Chapter 4

Postoperative anaemia after joint replacement surgery is not related to quality of life during the first two weeks postoperatively

Cynthia So-Osman[1], Rob Nelissen[2], Ronald Brand[3], Anneke Brand[1] and Anne M. Stiggelbout[4]

[1] Dept. of Research and Development, Sanquin Blood Bank South West Region, Leiden
[2] Dept. of Orthopaedic Surgery, Leiden University Medical Centre (LUMC), Leiden
[3] Dept. of Medical Statistics and BioInformatics, Leiden University Medical Centre (LUMC), Leiden
[4] Dept. of Medical Decision Making, Leiden University Medical Centre (LUMC), Leiden, the Netherlands

Transfusion 2011 Jan; 51:71-81

ABSTRACT

Background: Lower limb joint replacement surgery provides a considerable improvement in quality of life (QoL), but is associated with peroperative blood loss, and with anemia in the direct postoperative period. General acceptance of low transfusion thresholds and shorter postoperative hospital stays will result in patients leaving hospital with low hemoglobin (Hb) levels. To evaluate the role of QoL scores as a possible alternative for Hb values to serve as a further indicator for RBC transfusion, we performed a secondary analysis of a previously conducted randomized clinical trial (RCT) to compare QoL and fatigue scores with simultaneously measured pre- and postoperative Hb levels, in total hip and knee arthroplasty patients.

Methods: QoL measurement was measured preoperatively and twice up to 14 days postoperatively using the Functional Status Index (FSI), the Visual Analogue Score (VAS)-Fatigue score, and the Functional Assessment of Cancer Therapy Anemia (FACT-Anemia) subscale. Pearson correlation coefficients between (change in) FSI, VAS-Fatigue and FACT-Anemia subscale scores and (change in) Hb levels were calculated. Additionally, partial correlations were calculated and linear regression analysis was performed, correcting for possible confounding variables.

Results: 603 patients were evaluated. All patients scored worse postoperatively, but none of the scores correlated with Hb values, neither after correcting for confounding factors. Even more, the changes between preoperative and postoperative Hb levels were not correlated with changes in fatigue scores.

Conclusions: In hip- and knee-prosthesis surgery no correlation existed between postoperative Hb levels or acute postoperative decline in Hb values and QoL scores (FSI, VAS-Fatigue or FACT-Anemia).

Lower limb joint replacement (hip- and knee-) surgery provides a considerable improvement in quality of life (QoL), but is associated with peroperative blood loss and with anemia in the direct post-operative period [1-3]. General acceptance now exists for low transfusion thresholds. These latter, combined with an early postoperative discharge of patients from the hospital, will result in patients discharged with low hemoglobin (Hb) levels, which may compromise revalidation. To date, two studies are available on the effects of anemia on QoL, especially on fatigue, in the post-operative period after total hip and knee replacement surgery [4,5]. However, these studies comprised less than 100 patients each, studied different postoperative intervals and Hb values were not always measured simultaneously with the questionnaires. We investigated the relationship between QoL and fatigue scores and Hb levels, in order to see whether these scores could serve as a further indicator for RBC transfusion. We used data from a large prospective, randomized study that compared a liberal to a restrictive transfusion trigger with red blood cell use as a primary endpoint [6].

MATERIALS AND METHODS

Study design

Secondary analysis of a previously conducted prospective, randomized study that compared two different transfusion policies with the mean use of allogeneic leucocyte-depleted red blood cell (RBC) units as primary end point. In the original study, QoL measurement was pre-defined as secondary endpoint. The transfusion policies differed from a minimal threshold of 7.0 g/dL to a maximal threshold of 10 to 10.5 g/dL. The study included patients of 18 years and older scheduled for a primary or revision total hip replacement or total knee replacement surgery at either of three Dutch participating hospitals (Leiden University Medical Center, Leiden; HAGA hospital, The Hague; and Reinier de Graaf Hospital, Delft), during a three year period (2001-2003). Refusal of allogeneic transfusions (e.g. Jehovah's witnesses) was the only exclusion criterion.

Procedures

QoL scores were measured pre-operatively and at post-operative days +4 and + 14 using:

1. the Functional Status Index (FSI), which is a reliable and valid functional assessment instrument in rheumatoid arthritis (RA) and in patients after hip fracture (scale 0-4: with lower scores indicating better functioning, 0=not relevant) (Appendix 1) [7, 8]. Total scores were recalculated to range from 0 to 100. It should be noted that in literature FSI scores are reported as the higher, the better. For better comparison we reversed the scores in opposite direction to ensure that all scores were pointed at the same direction.
2. the VAS fatigue score (scale 1-10: lower scores indicate better functioning and well-being). For reasons of comparison, we recalculated the scores to range from 0 to 100.
3. the Functional Assessment of Cancer Therapy Anemia (FACT-Anemia) subscale (with 13 fatigue (F) items and 7 non-fatigue (NF) items), which was validated for the association with Hb levels in cancer patients (scale 0-4: lower scores indicate better functioning and well-being) (Appendix 2) [9]. Total scores were recalculated to range from 0 to 100 for FACT-F and FACT-NF items. The FACT-Anemia scale was used specifically for its fatigue items, although its validity and reliability is not known in an orthopaedic population.

