cohen's d)	Emergency Caesarean Section (N=34)	Effect size (Cohen's d)	Controls*
EQ-VAS	75.0 ± 14.5	69.3 ± 15.1	0.39	61.0 ± 15.3*	0.94	
MFI GF	13.1 ± 4.3	13.5 ± 4.0	0.10	16.5 ± 4.5*	0.77	
MFI PF	11.4 ± 4.5	14.4 ± 4.8*	0.64	15.7 ± 5.1*	0.89	
MFI RA	12.0 ± 3.8	15.0 ± 4.2*	0.75	15.0 ± 4.5*	0.72	
MFI RM	8.7 ± 3.4	8.4 ± 3.7	0.08	10.1 ± 4.8	0.34	
MFI MF	9.5 ± 4.7	9.5 ± 4.3	0.00	11.4 ± 5.7	0.36	
SF-36 PF	59.4 ± 20.7	45.0 ± 20.8*	0.69	32.8 ± 23.1*	1.21	91.9
SF-36 RP	26.9 ± 35.0	18.0 ± 18.4	0.32	16.4 ± 28.6	0.33	83.1
SF-36 BP	44.7 ± 16.1	38.8 ± 18.4	0.34	35.6 ± 19.5*	0.51	78.9
SF-36 GH	76.5 ± 17.1	75.9 ± 19.4	0.03	72.2 ± 19.7	0.23	78.3
SF-36 VI	55.8 ± 16.7	53.8 ± 15.3	0.12	42.4 ± 19.0*	0.75	67.4
SF-36 SF	64.6 ± 24.4	53.0 ± 26.8	0.45	47.0 ± 24.2*	0.72	85.9
SF-36 RE	70.4 ± 36.4	74.7 ± 36.4	0.12	54.0 ± 46.6	0.39	81.1
SF-36 MH	81.9 ± 15.4	78.7 ± 16.2	0.20	73.8 ± 16.9*	0.50	76.4
SF-36 PSC	35.6 ± 7.7	31.5 ± 7.4	0.54	29.9 ± 7.5*	0.75	53.8
SF-36 MSC	53.6 ± 9.9	53.4 ± 9.0	0.02	48.8 ± 11.2	0.45	48.2

Means scores (SD) of EQ-5D-VAS, MFI, and SF-36, and effect sizes at T= 1 week for the different type of delivery. $0.20 \leq d < 0.50$ indicates a small effect, $0.50 \leq d < 0.80$ a moderate effect, and $d \geq 0.80$ a large effect. *$p \leq 0.05$, with two tailed Mann Whitney U test.
Control scores are available from Hoeymans et al, and Aaronson et al. No reference scores were available for MFI and EQ-VAS.[12,15]

pected. The effect sizes for the differences in physical scale scores were moderate between patients after elective CS and patients after VD. They were (very) small for the mental subscales. Between patients after emergency CS and patients after VD, effect sizes for the differences between physical scale scores were moderate to large whereas the effect sizes indicated small differences for the mental scores.

Responsiveness over time

The ability of the three measures to discriminate between T = 0 (MFI, EQ-VAS)/T = 1 week (SF-36) and T = 6 weeks within a group is shown in table 2. The MFI, SF-36 and EQ-VAS scores showed highly significantly improvements in physical functioning between T=0 and T=6 weeks. The effect sizes were large with ranges between 0.91-1.68. The instruments showed smaller effects for improvement for mental functioning between T=0 and T=6 weeks, with effect sizes ranging from 0.42-1.29. SF-36 GH did not detect any changes between T=0 and T=6 weeks.

Table 4. EQ-5D scores (% patients who answered "no problem")

	Vaginal Delivery	Elective CS	Emergency CS
Mobility			
T = 0	35.2	13.9	0.0
T = 1 week	63.0	48.0	24.1
T = 3 weeks	88.5	73.7	60.7
T = 6 weeks	95.5	94.7	95.5
Controls*	90.0		
Self-care			
T = 0	63.4	22.2	8.8
T = 1 week	85.2	80.0	72.4
T = 3 weeks	96.2	94.7	89.3
T = 6 weeks	97.7	100.0	100.0
Controls*	97.9		
Usual Activities			
T = 0	19.7	8.3	2.9
T = 1 week	38.9	12.0	13.8
T = 3 weeks	63.5	31.6	17.9
T = 6 weeks	93.2	73.7	59.1
Controls*	85.3		
Pain/ discomfort			
T = 0	15.5	2.8	2.9
T = 1 week	24.1	16.0	6.9
T = 3 weeks	67.3	42.1	35.7
T = 6 weeks	84.1	89.5	59.1
Controls*	67.3		
Anxiety/ depression			
T = 0	90.1	83.3	76.5
T = 1 week	85.2	84.0	62.1
T = 3 weeks	90.4	94.7	82.1
T = 6 weeks	97.7	89.5	86.4
Controls*	87.2		

*Controls are female and age matched Dutch subjects.[15]

DISCUSSION

This evaluation of the international standard HRQoL measures MFI, EQ-5D and SF-36 established the feasibility, reliability and validity of these measures in a clinical obstetric setting. This study supports the discriminative ability of these measures by type of delivery and provides reference (norm) scores for patients after delivery.

Different HRQoL measures are used in studies with patients after delivery.[18-22] However, to our knowledge, no psychometric evaluation of HRQoL measures has been done in the postpartum period. MFI has already been used to measure fatigue in patients with

several diseases[23-26] and showed to be a useful tool to measure fatigue. On the basis of results of a psychometric analysis of 4 generic health measures in migraine patients, the SF-36 appeared to be the most suitable generic measure for describing HRQoL in that group of patients.[27] The SF-36 was already validated during pregnancy, but not in the postpartum period.[19] The EQ-5D appeared less sensitive probably due to the fewer items of this measure.[14] From the literature it is known that the EQ-5D has large ceiling effects (with over 95% at the ceiling for the functional dimensions) compared to the SF-36 (37-72%).[11,14]

Jomeen et al showed the SF-36 to be a potentially valuable measure in screening for the occurrence of HRQoL deficits during pregnancy, especially because of the correlations of the SF-36 mental subscales to mood measures.[19] However, the results of our study did not show differences of the SF-36 mental subscales in the first six weeks postpartum. Our scores concerning the physical HRQoL were as expected from clinical experience. At T = 6 weeks most SF-36- and MFI subscales showed percentages of respondents higher than 25% with the best possible scale score (the ceiling effect). This limits the use of these measures to detect changes after the first six weeks postpartum. The MFI scales showed Cronbach's alphas at T = 0 and T = 6 weeks that were adequate for comparisons of scores at group level. The SF-36 scales showed adequate Cronbach's alphas at T = 1 week and T = 6 weeks, except for SF-36 BP, which may be due to the fact that this is a 2-item scale.[9]

This study showed the ability of the SF-36 and MFI to discriminate between groups by type of delivery. HRQoL postpartum may also be influenced by other factors than type of delivery, such as mother-related factors (e.g. amount of blood loss, duration of gestation, first delivery or not, presence of co-morbid conditions) and child-related factors (e.g. the condition of the baby). We recommend further assessment of the validity of the MFI and SF-36 by comparing score patterns with clinical parameters of the patients.

