Chapter 3

The impact of a restrictive transfusion trigger on post-operative complication rate and well-being in elective orthopaedic surgery: a post-hoc analysis of a randomised study

Cynthia So-Osman[1], Rob Nelissen[2], Ronald Brand[3], Frank Faber[4], Ron Te Slaa[5†], Anne Stiggelbout[6] and Anneke Brand[1]

From the [1]Dept. of Research and Development, Sanquin Blood Bank South West Region, Leiden;
[2] the Dept. of Orthopaedic Surgery, Leiden University Medical Centre (LUMC), Leiden;
[3] the Dept. of Medical Statistics and BioInformatics, Leiden University Medical Centre (LUMC), Leiden;
[4] the Dept. of Orthopaedic Surgery, HAGA Hospital, Leyenburg location, The Hague;
[5] Dept. of Orthopaedic Surgery, Reinier de Graaf Hospital, Delft; and
[6] Dept. of Medical Decision Making, Leiden University Medical Centre (LUMC), Leiden, The Netherlands

[†] passed away

Submitted

ABSTRACT

Background: Peri-operative red blood cell transfusions have been associated with post-operative complications in patients undergoing elective orthopaedic hip- or knee replacement surgery.

Materials and methods: A post-hoc analysis of data extracted from a randomised study on transfusion triggers using pre-storage leukocyte-depleted red blood cells. Patients who received the most restrictive transfusion policy ("restrictive group") were compared with patients who received the most liberal policy ("liberal group"). Endpoints were red blood cell use, hospital stay, haemoglobin levels, postoperative complications and quality of life.

Results: Of 603 patients, 26.4% patients in the restrictive group and 39.1% in the liberal group were transfused (p=0.001). In the restrictive group, fewer postoperative infections (5.4 % versus 10.2 %; p=0.03) and respiratory complications (1.7% versus 4.9%; p=0.03) were observed, whereas hospital stay, cardiovascular complications and mortality rate were not different in both groups. Quality of life scores were not associated with type of transfusion policy, the number of red blood cell transfusions or the transfusion status.

Conclusion: A restrictive transfusion protocol was not associated with worse outcome and showed a trend towards fewer postoperative infections and respiratory complications compared to a liberal transfusion policy. Well-being was not associated with transfusion policy or with red blood cell transfusions.

INTRODUCTION

Reports on the role of allogeneic red blood cell (RBC) transfusions, whether or not leukocyte reduced, on post-operative infection rate in orthopaedic surgery are inconsistent [1-6]. Since many of these studies were observational or retrospective, selection bias at patient inclusion may have occurred. We recently reported the intention-to-treat results of a randomised study among elective orthopaedic surgery patients, that compared a new uniform, intentionally restrictive, transfusion policy with the standard hospital policy, with RBC use as primary endpoint [7]. No differences in RBC use between the randomised arms were observed because in one of the three participating hospitals, the new uniform study trigger for blood transfusion turned out to be less restrictive than their standard trigger, which resulted in an increased RBC use with this new transfusion policy. As well, no significant differences in post-operative complications between the original randomisation groups was present. In the current post-hoc analysis we investigated the effect of the most restrictive transfusion policy in all three participating hospitals, by pooling the patients who were randomised to the most restrictive trigger to a restrictive policy group and the patients who were randomised to the most liberal transfusion policy to a liberal policy group, thereby fully respecting the randomised nature of the data.

A second aim of the study was to evaluate the effect of the transfusion policy (restrictive or liberal) and of RBC transfusions on postoperative functional well being by measuring quality of life (QoL) scores. Previously, we were unable to show any correlation between QoL scores and Hb levels in the early postoperative period in this cohort, but, as suggested by Wallis, Hb and transfusions should be disentangled and thus separately analysed in QoL evaluations [8,9].

METHODS

Establishing groups for the post-hoc analysis

In the original study, within each participating hospital, patients were randomized to either protocol A (new policy) or protocol B (standard policy) [7]. The new transfusion trigger, was risk level based (depending on age and co-morbidity) and uniform among the three participating hospitals (Appendix). The new protocol (A) was more restrictive than the standard policy (B) for two hospitals and the patients randomized to A were labeled "restrictive " and to B "liberal ". In the third hospital, patients randomized to protocol A actually received more RBC transfusions and this group was now labeled "liberal" and the standard policy (protocol B) "restrictive". Only pre-storage leukocyte-depleted (LD-) RBC(s) were used.