Patients completed the first set of questionnaires preoperatively (T1). On postoperative days +4 (during hospitalisation) and +14 (in the outpatient setting) the patient completed the second (T2) and third set (T3) of questionnaires. Hb levels were measured at the same moment as the QoL scores were taken. Follow up ended at the outpatient clinic 14 days after surgery or after discharge of the patient (in case of a prolonged hospital stay of more than 14 days) (T3).

Defining clinically minimal important difference (MID)

To evaluate responsiveness, MID was defined using anchor-based approaches, when available [10].

Anchor-based methods assess which changes on the measurement instrument correspond with a minimal important change defined on the anchor. An external criterion, generally a global change or transition question, is used to operationalize a relevant or an important change. The advantage is that the concept of 'minimal importance' is explicitly defined and incorporated in these methods.

For FACT-Fatigue and VAS fatigue scores, MID was defined as a difference in score of 3.0 (score range 0-42) and 10 (score range 0-100), respectively [11,12]. As FACT-Fatigue scores were recalculated to a range from 0 to 100, MID was recalculated to a difference of 7.1. Concerning the FSI, anchor-based estimates were not available. Therefore we used a difference of 0.5 SD for MID at all time points, based on distribution-based methods [13]. All validation studies for FSI had only been performed among rheumatoid arthritis patients and not always in a surgical setting, whereas for Fact-Fatigue these were all performed among cancer patients.

Statistical analysis

Variables were described as mean and SD, or median and inter-quartile (IQ) range in case of a non-normal distribution. Pearson correlation coefficients (+ 95% confidence interval [CI]) were calculated for time points T1, T2 and T3, between FSI, Fact-Anemia, VAS scores and Hb values as well as between changes in scores and Hb levels from preoperative to postoperative values obtained at T2 and T3. Subgroup analysis was performed to compare scores between groups concerning age, gender, type of surgery, preoperatively anemia, and comorbidity (cardiovascular, respiratory, RA, diabetes), randomization group and numbers of RBC transfusions. Partial correlation coefficients were calculated, individually controlling for the variables mentioned. Hb levels were additionally analyzed as categorized variables (using tertiles: low, intermediate and high Hb groups), and mean QoL scores were compared between the highest and lowest group using Student's t-tests. By linear regression analysis, the correlation between Hb and QoL scores was evaluated after adjusting for the same variables mentioned. Pre-operative anemia was based on WHO criteria [14]. P values of less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Of 619 included consecutive patients, 16 patients could not be analyzed because of the following reasons: cancellation of surgery in seven, death before surgery in one, consent

withdrawn before surgery in six and charts missing in two cases. Baseline characteristics of the excluded group were comparable with those of the analyzed group (data not shown). In Table 1, characteristics of the remaining 603 included patients are shown. During surgery, 78 patients (13%) received general anaesthesia and 525 (87%) patients received a loco-regional technique (spinal with or without epidural anaesthesia). Median total blood loss was 400 mL (IQ range 0-600 mL). Overall mean RBC usage was 0.78 U/patient in the new uniform policy group and 0.86 U/patient in the standard care policy group (mean difference 0.08; 95% CI, -0.3 to 0.2; p=0.53).

QoL Outcomes

All 603 patients completed the first set (T1) of questionnaires (pre-operatively), 92% (n=554) completed the second set (T2) (4 days after surgery) and 81% (n=487) the third set (T3). Ten percent of patients (n=59) had a hospital stay of more than 14 days, with a maximum of 100 days (median 18 days, IQ range 16-21 days). In Table 2, mean Hb levels and mean scores of all questionnaires are shown for all time points which show that at postoperative days 4 and 14 patients deteriorated in all scores except the FACT-NF score. Patients with RA scored worse compared to the group without RA at all time points for VAS-Fatigue and FACT-Fatigue, but mainly preoperatively (mean difference -12.4 [95% CI, -20.3 to -4.6], p=0.02 and -10.2 [95% CI, -15.0 to -5.4], p<0.001, respectively). Also the FSI scores were worse, but only preoperatively (T1) and postoperatively at T2 (mean difference at T1 of -9.3 [95% CI, -17.3 to -1.4], p=0.002 and at T2 of -9.3 [95% CI, -15.7 to -2.8], p=0.005, respectively).