Limitations of our study include the low total questionnaire response at T = 6 weeks, despite the recall by telephone. Subgroup analysis showed 70% of ethnic Dutch women returned the questionnaires, but only 44% of the patients from non-Dutch ethnic origin. This phenomenon is well known from other studies.[28] Of the patients who returned the questionnaires, many patients completed either all questionnaires (55%) or only the one at T = 0 (20%). All three measures showed a low percentage of missing values. Completing the questionnaires was thus not difficult for these patients. In the Rotterdam region, the proportion of pregnant women of non-Dutch ethnic origin approaches 75%. Therefore, further efforts need to be made to increase response rates among immigrants.

Given the prevalence and, sometimes, serious consequences of fatigue after delivery, research efforts aimed improving HRQoL postpartum. To achieve this goal the development of a reliable and valid instrument for assessment is essential. It is anticipated that this line of research will contribute to a better understanding of impaired HRQoL postpartum, its prevalence, characteristics, course and correlates. An understanding of the likelihood of HRQoL impairments postpartum can enhance the health professional's ability to evaluate individual cases, inform patients, and plan and evaluate therapy. The combination of MFI, SF-36 and EQ-5D showed good psychometric performance and is a good choice to measure HRQoL after delivery. Further research is needed to investigate the role of clinical variables of the delivery on the HRQoL of the mother and to increase the response rates among immigrants.

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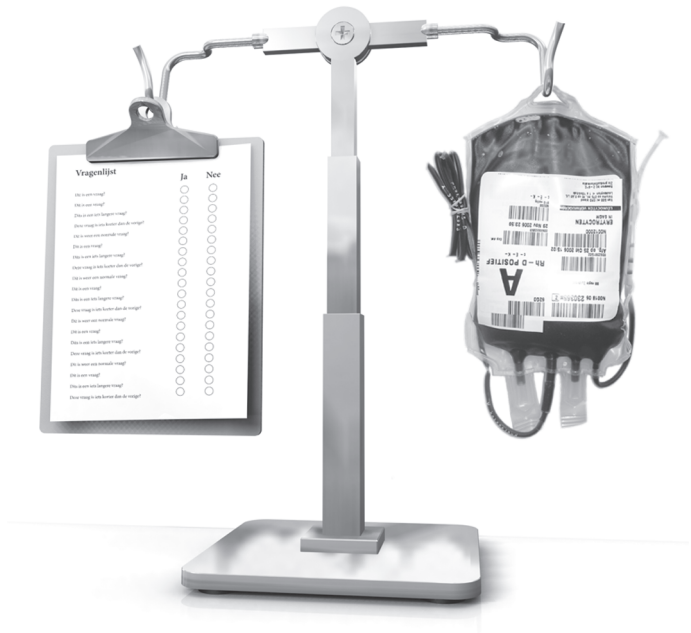
CHAPTER 7

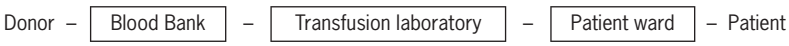
General discussion



RISKS OF BLOOD TRANSFUSION

The process of clinical blood transfusion is a complex chain beginning with a comprehensive health screening of the blood donor and ending with the clinical effects of the transfusion in the recipient (Figure 1).

Figure 1. Clinical blood transfusion chain



Every step in this process possesses the potential risk for complication. Fortunately, more stringent donor screening, the increased sensitivity of blood screening and improved storage conditions have contributed to a decline in the rate of transfusion complications. IN addition, improvement of the production process of blood components, more refined leukocyte depletion, and gamma irradiation have also decreased the complication rate through increased mmulogical safety.[1-6] However, the limitations of the microbial safety techniques include:

1) Transmission is only prevented on detectable pathogens
2) Detection efficacy is dependent on the sensitivity of the technique
3) With all techniques, detection is delayed by the window-phase (Table 1)
4) Currently, there are no available screening tests for protozoa
5) Risks of vacterial transmission persist

The risk of bacterial transmission in platelets and red blood cells is approximately 1 per 3000 units transfused.[7] Buffy coat derived platelet concentrates harbor an increased risk as they have higher storage temperatures (20°C), are pooled from multiple donors and have of a Sterile Connecting Device (SCD). The French hemovigilance system reports incidences of clinical bacterial complications of 2: 100,000 and 6 viral complications in the period 1996 to 1998.[8] The Dutch hemovigilance system Transfusie Reacties In Patiënten (TRIP) reported in 2004 5 cases of bacterial contamination, where 1 case was proved

Table 1. Window period infections in the US[3]

	Window period (days)	Risk per unit	NAT window period reduction (Days)	Risk with NAT (undiluted)
HIV	22	1 : 493,000	11	1 : 986,000
HIV plus p24	16	1 : 676,000	5	1 : 986,000
HTLV	51	1 : 641,000	NA*	NA*
HCV	82	1 : 103,000	59	1 : 368,000
HBV	59	1 : 63,000	25	1 : 110,000

*Not applicable

(contamination with Bacillus Cereus). 6 Cases of viral transmission were reported (4 CMV transmission, 1 HCV, and 1 HBV) but none could be proved.[9]

Remaining immunological risks include the risks of Graft-versus-Host Disease, RBC alloantibody formation and the occurrence of transfusion-associated acute lung injury (TRALI). More specifically, the incidence of RBC alloantibodies formation after elective surgery is approximately 8%.[10] Multitransfused patients have a risk varying from 12-22% to develop red blood cell alloantibodies.[10-13] In 2004, nine cases of TRALI were reported to the Dutch hemovigilance system TRIP, of which 3 could be proven and 1 was classified as a possible case of TRALI.[9] Finally, the US Food and Drug Administration reported an increase in the occurrence of TRALI cases from 2001 to 2003 from 15.8% to 22.3%.[14]

RISK REDUCTION IN CLINICAL BLOOD TRANSFUSION

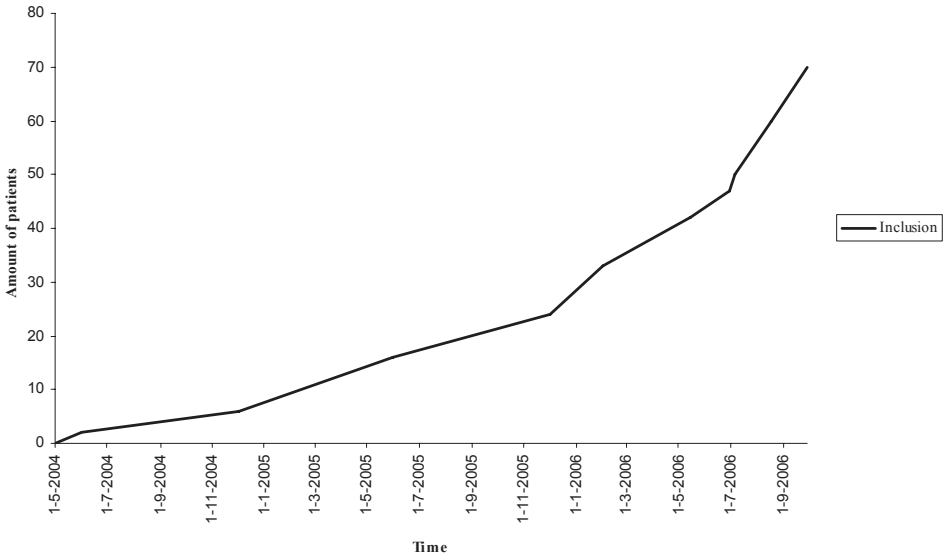
Risk reduction in clinical blood transfusion can be attained through the use of more patient centered HRQoL criteria. In addition, other potential areas of risk reduction include improvement of the identification procedure, a better understanding of the function of blood cells, pathogen inactivation techniques and TRALI prevention.