At each time point, the three fatigue questionnaires correlated with variable extent: correlations were weak between FSI and VAS fatigue (r=0.29, [95% CI, 0.20 to 0.37], p<0.001) and Fact-F (r=0.39, [95% CI, 0.32 to 0.46], p<0.001), whereas a better correlation was found between VAS fatigue and Fact-F (r=0.70, [95% CI, 0.65 to 0.74],p<0.001). Within each type of questionnaire, pre-operative scores were weakly correlated with postoperative scores: for FSI, at T2 (r=0.41, [95% CI, 0.32 to 0.48], p<0.001) and at T3 (r=0.25, [95% CI, 0.16 to 0.34], p<0.001); for VAS, at T2 (r=0.43, [95% CI 0.34 to 0.51], p<0.001) and at T3 (r=0.47, [95% CI, 0.37 to 0,56], p< 0.001); for FACT-F at T2 (r=0.40, [95% CI, 0.32 to 0.47], p<0.001) and at T3 (r=0.41, [95% CI, 0.33 to 0.49], p<0.001) and for FACT-NF at T2 (r=0.44, [95% CI, 0.37 to 0.51], p<0.001) and at T3 (r=0.40, [95% CI, 0.32 to 0.48], p<0.001).

We found significant differences between the FSI and Fact-F scores of preoperatively anaemic patients (mean ± SD Hb level of 11.6 ± 0.8 g/dL) compared to pre-operatively nonanaemic patients (mean Hb (SD) of 14.0 (1.1) g/dL) at several time-points (not shown). However, these differences were small and less than the defined clinically MID.

Table 1. Baseline characteristics of 603 patients undergoing total hip or knee replacement surgery

	All subjects
Demographics	
Age, years	70.4 (9.9)
Male/Female	202/401
Weight, kilograms	78.6 (13.3)
Type of surgery	
Total hip replacement	339 (56.2)
Total knee replacement	224 (37.1)
Revision total hip replacement	34 (5.6)
Revision Total knee replacement	6 (1.0)
Underlying diseases	
Rheumatoid arthritis	67 (11.1)
COPD	46 (7.6)
Hypertension	269 (44.7)
Myocardial infarction	27 (4.5)
Cardiac failure	58 (9.6)
CVA/TIA	32 (5.3)
Peripheral vascular disease	34 (5.6)
Arythmia	50 (8.3)
Laboratory findings	
Pre-operative hemoglobin, g/dL	13.7 (1.3)
Pre-operative hematocrit, L/L	0.41 (0.04)
Pre-operative anemia	98 (16.3)

Continuous data are presented as mean (SD) and categorical data as number (%).
COPD=chronic obstructive pulmonary disease; CVA/TIA=cerebrovascular accident/transient ischemic attack.

Table 2. Mean hemoglobin levels and score values* of the three questionnaires at the three measured time points (T1=preoperatively, T2= four days postoperatively, T3=14 days postoperatively / at discharge)[a]

Mean (SD) scores of:	T1	T2	T3
Hemoglobin (g/dL)	13.7 (1.3)	10.5 (1.1)	11.4 (1.2)
FSI	14.6 (17.0)	47.5 (23.0)	31.4 (19.0)
VAS	31.0 (27.5)	38.9 (28.6)	32.4 (27.0)
Fact-F	26.9 (18.4)	34.9 (19.7)	29.3 (18.5)
median (IQR)	23 (11-40)	32 (20-48)	25 (14-41)
Fact-NF	10.5 (12.5)	11.8 (13.9)	8.5 (12.7)
median (IQR)	6 (0-19)	6 (0-19)	6 (0-13)

*Range of scores of FSI, VAS and Fact-Anemia (both Fact-F and Fact-NF) questionnaires from 0 to 100.
[a] Lower scores indicate better functioning.

Table 3. Correlations (r) of Hb values with FSI, VAS, FACT-F, and FACT-NF scores on several time points (T1=preoperatively, T2= four days postoperatively, T3=14 days postoperatively / at discharge)

Correlations r of Hb values with:	T1 [95% CI]; p	T2 [95% CI]; p	T3 [95% CI]; p
FSI	0.22 [0.14, 0.30]; p<0.001	0.21 [0.13, 0.29]; p<0.001	0.22 [0.13, 0.30]; p<0.001
VAS	-0.04 [-0.12, 0.04]; p=0.33	-0.04 [-0.12, 0.04]; p=0.34	-0.02 [-0.11, 0.07]; p=0.66
FACT-F	-0.11 [-0.19, -0.03]; p=0.007	-0.10 [-0.18, -0.02]; p=0.02	-0.05 [-0.14, 0.04]; p=0.27
FACT-NF	-0.05 [-0.13, 0.03]; p=0.22	-0.05 [-0.13, 0.03]; p=0.24	+0.03 [-0.06, 0.12]; p=0.51

Hb levels and QoL scores

Mean ± SD postoperative Hb values on days +4 and +14/discharge were 10.5 ± 1.1 and 11.4 ± 1.2 g/dL, respectively. Hb values were not correlated with VAS-scores and weakly correlated with FSI-, and FACT-Anemia scores at several time points (Figure 1A-L and Table 3). Although some correlations were significant, these were very weak, as the magnitude (expressed by R^2) did not exceed 0.04 (0.22 times 0.22), so at most 4% of the total variability in any of the four scores was explained at any time point by Hb. When Hb levels were categorized into three equal subgroups, significantly different scores on the FSI and Fact-F were seen between the lowest (mean Hb level, 12.2 g/dL) and highest Hb subgroup (mean Hb level, 15.1 g/dL) at T1, and on the FSI, Fact-F and VAS at T2 (mean Hb levels, respectively, 9.3 and 11.8 g/dL), but not at T3 (mean Hb levels, respectively, 10.1 and 12.9 g/dL). Again, these differences were small and less than the clinically MID. Fact-NF scores showed no differences at any time points. No correlation of greater than 0.30 between Hb and fatigue scores was found, neither after individually controlling for clinical and demographic characteristics by partial correlation analysis nor after simultaneous correction for these variables in linear multivariable regression analysis. The randomization group, which included a more or less restrictive transfusion policy, and the number of RBC transfusions were not of any influence on the outcome of QoL and fatigue scores either.

Change in scores compared to (change in) Hb levels

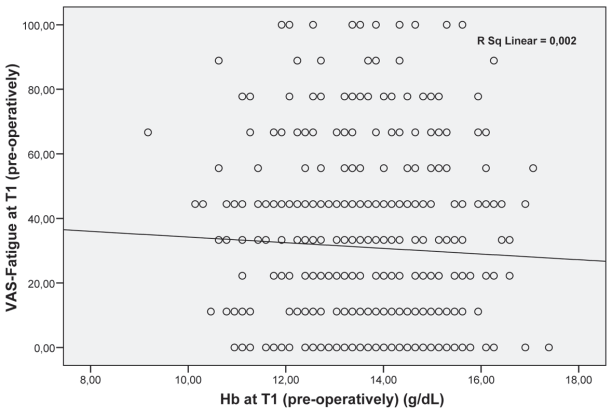
We compared changes in scores between the preoperative and postoperative follow-up moments T2 and T3 with the absolute Hb values at the same endpoints in accordance with Conlon et al, for the elderly population (aged from 65 years onwards, n=455), and found no

correlation of any significance. This was also the case when we compared the change scores with the change in Hb values (delta Hb; Table 4A). For the total study population, the results were also not different (Table 4B).

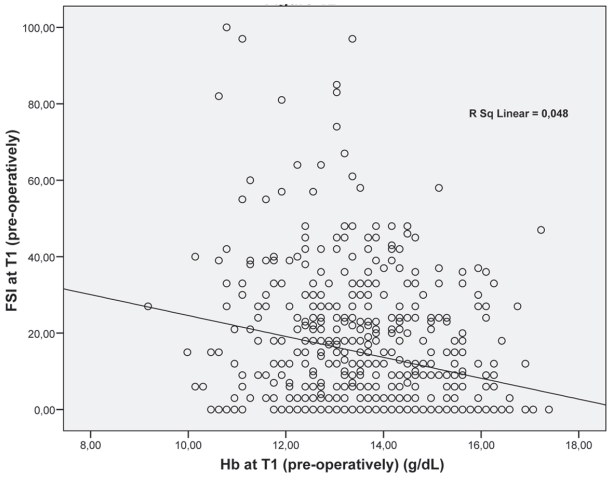
Table 4. Correlations between (delta) Hb level and changes of FSI, VAS and FACT scores at T1 compared to T2 (T2-T1) and T3 (T3-T1) including 95% CI and p-values