Health related quality of life

Anemia is associated with increased morbidity and all-cause mortality in patients with chronic kidney disease and in elderly patients.[15-17] Various studies have recommended a reconsideration of transfusion policies.[18-20] Currently, transfusion triggers are focused on laboratory parameters of the patients, i.e. the platelet count or Hb value.[21-22] The adoption of a lower transfusion trigger is a clinical method gaining acceptance as a means of transfusion risk reduction. For example, the most common used RBC transfusion trigger in the Netherlands is the "4-5-6 rule", based on Hb and symptoms of the patients (appendix I). However, there is a wide variance in RBC transfusion policy among hospitals and among physicians (appendix II).

However, blood transfusion should be given to improve the health related quality of life (HRQoL) of the patient instead of laboratory values of the patient. Various reports in the literature recommend incorporation of HRQoL measures in clinical transfusion medicine.[23,24] Culleton et al suggest a redefinition of "normal" hemoglobin values in the elderly further clinical trials to determine whether anemia correction improves quality of life in this population.[25] The relationship between HRQoL and anemia has been confirmed mostly in studies using recombinant erythropoietin in oncological patients. However, the effect of a physiologic anemia on the (physical) HRQoL has not yet been investigated.

Figure 2. Amount of included patients since the start of the WOMB study.



This thesis suggests that the internationally validated generic HRQoL measures SF36, EQ-5D, and the domain specific MFI are suitable to measure generic HRQoL and fatigue in patients with acute and chronic anemia. The Hb values of the patients could partly explain the lower HRQoL scores of the anemic patients, which is comparable to other studies that link laboratory parameters to HRQoL scores.[26] Thus, HRQoL as well as Hb values should be involved in a new transfusion trigger model. Oncoloy has commonly employed the use of HRQoL scores for therapy. For example the Visual Analogue Scale is used in several hospitals to measure the pain level of clinical patients. Pain medication doses are partly based on these scores. A similar questionnaire could be applied to the evaluation of the physical fatigue of the patients with acute and chronic anemia.

A clinical trial that investigates the effect of RBC transfusion on HRQoL is the WOMB study: Well-being of Obstetric patients on Minimal Blood transfusions (ClinicalTrials.gov identifier: NCT00335023). The WOMB study is implementing a multicenter randomized clinical trial comparing RBC transfusion treatment versus expectative therapy in patients with PPH resulting in anemia. Primary outcome in this study is fatigue measured with the MFI questionnaire. The characteristics of the questionnaires are described in chapter 4 to 6. The inclusion criteria and study design are shown in appendix III. The participating hospitals are shown in appendix IV. Figure 2 demonstated current numbers of included subjects.

This study contributes to a new RBC transfusion model for patients with acute anemia after PPH. This patient group consists in general of healthy young women. This will decrease the external validity of the study and results of this study may be therefore only used in these patients. In addition, logistical reasons make it difficult for the WOMB study to be blinded. Although there are limitations, this study describes clearly the role of acute anemia on HRQoL. The WOMB study will contribute to the discussion on the optimal RBC transfusion triggers based on Hb values and HRQoL scores, for patients with acute anemia after PPH.

Identification procedure

The 'near miss' events and the incorrect blood components transfused (IBCT) were the most frequently reported events, e.g. 60% in the UK.[27] Near miss events are any error that, if undetected, could result in the determination of a wrong blood group, or issue, collection or administration of an incorrect, inappropriate or unsuitable component, but which was recognized before transfusion took place. According to the French result 29.7% of the IBCT was due to technical failure, 17.8% to logistic failure, 51.5% to human error and for 1% no explanation was found.[8] More attention should be given to the reduction of these 'near miss' events and IBCT.

Functioning of blood cells

Despite hematologic advances, there are still gaps in ourknowledge of the functioning of blood cells. In particular, the specific role of platelets is unclear. No in vitro tests are available for measurement of platelet function in vivo. The introduction of a pathogen inactivation technique (discussed below) could increase the storage time of platelet concentrates. This necessitates a better understanding of platelet aging. Platelet surface glycoproteins might play an important role in the aging of platelets.[28-30] A better understanding of the platelet signaling process could lead to improvement of platelet concentrates.

Pathogen inactivation

A new important technique to increase microbial safety of blood components is the introduction of a pathogen inactivation technique. The current role of pathogen inactivation for plasma units, platelet concentrates and RBC concentrates will be briefly discussed below.

Plasma

For plasma units two different techniques are already used in routine practice: the Solvent Detergent treatment (SD-FFP) and the Methylen Blue treatment.[31] Concerns of the occurrence of unexpected venous thrombotic events after large-volume exposure have made the SD-FFP method no longer applicable in the United States. However in Europe it

is still used.[32] Plasma treated with the psoralen compound amotosalen HCL (S59) proved to be non-toxic and still has acceptable functional characteristics.[33] Various studies have demonstrated the increased clinical efficacy of SD-FFP method when compared with the FFP method in patients with acquired liver disease and in patients with thrombotic thrombocytopenic purpera.[34-36] In addition, treatment with riboflavin (vitamin B_2) and UV-A or visible light have shown promise in experimental trials.[37-39]

Platelet concentrates

Two different trials showed no differences between platelet concentrates treated photochemical treatment using the psoralen compound amotosalen HCL (S59) and for clinical hemostasis, hemorrhagic adverse events, and overall adverse events. Platelet components prepared with PCT offer the potential to further improve the safety of platelet transfusion using technology compatible with current methods to prepare buffy coat platelet components and can be used in routine clinical practice.[40,41] Other pathogen inactivation techniques, e.g. treatment with Riboflavin (Vitamin B2) and photochemical treatment with the 8-methoxypsoralen and the 4' aminomethyl 4,5',8-trimethylpsoralen are more experimental.[42,43]

RBC concentrates

For RBC concentrates two different pathogen inactivation methods are currently in an experimental phase. The first, inactine, inactivates different viruses and bacteria in whole blood and RBC concentrates.[44-49] Concerns have been raised about the formation of RBC alloantibodies using this technique.[50] The other technique uses S-303, which is a compound that belongs to a class of compounds called frangible anchor-linked effectors (FRALEs). FRALEs are activated by a pH shift when added to packed red cells suspended in residual plasma and a red cell additive solution at neutral pH. However, also formation of RBC alloantibodies against S-303-treated RBCs is described.[51]

TRALI prevention

TRALI is a life-threatening adverse event of blood transfusion. It is the leading cause of transfusion-related death in the United States (FDA) (Table 2).