Change of	Hb (T2)	Delta Hb (T2-T1)	Hb (T3)	Delta Hb (T3-T1)
A. Population aged 65 years and older (n=455)				
FSI	0.08 [-0.03, 0.19]; p=0.17	0.11 [0.002,0.22]; p=0.05	0.08 [-0.04, 0.19]; p=0.16	0.16 [0.05, 0.28]; p=0.006
VAS	-0.03 [-0.16, 0.10]; p=0.68	0.05 [-0.08, 0.18]; p=0.46	0.11 [-0.04, 0.25]; p=0.14	0.15 [0.005, 0.30]; p=0.04
FACT-F	-0.09 [-0.19, 0.01]; p=0.07	-0.07 [-0.17, 0.03]; p=0.16	0.08 [-0.04, 0.19]; p=0.18	0.06 [-0.06, 0.17]; p=0.29
FACT-NF	-0.07 [-0.17, 0.03]; p=0.17	-0.05 [-0.15, 0.05]; p=0.34	0.02 [-0.10, 0.14]; p=0.68	0.06 [-0.06, 0.18]; p=0.30
B. Total study population				
FSI	0.08 [-0.01, 0.17]; p=0.08	0.06 [-0.03, 0.15]; p=0.22	0.05 [-0.05, 0.15]; p=0.28	0.16 [0.06, 0.25]; p=0.002
VAS	-0.03 [-0.14, 0.08]; p=0.56	0.03 [-0.08, 0.14]; p=0.57	0.06 [-0.06, 0.18]; p=0.30	0.08 [-0.04, 0.20]; p=0.20
FACT-F	-0.09 [-0.18, 0.002]; p=0.04	-0.05 [-0.14, 0.04]; p=0.27	0.05 [-0.05, 0.15]; p=0.32	0.05 [-0.05, 0.15]; p=0.30
FACT-NF	-0.10 [-0.19, -0.01]; p=0.03	-0.07 [-0.16, 0.02]; p=0.13	-0.001 [-0.10, 0.10]; p=0.99	0.02 [-0.08, 0.12]; p=0.73

A



B



C

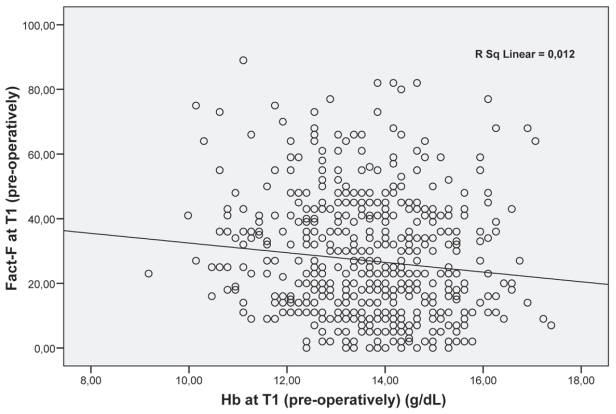
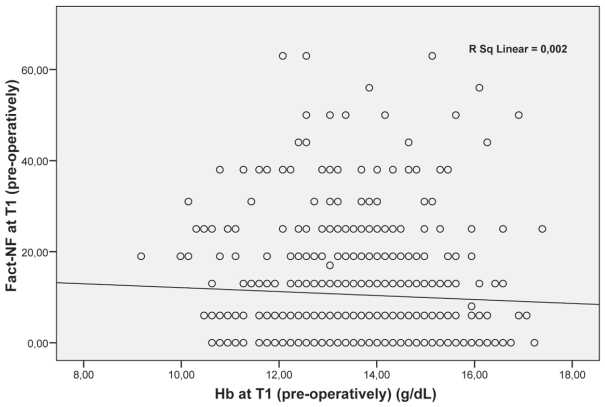
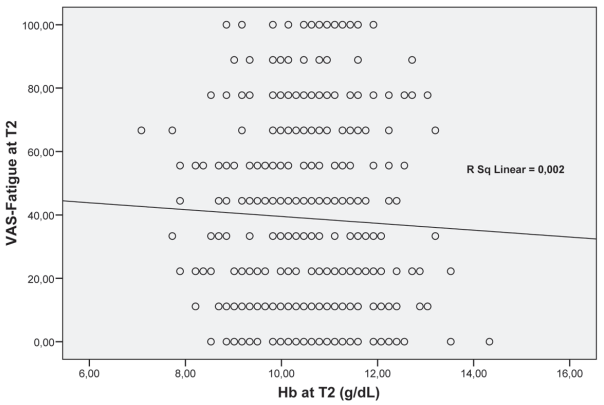


Figure 1. Correlation of scores with Hb levels, measured pre-and postoperatively (A-L). Scatter plots of VAS-Fatigue, FSI, Fact-F and Fact-NF in relation to the Hb values at T1 (preoperatively; A-D), at T2 (4 days post-operatively; E-H) and at T3 (14 days post-operatively; I-L). Linear regression lines with associating R^2 values were added.