Clinical criteria for the diagnosis of TRALI include the criteria of Acute Lung Injury (ALI):

1) insidious, acute onset of pulmonary insufficiency
2) profound hypoxemia $PaO_2/FiO_2 < 300$ mm Hg
3) bilateral fluffy infiltrates consistent with pulmonary edema
4) pulmonary artery wedge pressure less than or equal to 18 mm Hg, with no clinical evidence of left atrial hypertension[52]

Table 2. Transfusion-Related Fatalities Reported to the FDA, FY 2001 to 2003[14]

Reported Fatalities			
Categories	FY 2001 (%)	FY 2002 (%)	FY 2003 (%)
TRALI	12 (15.8)	16 (16.8)	21 (22.3)
ABO hemolytic transfusion Rx	10 (13.2)	14 (14.7)	11 (11.7)
Bacterial contamination	8 (10.5)	17 (17.9)	11 (11.7)
Other transfusion related causes	27 (35.5)	24 (25.3)	26 (27.7)
Transfusion relation not ruled out	11 (14.5)	9 (9.5)	13 (13.8)
Not transfusion related	4 (5.3)	5 (5.3)	4 (4.3)
Donor fatalities	4 (5.3)	10 (10.5)	8 (8.5)
Total	76	95	94

Abbreviation: FY, Fiscal year

For TRALI other criteria are:

1) new ALI temporally related to transfusion
2) the new ALI is thought to be mechanistically related to the transfusion
3) worsening of pre-existing pulmonary insufficiency temporally related to transfusion[53]

Thus the considered inciting factors of ALI should include TRALI if a blood transfusion is the inciting event. There are different definitions used for the occurring time of TRALI: within 6 (TRIP) or 24 (SHOT) hours after transfusion. Two different models are described for the explanation of the pathology of TRALI. The first is antibody-mediated event whereby transfusion of anti-HLA, class I or class II, or anti-granulocyte antibodies into patients whose leucocytes express the cognate antigens. This antibody-antigen interaction causes complement-mediated pulmonary sequestration and activation of neutrophils resulting in TRALI.[54,55] The second model is a two-event model: the first event is the clinical condition of the patient resulting in pulmonary endothelial activation and neutrophil sequestration, and the second event is the transfusion of a biologic response modifier (including anti-granulocyte antibodies, lipids, and CD40 ligand) that activates these adherent neutrophils resulting in endothelial damage, capillary leak, and TRALI.[56-58]

Although lack of scientific evidence, the Dutch Sanquin Blood Supply Foundation recommends to exclude donors, who could be immunized, e.g. female donors who had pregnancy and donors who received red blood cell transfusion (before 1980), from plasma apheresis.

FUTURE DEVELOPMENTS IN CLINICAL BLOOD TRANSFUSION THERAPY

Recently, two approaches have been used to produce RBCs that could be transfused, regardless of the ABO group of the donor and recipient, the so-called "universal donor" RBCs. The first approach has involved converting group A and B RBCs to group O by cleaving off the terminal immunodominant sugars.[59] The terminal galactose of group B RBCs is removed with the use of a recombinant α-galactosidase. This procedure is also available for group A RBCs with a N-acetyl-galactosamine as epitope. Increased anti-B titers are described after transfusion.[60] The second approach involves masking the blood group antigens with polyethylene glycol (PEG).[61] Clinical trials should prove the effectiveness of these new products.

Other developments to increase blood transfusion safety are blood substitutes, e.g. hemoglobin solutions and the use of recombinant erythropoietin. Hemoglobin solutions have been used with success in Jehovah's witness patients.[62,63] The use of recombinant erythropoietin is increasing to reduce the amount RBC transfusions in patients with disease states requiring multiple transfusion, i.e. cancer patients receiving chemotherapy, chronic and end stage renal failure, heart failure and critically illness.[64-68] However, RBC transfusion remains the first choice of treatment for acute anemia.

CONCLUSION

Blood components have never been safer. With the recent introduction of pathogen inactivation methods, the international goal of zero risk of microbial blood transfusion complications comes within reach. To further strengthen the chain of events of the process of clinical transfusions, more attention should be devoted to the hospital portion of the chain, specifically a more detalied understanding of the functioning of blood cells and not by the safety of the blood products as such. Reduction of the human errors can by reached by introduction of automatic computer assisted production and teaching of the persons who are involved in the clinical transfusion process. Also more attention should be given to a better knowledge of clinical transfusion practice, which leads to a diminished use of blood components and thereby to fewer complications.

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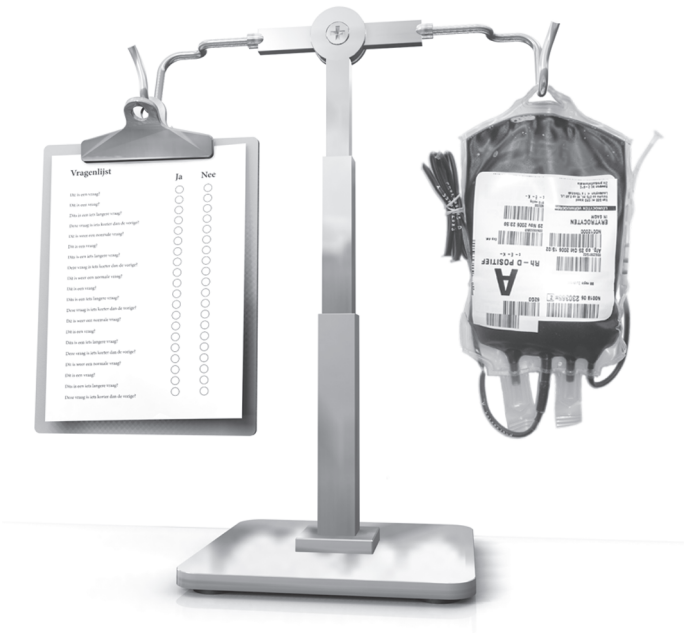
CHAPTER 8

Summary



After the introduction of blood component therapy in the 1960s, more and more attention is given to clinical transfusion medicine. Although blood transfusion is an important treatment in different clinical settings, there are still lack of much randomized clinical trials. Nowadays blood transfusion can be called a safe treatment. This might be due to an increasing awareness of the effects and risks of blood transfusion. In clinical transfusion practice a transfusion trigger is handled for the prescription of blood transfusion. This transfusion trigger is based on hemoglobin (Hb) levels for red blood cell (RBC) transfusion and on platelet count for platelet transfusions. Possibilities to improve the safety of blood transfusion are improvement of the blood components and reduction of the amount of blood transfusions.

This thesis describes 1) an in vitro study of a new pathogen technique for platelet concentrates and 2) a new model for RBC transfusion therapy for acute anemia. This model uses subjective health related quality of life criteria, which are validated in this thesis.

CHAPTER 1

Chapter one provides a general introduction to the history of blood transfusion and component therapy. Studies about the transfusion trigger for RBC transfusion and platelet transfusion are reviewed. Special attention is hereby given to health related quality of life and the role with anemia. An overview of the literature about the risks of blood transfusion is presented. The relationship between platelet transfusion and bacterial contamination is described briefly and a new pathogen inactivation technique for platelet concentrates is introduced.

CHAPTER 2

In chapter two functional characteristics of platelets after treatment with a pathogen inactivation technique using the psoralen compound amotosalen HCL (S59) and long wavelength UVA light were measured in vitro. Platelet concentrates were treated with one of the two different processing systems: 1) the experimental clinical processing system T-bag S59 reduction device (SRD) or 2) the commercially available integral processing system Wafer SRD. Treated platelets were compared with control platelet concentrates in a plasma/PAS III solution. No differences were found in product quality variables, in activation, and apoptosis variables. Platelets treated with the experimental T-bag SRD had a significant decrease in aggregation capacity and a significant increase in plasma LDH. These tests showed no differences for platelets treated with the commercially

available Wafer SRD. This in vitro study showed that treatment with the experimental T-bag SRD led to a significant decrease in platelet function. However, treatment with the commercially available Wafer SRD had only minor in vitro effects on the quality of the platelets.