D



E



F

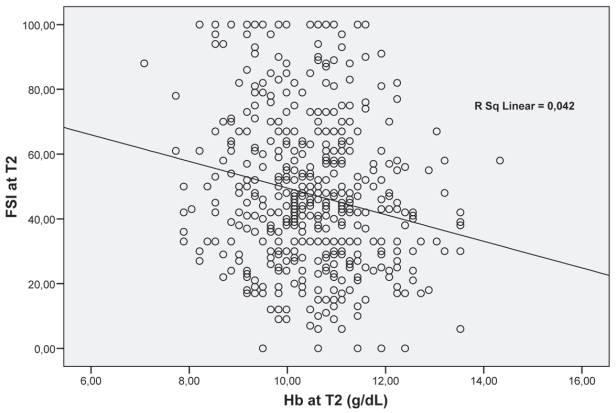
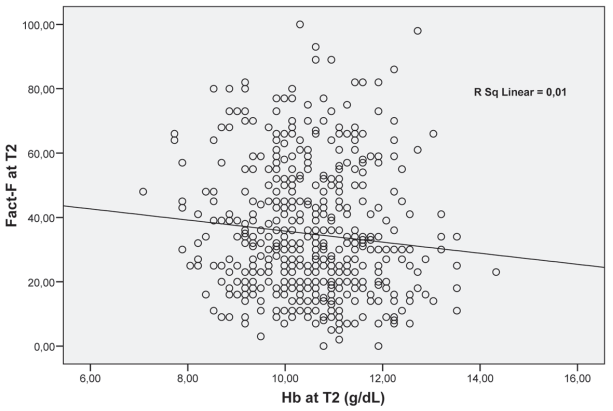
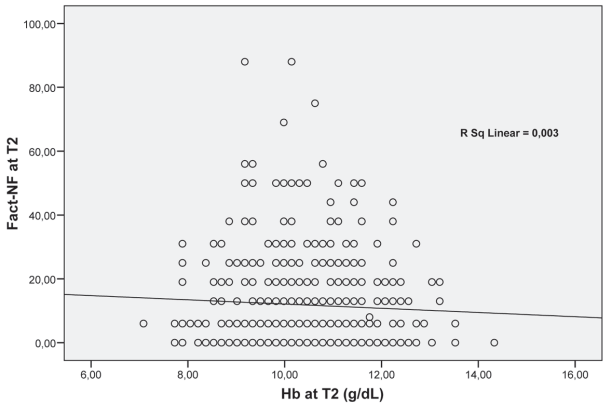


Figure 1. *Continued*

G



H



I

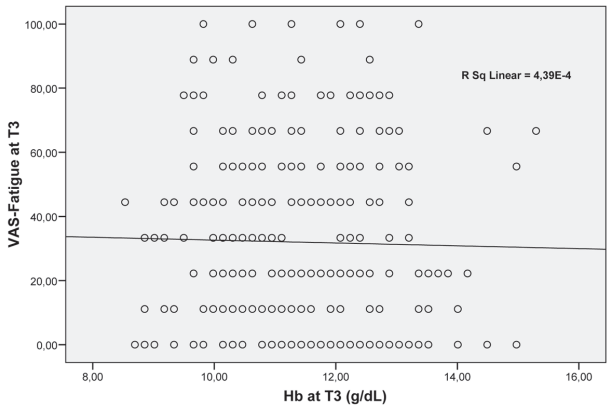
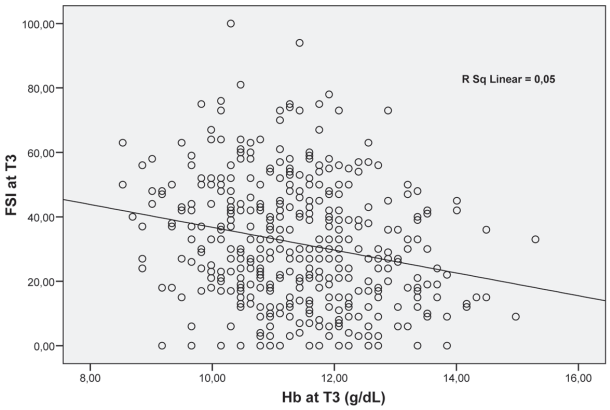
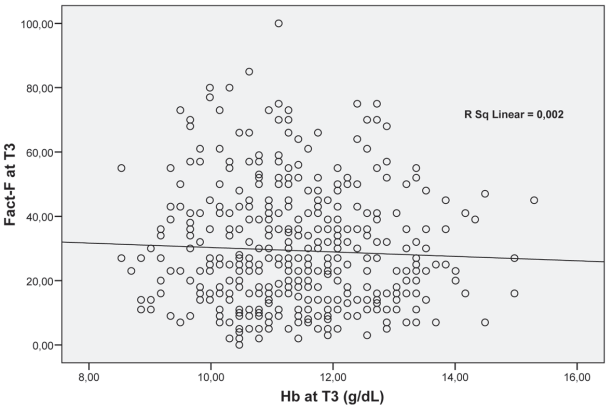


Figure 1. *Continued*

J



K



L

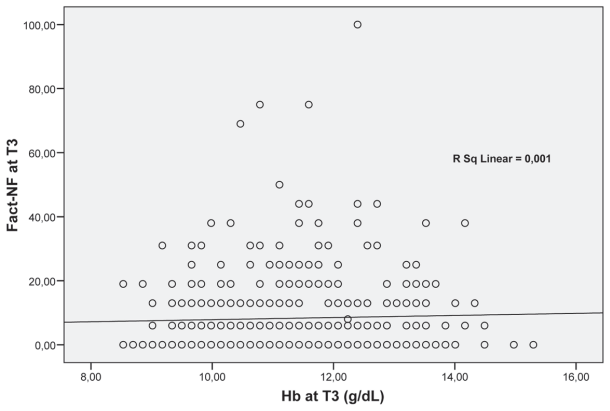


Figure 1. *Continued*

DISCUSSION

This study was based on a large orthopaedic population of more than 600 patients, in which Hb levels and QoL- and fatigue scores were measured at simultaneous time points. In this elective surgery population, symptoms of fatigue were not correlated with Hb levels at any time-point up to 14 days after surgery. All scores deteriorated in this early postoperative period. Some correlations with Hb level were significant, but these were very weak, and at most 4% of the total variability with a maximum of 9% in any of the four scores could be explained at any time point by Hb levels. After controlling for clinical and demographic factors, the association between Hb and QoL scores remained weak. Not even the randomisation group and the number of RBC transfusions influenced this outcome. Scores of anaemic patients were slightly worse at all time points compared to non-anemic patients, as well as scores of the lowest Hb group compared to the highest group, but the differences did not meet the definition of clinically important difference.

The findings are in agreement with the findings of Wallis and coworkers, who compared the SF-36 questionnaire and an in-house linear analogue QoL scale with Hb levels up to 8 weeks after total hip surgery in 30 patients and found no correlation [4]. Conlon et al [5] found a linear correlation in the change of FACT-Anemia and SF-36 scores, taken pre-operatively and 2 months after total hip arthroplasty, and the absolute Hb values taken pre-operatively and 8 days post-operatively in 87 patients. Improvement in overall SF-36 score was 8.6 points for every Hb increase of 1 g/dL on day 8, and improvement in FACT-Anemia score was 2.9 points for a similar Hb increase, indicating that patients with a lower Hb at discharge at day 8 consistently reported less improvement in QoL and fatigue than those discharged with a higher Hb level. Our data could not confirm this.

Both the studies performed by Wallis et al and Conlon et al differed in design from ours by obtaining questionnaires at different and later postoperative time points and -more importantly- without a simultaneous Hb measurement. Because our follow up period ended at two weeks postoperatively, it is possible, that FACT-Anemia scores correlate with Hb values at later time points. We did not include a more prolonged follow-up, since the basic goal of the original study was to evaluate the effect of a restricted perioperative transfusion trigger on RBC use and to investigate direct postoperative effects such as hospital stay, delay of mobilisation and, in this report, quality of life, fatigue and function with the purpose to find a further indicator for RBC transfusion.

The FACT-Anemia questionnaire was originally developed for cancer patients and seems less applicable to lower joint surgery patients, who generally suffer a more acute anemia due to intra- and postoperative blood loss as compared to anemia due to a chronic disease (e.g. cancer, use of chemotherapy).

In the immediate postoperative period, the three used questionnaires, showed intercorrelations between 11 and 70%, suggesting that these scoring systems measure

a similar construct with respect to QoL and fatigue. As the FACT-NF subscale was not responsive, it seems not informative in this context.

Although the FSI is a reliable and valid instrument to measure functional outcome in orthopaedic patients, this functional scale did not correlate with postoperative acute Hb level decrease or absolute Hb levels. Other factors in the postoperative period apparently overrule the inconvenience of anemia or a decrease in Hb level.

In hip fracture patients, Carson and coworkers investigated postoperative recovery in relation to Hb levels and found no difference in recovery between a discharge Hb of 8 to 10 g/dL and more than 10 g/dL [15]. Halm et al used the Functional Independence Motor (FIM) mobility score to measure functional mobility within 60 days follow up after hip fracture surgery, also found no association with pre- or post-operative Hb levels [16]. These findings as well as our study show that the used QoL and fatigue questionnaires, are not suitable as a monitor for acute postoperative anemia, at least not in the range of Hb levels observed in this study.