CHAPTER 3

In a retrospective study two different hemoglobin transfusion triggers were compared in patients with acute myeloid leukemia who were treated with combination chemotherapy: 1) a Hb transfusion trigger ≤ 4.5-5.5 mmol/L, dependent on age and symptoms and 2) a more liberal therapy with a Hb transfusion trigger ≤ 6.0 mmol/L. The restrictive transfusion policy led to a significant decrease of 11% of red blood cell (RBC) transfusions. No significant differences were found in the incidence of infections, number of platelet units transfused, bleeding complications, cardiac symptoms, or response to chemotherapy. The restrictive transfusion policy, based on age and symptoms, was feasible in this clinical setting and it might be concluded that a restrictive transfusion policy is safe in supporting clinical patients treated with intensive chemotherapy for AML. Due to its retrospective nature, health related quality of life (HRQoL) of these patients could not be measured.

CHAPTER 4

Chronic anemia is a common complication of patients with Myelodysplastic Syndromes (MDS), with fatigue as most important symptom. Chapter four deals with fatigue and HRQoL of this patient group. Fifty consecutive MDS patients completed once the Short Form-36, the Multidimensional Fatigue Inventory and the EQ-5D Visual Analogue Scale. Hb level was measured during the same visit. The questionnaires showed a high feasibility, reliability and validity. Compared to the age and sex matched general population, MDS patients had worse HRQoL scores. A positive correlation between Hb level and HRQoL was found. This study provided insights into the suitability of established HRQoL measures for the evaluation of interventions in MDS patients. Hb values and HRQoL scores were complementary variables for evaluation of the severity of chronic anemia in patients with MDS.

CHAPTER 5

A common complication during delivery is blood loss. Chapter five describes fatigue and health related quality of life (HRQoL) in women after vaginal delivery (VD), elective caesarean section (CS) and emergency CS and its relationship with postpartum Hb levels during the first six weeks postpartum. 141 patients completed the HRQoL questionnaires MFI, SF36 and EQ-5D during the first six weeks postpartum. Patients after VD had higher mean physical HRQoL scores than after CS. Patents after VD needed on average three weeks for full physical recovery, patients after elective CS six weeks and patients after emergency CS more than six weeks. Mean mental HRQoL scores of the study groups were similar or even better compared to reference values. The significant correlation between Hb level and mean physical HRQoL scores found at t=0, had disappeared at one week postpartum. The HRQoL measures of this study can be used in future clinical trials to assess the effects of interventions postpartum.

CHAPTER 6

After the clinical examination of the HRQoL measures in chapter five, psychometric properties of these measures were evaluated in chapter six. Feasibility (response, completion time, reported difficulties, item non response), reliability (Cronbach's alpha), discriminative validity between groups by type of delivery, and responsiveness over time (Wilcoxon's signed rank tests and effect sizes) were analyzed. The MFI, SF-36 and EQ-5D proved to be highly feasible and reliable in this group of respondents. The measures could discriminate between groups by mode of delivery, and to detect moderate recovery in physical and small recovery in mental status over time in the first 6 weeks after delivery. After six weeks postpartum only 60% of the patients returned the HRQoL measures. This suboptimal total questionnaire response was attributable to a low response among women of non-Dutch ethnic origin. After the good clinical properties of these measure described in chapter five, the combination of MFI, SF-36 and EQ-5D showed good psychometric performance. The measures are feasible to measure fatigue and HRQoL after delivery. Additional efforts need to be made to increase response rates among immigrants.

CHAPTER 7

Chapter seven is the general discussion of this thesis. The risks of blood transfusion are described broadly. Different techniques for risk reduction are discussed, where special attention is given to health related quality of life and the WOMB study, a multicenter

randomized clinical trial that investigates the role of RBC transfusion therapy in the treatment of postpartum anemia and its possible effects on health related quality of life. The results of the WOMB study will contribute to the discussion of the optimal RBC transfusion policy for patients with postpartum anemia. Besides the identification procedure, functioning of blood cells and pathogen inactivation techniques will be discussed. More briefly the prevention of transfusion-related acute lung injury (TRALI) is presented. Finally, future developments in clinical blood transfusion therapy are discussed.

CHAPTER 9

Samenvatting

Na de introductie van diverse bloedcomponententherapieën in de jaren ’60 is er steeds meer aandacht gekomen voor klinische transfusiegeneeskunde. Ondanks dat bloedtransfusie een belangrijke behandeling is binnen diverse specialismen zijn er nog weinig gerandomiseerde klinische studies. Heden ten dage kan bloedtransfusie als veilig beschouwd worden. Dit wordt mogelijk veroorzaakt door een toegenomen bewustwording van de effecten en risico’s van bloedtransfusie. In de klinische transfusiepraktijk wordt een transfusietrigger gebruikt bij het voorschrijven van een bloedtransfusie. Deze transfusietrigger is gebaseerd op de hemoglobine (Hb) waarde voor erytrocytentransfusies en het aantal trombocyten voor trombocytentransfusies. Mogelijkheden om bloedtransfusie te verbeteren zijn verbetering van de bloedproducten en vermindering van het aantal bloedtransfusies.

Dit proefschrift beschrijft 1) een in vitro studie naar een nieuwe pathogeen inactivatie techniek voor trombocyten concentraten en 2) een nieuw erytrocyten transfusiemodel voor patiënten met een acute anemie. Dit model gebruikt subjectieve kwaliteit van leven criteria welke gevalideerd zijn in dit proefschrift.

HOOFDSTUK 1

In het eerste hoofdstuk wordt een algemene introductie gegeven over de historie van bloedtransfusie en bloedcomponententherapie. Studies over transfusietriggers voor erytrocyten- en trombocytentransfusies worden beschreven. Speciale aandacht gaat hierbij uit naar kwaliteit van leven en anemie. Er wordt een overzicht van de literatuur gegeven over de risico’s van bloedtransfusie. De relatie tussen trombocytentransfusie en bacteriële contaminatie wordt beschreven en een nieuwe pathogeen inactivatie techniek voor trombocytenconcentraten wordt geïntroduceerd.

HOOFDSTUK 2

In hoofdstuk twee worden in vitro functionele karakteristieken beschreven van trombocyten na behandeling met een pathogeen inactivatie techniek waarbij gebruik gemaakt wordt van het psoraleen product amotosalen HCL (S59) en UVA licht. Trombocytenconcentraten werden behandeld met 1 van de 2 verschillende S59 verwijderingssystemen: 1) het experimentele T-bag S59 verwijderingssysteem of 2) het commercieel beschikbare integrale Wafer S59 verwijderingssysteem. De behandelde trombocyten werden vergeleken met controle trombocytenconcentraten in een PAS/Plasma bewaarvloeistof. Er werden geen verschillen gevonden in product kwaliteitparameters, mate van activatie en

apoptose variabelen. Trombocyten behandeld met het T-bag S59 verwijderingssysteem hadden een slechtere aggregatiecapaciteit en een significant verhoogde plasma LDH concentratie. Deze testen toonden geen verschil voor trombocyten behandeld met het Wafer S59 verwijderingssysteem. Deze in vitro studie toonde een significante afname in trombocytenfunctie na behandeling met het T-bag S59 verwijderingssysteem. Echter, behandeling met het commercieel beschikbare Wafer S59 verwijderingssysteem had slechts minimale effecten op de kwaliteit van de trombocyten.