In conclusion, we found that Hb levels do not correlate with the FSI, VAS and FACT-Anemia scores in the immediate postoperative period after lower limb joint replacement surgery, which is associated with a more acute decrease in Hb level and which is different from the setting of chronic anemia for which some questionnaires were developed. However, this does not preclude an effect after a longer postoperative interval or in patients with lower absolute Hb levels.

Acknowledgements

The authors thank Tineke van der Heide for data collection and the Orthopaedic staff of the Leiden University Medical Center, The HAGA Hospital Leyenburg and the Reinier de Graaf Gasthuis for participating in this study. No conflict of interest is present.

REFERENCES

1. Laupacis A, Bourne R, Rorabeck C, Feeny D, Wong C, Tugwell P, Leslie K, Bullas R. The effect of elective total hip replacement on health-related quality of life. J Bone Joint Surg [Am] 1993; 75(11):1619-26.
2. Norman-Taylor FH, Palmer CR and Villar RN. Quality-of-life improvement compared after hip and knee replacement. J Bone Joint Surg [Br] 1996; 78(1):74-77.
3. Rosencher N, Kerkkamp HEM, Macheras G, Munuera LM, Menichella G, Barton DM, Cremers S and Abraham IL for the OSTHEO Investigation. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion 2003; 43:459-69.
4. Wallis JP, Wells AW, Whitehead S and Brewster N. Recovery from post-operative anemia. Transf Med 2005; 15:413-8.
5. Conlon NP, Bale EP, Herbison GP and McCarroll M. Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. Anesth Analg 2008; 106:1056-61.
6. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leukocyte-depleted red blood cells. Vox Sang 2010; 98:56-64.
7. Jette AM. Functional Status Index: reliability of a chronic disease evaluation instrument. Arch Phys Med Rehabil 1980; 61:395-401.
8. Jette AM. The functional Status Index: reliability and validity of a self-report functional disability measure. J Rheumatol Suppl 1987;14 suppl 15: 15-21.
9. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol 1997; 34 (3 suppl 2):13-9.
10. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidem 2008; 61:102-9.
11. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue scales. J Pain Symptom Manage 2002; 24(6):547-61.
12. Wells G, Li T, MacLean R, Tugwell P. Determining the minimal clinically important difference in activity, fatigue, and sleep quality in patients with rheumatoid arthritis. J Rheumatol 2007; 34(2):280-9.
13. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003; 41(5):582-92.
14. Nutritional anemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968; 405:5-37.
15. Carson JL, Duff A, Berlin JA, Lawrence VA, Poses RM, Huber EC, O'Hara DA, Noveck H, Strom BL. Perioperative blood transfusion and postoperative mortality. JAMA 1998; 279:199-205.
16. Halm EA, Wang JJ, Boockvar K, Penrod J, Silberschweig SB, Magaziner J, Koval KJ, Siu AL. The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. J Orthop Trauma 2004; 18(6):369-74.

APPENDIX 1

The Functional Status Index (FSI) has 11 questions. Each question is scored from 0 to 4 with lower scores (except for 0) indicating better functioning.

0= this question is not relevant
1= no help needed
2= uses a device
3= needs human assistance
4= not possible due to health reasons

1. walking 10 feet
2. getting into and out of bed
3. putting socks and shoes on
4. getting on and off the toilet
5. rising from an armless chair
6. getting in and out of a bath/shower
7. taking a bath or shower
8. walking a block
9. .getting into a car
10. putting on pants
11. climbing five stairs

APPENDIX 2

The FACT-Anemia questionnaire comprises of fatigue (F) items and non-fatigue (NF) items. Each item is scored from 0 to 4, with lower scores indicating better functioning and well-being.

0=not at all
1=a little
2=more than a little
3=very much
4=very strongly

I feel fatigued (F)
I feel weak all over (F)
I feel listless ("washed out") (F)
I feel tired (is skipped because of VAS fatigue score asked separately)
I have trouble starting things because I am tired (F)
I have trouble finishing things because I am tired (F)
I have energy (F)
I have trouble walking (NF)
I am able to do my usual things (F)
I need to sleep during the day (F)
I feel light-headed (dizzy) (NF)
I get headaches (NF)
I have been short of breath (NF)
I have pain in my chest (NF)
I am too tired to eat (F)
I am motivated to do my usual activities (NF)
I need help doing my usual activities (F)
I am frustrated by being too tired to do the things I want to do (F)
I have limited my social activities because I am tired (F).