HOOFDSTUK 3

In een retrospectieve studie werden 2 verschillende Hb transfusietriggers met elkaar vergeleken bij patiënten met een acute myeloide leukemie (AML) die behandeld werden met een combinatie chemotherapie: 1) een Hb transfusietrigger van ≤ 4.5–5.5 mmol/L, gebaseerd op leeftijd en symptomen en 2) een meer liberale transfusietrigger van ≤ 6.0 mmol/L. De restrictieve transfusietrigger leidde tot een significante reductie van 11% in aantal erytrocytentransfusies. Er werden geen significante verschillen gevonden in aantal infecties, aantal trombocytentransfusies, bloedingcomplicaties, cardiale klachten en respons op de chemotherapie. Het restrictieve beleid, gebaseerd op leeftijd en symptomen, was geschikt in deze klinische setting en er zou geconcludeerd kunnen worden dat een restrictief transfusiebeleid veilig als ondersteunende behandeling gebruikt kan worden voor patiënten die behandeld worden met chemotherapie voor AML. Vanwege het retrospectieve karakter van de studie kon er geen kwaliteit van leven gemeten worden.

HOOFDSTUK 4

Chronische anemie is een vaak voorkomende complicatie bij patiënten met een Myelodysplastisch Syndroom (MDS), waarvan vermoeidheid het meest belangrijke symptoom is. Hoofdstuk vier gaat over vermoeidheid en kwaliteit van leven (KvL) in deze patiëntenpopulatie. Vijftig opeenvolgende MDS patiënten vulden eenmalig de Short-Form 36, de Multidimensionele Vermoeidheids Index 20 en de EQ-5D in. Het hemoglobine gehalte werd gemeten tijdens hetzelfde bezoek. De vragenlijsten hadden een grote feasibility, reliability en validiteit. MDS patiënten hadden slechtere KvL-scores dan personen uit de algemene populatie, gecorrigeerd voor leeftijd en geslacht. Deze studie toonde inzicht in de geschiktheid van bestaande KvL vragenlijsten voor evaluatie van interventies bij patiënten met een MDS. Hb-waarden en KvL-scores waren complementaire variabelen voor de evaluatie van de ernst van de chronische anemie in patiënten met MDS.

HOOFDSTUK 5

Een vaak voorkomende complicatie tijdens een bevalling is bloedverlies. Hoofdstuk vijf beschrijft vermoeidheid en kwaliteit van leven (KvL) van vrouwen na een vaginale partus, geplande keizersnede en spoed keizersnede en de relatie met de postpartum Hb-waarde gedurende de eerste zes weken postpartum. Door 141 patiënten werden de KvL vragenlijsten MVI-20, SF-36 en EQ-5D ingevuld gedurende de eerste zes weken postpartum. Patiënten met een vaginale partus hadden hogere gemiddelde fysieke KvL-scores dan patiënten met een keizersnede. Patiënten met een vaginale partus hadden gemiddeld drie weken nodig voor volledig herstel van de fysieke KvL, patiënten na een geplande keizersnede zes weken en patiënten na een spoed keizersnede meer dan zes weken. De gemiddelde mentale KvL scores van de studiepopulatie waren gelijk of zelfs beter dan de referentiescores. De significante relatie tussen de Hb-waarde en de gemiddelde fysieke KvL-scores op t=0 waren een week postpartum verdwenen. De KvL vragenlijsten van deze studie kunnen gebruikt worden in toekomstige klinische onderzoeken om het effect van interventies postpartum te meten.

HOOFDSTUK 6

Na de klinische evaluatie van de KvL vragenlijsten in hoofdstuk vijf worden de psychometrische eigenschappen van deze vragenlijsten getest in hoofdstuk zes. De feasibility (respons, invultijd, gerapporteerde moeilijkheden, item non respons), reliability (Cronbach's alfa), discriminerende validiteit tussen groepen bij type bevalling, en responsiviteit in de tijd werden geanalyseerd. De MVI-20, SF-36 en EQ-5D hadden een grote feasibility en reliability in deze groep respondenten. De vragenlijsten konden onderscheid maken binnen de studiegroep bij type bevalling en ze konden een mild herstel in fysieke en een klein herstel in mentale KvL gedurende de eerste zes weken na de bevalling aantonen. Zes weken postpartum retourneerden slechts 60% van de patiënten de KvL vragenlijsten. Deze suboptimale respons werd veroorzaakt door een lage respons onder allochtone patiënten. Na de goede klinische eigenschappen van deze vragenlijsten gemeten in hoofdstuk vijf, toonde de combinatie MVI-20, SF-36 en EQ-5D goede psychometrische eigenschappen. De vragenlijsten zijn geschikt om vermoeidheid en KvL na een bevalling te meten. Meer aandacht moet besteed worden aan de lage respons onder allochtonen.

HOOFDSTUK 7

Hoofdstuk zeven is de algemene discussie van dit proefschrift. De risico's van bloedtransfusie worden beschreven. Verschillende technieken voor risicoreductie worden bediscussieerd, waarbij speciale aandacht gegeven wordt aan kwaliteit van leven en de WOMB studie. Deze studie is een multicenter gerandomiseerde klinische studie welke de rol van erytrocytentransfusies in de behandeling van postpartum anemie onderzoekt en hierbij de mogelijke effecten op KvL. De resultaten van de WOMB studie zullen bijdragen aan de discussie over het optimale erytrocytentransfusiebeleid voor patiënten met een acute anemie. Daarnaast worden de identificatie procedure, het functioneren van bloedcellen en de pathogeen inactivatie technieken besproken. Er wordt dieper ingegaan op de preventie van transfusion-related acute lung injury (TRALI). Uiteindelijk worden toekomstontwikkelingen in de klinische bloedtransfusietherapie beschreven.

DANKWOORD

Het proefschrift is nu eindelijk klaar!!! Velen hebben een bijdrage geleverd aan de totstandkoming van dit proefschrift. Daarom rest mij nu nog een ieder te bedanken die actief dan wel passief hieraan heeft bijgedragen. Het is niet mogelijk om iedereen bij naam te noemen, maar toch wil ik graag een aantal personen speciaal bedanken:

Als eerste mijn promotor professor van Rhenen. Beste Dick, hartelijk dank voor de ruimte en de vrijheid die je mij hebt gegeven om dit onderzoek te verrichten. Onderzoek doen kent pieken en dalen. Altijd stond je klaar om mij te helpen de juiste richting te kiezen. Je betrokkenheid en ervaring waren voor mij van grote invloed. Ik heb veel van je geleerd en je enthousiasme voor het onderzoek op het gebied van de klinische transfusiegeneeskunde werkt aanstekelijk.
Vervolgens dr. Duvekot, mijn co-promotor, die als begeleider een zeer grote bijdrage heeft geleverd aan de studies op de afdeling Obstetrie. Beste Hans, telkens stond je klaar met adviezen, steun en waardering. Zonder jouw enthousiasme en inzet was dit proefschrift nooit in deze vorm tot stand gekomen. Ik ben er trots op je eerste promovendus te zijn.
Aanvullend wil ik de hooggeleerde professoren Brand, Löwenberg, en Steegers bedanken voor het zitting nemen in de kleine commissie. Beste Anneke, ik wil je daarnaast bedanken voor het in contact brengen met Karin Hoffmeister uit Boston waardoor ik mijn onderzoek naar trombocytenfunctie daar kan voorzetten. Beste Eric, hartelijk dank voor de mogelijkheid om samen onderzoek te doen en voor het kritisch lezen van de manuscripten.

Dr. Schipperus heeft mij als student geneeskunde geïntroduceerd in de fascinerende wereld van de transfusiegeneeskunde. Ons onderzoek is beschreven in hoofdstuk 3 en was de basis van dit proefschrift. Dr. Harteloh heeft het onderzoeksthema van mijn proefschrift, de mogelijke rol van Kwaliteit van Leven in de klinische bloedtransfusiepraktijk geïnitieerd. Beste Peter, hartelijk dank voor het opstarten van het onderzoek.
Dr. van Vliet heeft een zeer belangrijke rol gespeeld bij de totstandkoming van hoofdstuk 2. Beste Huub, je onderwijs en enthousiasme over trombocytenonderzoek waren zeer inspirerend. Ik hoop in Boston antwoord te krijgen op de vragen die ontstonden naar aanleiding van ons onderzoek.

De statistische ondersteuning werd verleend door dr. Essink-Bot en dr. Hop. Beste Marie-Louise, de adviezen betreffende de "Kwaliteit van Leven" waren zeer belangrijk voor dit proefschrift. Onze discussies en je snelle reactie op manuscripten zijn onvergetelijk. Ik

hoop dat we in de toekomst nog veel samen zullen werken. Beste Wim, als statisticus was je betrokken bij al mijn onderzoeken. Je enthousiasme en de manier waarop je statistiek behapbaar maakt is indrukwekkend.

Op deze plaats wil ik de medewerkers van de Bloedbank bedanken, met name de collega's van de afdelingen O&O en KCD en de donorartsen voor hun hulp en de gezelligheid op het werk en tijdens de congressen. Mede dankzij jullie kijk ik terug op een hele leuke periode. Speciaal wil ik noemen dr. Beckers en drs. Przespolewski. Beste Erik, je kritische blik op het onderzoek en de manuscripten waren inspirerend. Ik heb veel van je geleerd. Onvergetelijk zijn de congressen samen! Beste Edward, je was er altijd om mijn pieken en dalen op te vangen en te relativeren. Ik kan geen betere roommate bedenken.
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Nelly. Dankzij jouw inzet en enthousiasme loopt de inclusie voor de WOMB studie zeer goed. Ik hoop dat we de WOMB besprekingen volgend jaar voort kunnen zetten.

Alle leden van de Bella Obstetrica wil ik bedanken voor de mogelijkheid om de WOMB studie te verrichten in de ziekenhuizen en de (voorlopige) resultaten te presenteren tijdens de onvergetelijke Bella bijeenkomsten.

Jeannine en Niek. Hartelijk dank voor jullie steun en ontspannende momenten. De search naar het beste restaurant is wat mij betreft nog zeker niet afgelopen. Ik ben blij dat jullie mijn paranimfen willen zijn.

Natuurlijk kan een proefschrift niet geschreven worden zonder de steun van familie en vrienden. Mijn ouders en Maarten wil ik bedanken voor alle support en de mogelijkheden die zij geboden hebben om dit onderzoek succesvol te maken. Dit ondanks mijn vaak fysieke en waarschijnlijk nog vaker mentale afwezigheid.

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En last, but zeker not least, wil ik Sjoukje bedanken. Lieve Sjoukje, de laatste loodjes wegen het zwaarst. Ik ben blij dat ik deze periode samen met jou heb kunnen delen. Dit heeft het voor mij veel makkelijker gemaakt. Ik zie uit om samen met jou naar Boston te gaan.

CURRICULUM VITAE

The author of this thesis was born on June the 30th, 1977, in Cali, Colombia. In 1996 he passed his secondary school exam at the Geert Groote College in Deventer and started to study Medicine at Erasmus Medical Center in Rotterdam that same year. During his studies he perfomed research projects at the department of Hematology (supervisor: dr. MR Schipperus) and Nephrology (supervisors: prof. dr. W Weimar and dr. CC Baan). He graduated in 2000 and continued as a PhD student at Sanquin Blood Bank South West Region (promotor: prof. dr. DJ van Rhenen) and performed the research as described in this thesis. For his research he won the Young Investigator's Awards from the British Blood Transfusion Society in 2001 and 2003. Concurrent with his PhD he trained in Clinical Epidemiology at the Free University of Amsterdam (tutor: prof. dr. A Hofman) and finished his study Medicine at the Erasmus Medical Center. After his PhD research he will perform a one year postdoc research project at the lab of dr. KM Hoffmeister at the department of Hematology, Brigham and Women's Hospital in Boston, USA. In January 2008 he will start his trainee for internal medicine at the Erasmus Medical Center Rotterdam.

LIST OF PUBLICATIONS

1. Temple studie: Transfusion Effects in Myelodysplastic Patients: Limiting Exposure
   AJG Jansen, MR Schipperus, WCJ Hop, EAM Beckers, PAW te Boekhorst, P Sonneveld, DJ van Rhenen
   NVB Bulletin oktober 2002;3:2-5

2. Quality of life measurement in patients with transfusion dependent Myelodysplastic Syndromes.
   AJG Jansen, ML Essink-Bot, EAM Beckers, WCJ Hop, MR Schipperus, DJ van Rhenen
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3. Transfusietriggers en Kwaliteit van Leven
   AJG Jansen, ML Essink- Bot, WCJ Hop, EAM Beckers, DJ van Rhenen
   Nederlands Tijdschrift voor Klinische Chemie 2003; 28: 280-284

4. Functional characteristics of photochemically treated platelets
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   Transfusion 2004;44(3):313-319

5. Feasibility of a restrictive transfusion policy for patients treated with intensive chemotherapy for acute myeloid leukemia
   AJG Jansen, MAA Caljouw, WCJ Hop, DJ van Rhenen, MR Schipperus
   Transfusion Medicine 2004;14(1):33-38

6. WOMB studie: Well being of Obstetric patients on Minimal Blood transfusions.
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   NVB Bulletin oktober 2004;3:10-12

7. Postpartum haemorrhage and transfusion of blood and blood components
   AJG Jansen, DJ van Rhenen, EAP Steegers, JJ Duvekot
   Obstet Gynecol Surv. 2005 Oct;60(10):663-71.

8. New insights into fatigue and health-related quality of life after delivery.
   AJG Jansen, JJ Duvekot, ML Essink-Bot, WCJ Hop, EAM Beckers, VHM Karsdorp, SA Scherjon, EAP Steegers, DJ van Rhenen.
   Submitted

9. Health Related Quality of Life measurement after different types of delivery.
   AJG Jansen, ML Essink-Bot, JJ Duvekot, DJ van Rhenen.
   Submitted

10. Transfusiebeleid postpartum en de rol van Kwaliteit van Leven.
    AJG Jansen, JJ Duvekot, VHM Karsdorp, ML Essink-Bot, WCJ Hop, EAM Beckers, SA Scherjon, EAP Steegers, DJ van Rhenen.
    Submitted

11. The relationship between Hb change and blood loss after delivery
    AJG Jansen, P leNoble, EAP Steegers, DJ van Rhenen, JJ Duvekot
    In preparation

12. An usual presentation of chronic myelomonocytic leukemia
    AJG Jansen, MBL Leijs, TT Tio
    In preparation

APPENDIX

APPENDIX I

The "4-5-6 rule" is the recommended RBC transfusion trigger in the Netherlands for patients with acute or chronic anemia based on the Hb value and symptoms of patients (see table).

Table. "4-5-6 rule"

Consider a RBC transfusion at a Hb < 4.0 mmol/l (Hct 0.20) when:
– Acute blood loss in ASA I patients < 60 years, normovolemic blood loss from one locus
– Chronic asymptomatic anemia
Consider a RBC transfusion at a Hb < 5.0 mmol/l (Hct 0.25) when:
– Acute blood loss in ASA I patients > 60 years, and normovolemic blood loss from one locus
– Acute blood loss in healthy patients < 60 years, normovolemic blood loss from different loci (poly trauma patients)
– Patients < 60 years, preoperative, with an expected blood loss of more than 500 mL
– Fever
– Postoperative phase after open-heart surgery, uncomplicated
– ASA II and ASA III patients without complications
Consider a RBC transfusion at a Hb < 6.0 mmol/l (Hct 0.30) when:
– ASA IV patients
– Patients who are not capable to increase the heart-minute-volume for the compensation of the hemodilution
– Patient with sepsis or toxic patients
– Patient with a severe lung disease
– Patients with symptomatic cerebrovascular disease
ASA-criteria
I healthy persons
II patients with mild systemic disorder, without functional symptoms
III patients with severe functional limiting systemic disorder
IV patients with systemic disorder that constantly causes life threatening
V patients who are moribund and who will, with or without surgery, die probably within 24 hours

APPENDIX II

The results of a questionnaire about red blood cell transfusion policy after postpartum hemorrhage held in 2003 in 40 teaching hospitals in The Netherlands.

1) The RBC transfusion trigger is based on (N)	Hb value 1	Symptoms 2	Both 29
2) Under which Hb value do you consider to give a RBC transfusion? (N=32), mean ± SD (range)	5,0 ± 0,53 (4,0 – 6,0) mmol/l		
3) Under which Hb value do you actually give a RBC transfusion? (N=32), mean ± SD (range)	4,2 ± 0,51 (3,0 – 5,5) mmol/l		
4) Which symptoms are important in the decision to give a RBC transfuse on? (more answers possible) (N=33)	YES	NO	
– Dyspnoea	23	10	
– Syncope	31	2	
– Orthostatic complaints	25	8	
– Tachycardia (> 100 bpm)	22	11	
– Angina Pectoris	16	17	
– Transient Ischemic Attack (TIA)	13	20	

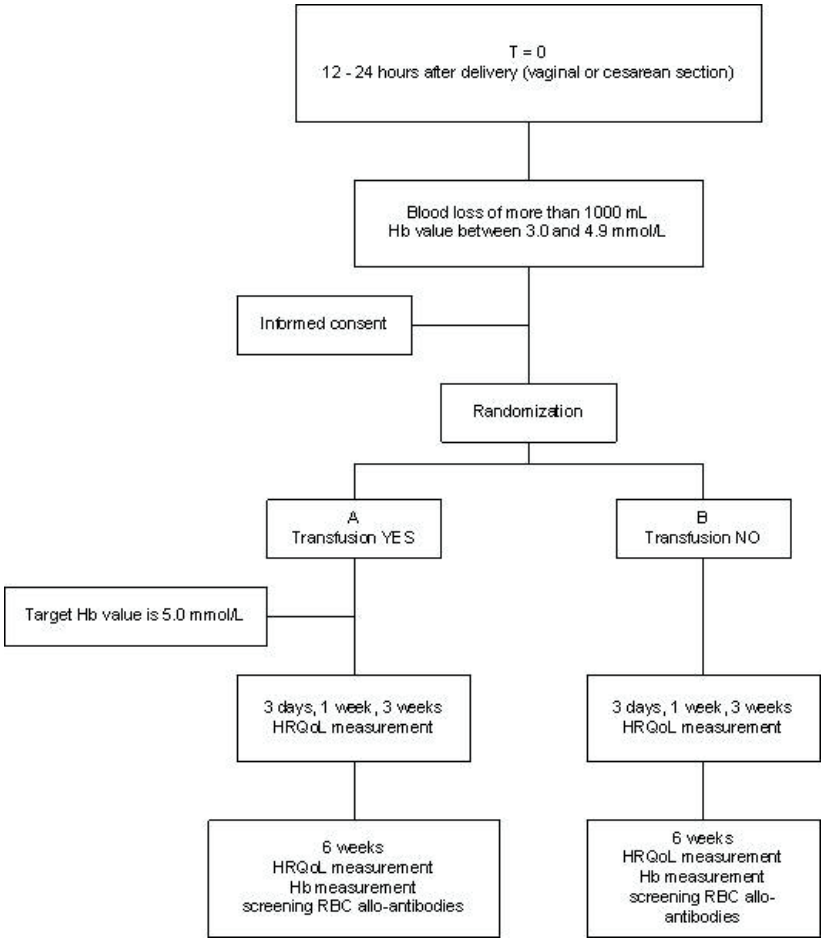
APPENDIX III

Inclusion criteria, study design and statistics of the WOMB study

Inclusion criteria WOMB study are:

1) Time: 12-24 h after VD or CS;
2) Hb level: 3.0 ≤ Hb ≤ 4.9 mmol/l;
3) PPH: blood loss ≥ 1000mL;
4) Age: age ≥ 18 years;
5) Symptoms: no anemic symptoms.

Study design WOMB study



Statistics

The sample size is based on the investigation of the relationship between fatigue (and HRQoL), measured with HRQoL questionnaires, and different RBC transfusion triggers. The HRQoL questionnaires are validated in the study described in chapter 5 and 6. Fatigue, measured with the MFI questionnaire, is the primary outcome.

The sample size is 400 patients: 200 patients after a VD (where 100 patients receive a RBC transfusion and 100 patients not) and 200 patients after a CS (also 100 patients with and 100 patients without a RBC transfusion). With this amount of patients, differences per type of delivery (VD and CS) for HRQoL scores are detectable ($\alpha = 0.05$, $\beta = 0.20$) when these differences are 0.4 SD. These differences are called small.

The MFI and other HRQoL questionnaires will be analyzed using Repeated Measurement ANOVA. The amount of RBC transfusions and the hospital stay will be analyzed using two-sided Mann-Whitney U test.

In the Netherlands, the incidence of a RBC transfusion after delivery is approximately five percent. The incidence is, with approximately 200,000 deliveries per year, 10,000 patients in the Netherlands.

APPENDIX IV

Participating hospitals

At this moment the WOMB study is performed in 10 hospitals in the Netherlands

Participating hospitals

Hospital	City
Albert Schweitzer Hospital	Dordrecht
Academic Medical Center	Amsterdam
Amphia Hospital	Breda
Erasmus MC, University Medical Center	Rotterdam
Ikazia Hospital	Rotterdam
Leiden University Medical Center	Leiden
Maxima Medical Center	Veldhoven
Medical Center Rijnmond-Zuid	Rotterdam
Reinier de Graaf Gasthuis	Delft
Sint Franciscus Gasthuis	Rotterdam