Outcome measures

The original primary outcome variable was the number of transfused RBCs. Postoperative complications and QoL were secondary outcome measures and prospectively scored. Complications were categorised in: infections, respiratory complications (pneumonia excluded), neuro-psychiatric, cardiovascular and haemorrhagic complications, mobilisation delay, and mortality. Post-operative infections were pre-defined according to CDC criteria [10]. All wounds were prospectively scored for possible wound infection at postoperative day 5 according to Gaine and coworkers [11]. Cases of unclassified hypoxaemia were further investigated by detailed chart review to investigate their relationship with RBC transfusions (e.g Transfusion Associated Circulatory Overload or Transfusion Related Acute Lung Injury) . QoL questionnaires were scored preoperatively (time point T1) and at postoperative days +4 (time point T2) and +14 (time point T3), using the Functional Status Index (FSI), measuring functionality in daily living; a Visual Analogue Scale (VAS) for fatigue; and the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) subscale, measuring fatigue and other anaemia-related symptoms. All scores ranged from 1 to 100, with lower scores indicating better functioning. Follow up ended at the outpatient clinic 14 days after surgery or at final discharge (if hospital stay was longer than 14 days). Details of the original study and overall results have been reported previously [7,9].

Analysis and statistical methods

Continuous data are summarized as mean and SD, or median and inter-quartile (IQ) range in case of a non-normal distribution. A comparison of laboratory parameters and other numerical endpoints (like hospital stay and age) between groups was performed by a Student t-test in case of normal distributions and by the non-parametric counterpart (Mann-Whitney) in case of non-normal distributions (the number of patients receiving RBC transfusions and the total number of units RBC administered). In case of categorical endpoints, comparisons were made on proportions using the Chi-square statistic or Fisher's Exact test. A common (pooled) Odds Ratio was computed as an overall effect measure among the three hospitals since all tests for heterogeneity were non-significant ($p>0.10$). RBC use of both groups was compared to verify that the restrictive group indeed used fewer RBCs (significant p-value of less than 0.05). Pearson correlation coefficients [+ 95% CI] were calculated between FSI, Fact-Anemia and VAS scores and number of RBC transfusions for time points T1, T2 and T3. If $r \geq 0.20$, scores at T2 and T3 were corrected for preoperative scores of FSI, Fact-Anemia and VAS, and for peri- and post-operative variables (duration of surgery, surgical blood loss and post-operative complications) as possible confounders. Student's t-tests were used to compare the QoL scores with dichotomous variables (transfusion status: yes/no or type of transfusion policy: restrictive/liberal). In case of a significant difference between means ($p<0.05$), regression analysis was performed to further evaluate the association of FSI, Fact Anemia and VAS scores, correcting for possible confounders.

For the analysis of the post-operative endpoints, we used a Bonferroni correction to adjust for multiple testing of seven variables (infections, respiratory complications (pneumonia excluded), neuro-psychiatric, cardiovascular and haemorrhagic complications, mobilisation delay and mortality) (significant p - value of less than 0.01). Data were analysed using the SPSS statistical program (version 15.0) for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of 603 included patients, 299 were assigned to the restrictive group and 304 to the liberal group. The baseline characteristics (age, sex, type of surgery, co-morbidities, use of medication, pre-operative haemoglobin (Hb) level) were balanced in both groups except for history of chronic obstructive pulmonary disease (COPD), of which 32 (10.7%) patients were in the restrictive group versus 14 (4.6%) in the liberal group (p=0.005) (Table 1).

Table 1. Patient baseline characteristics

Parameter **Numbers (%) or mean (SD)**	**Restrictive group**[a] **n=299**	**Liberal group**[b] **n=304**	**P-value**
Females	190 (63.5)	211 (69.4)	0.13
Mean age (years)	70.2 (10.3)	70.7 (9.6)	
Mean weight (kg)	79.5 (13.4)	77.7 (13.1)	
Smoking	43 (14.4)	47 (15.5)	
Total hip replacement (THR)	166 (55.5)	173 (56.9)	
Total knee replacement (TKR)	113 (37.8)	111 (36.5)	
Revision THR	16 (5.4)	18 (5.9)	
Revision TKR	4 (1.3)	2 (0.7)	
Low risk[c]	12 (4.0)	14 (4.6)	
Intermediate risk[d]	81 (27.1)	80 (26.3)	
High risk[e]	206 (68.9)	210 (69.1)	
Rheumatoid arthritis	27 (9.0)	40 (13.2)	0.11
Chronic Obstructive Pulmonary Disorder	32 (10.7)	14 (4.6)	0.005
Mean pre-operative Hb (g/dL)	13.8 (1.4)	13.5 (1.3)	0.02
Mean pre-operative Hct (L/L)	0.41 (0.04)	0.40 (0.04)	

Percentages are within policy group.
[a] restrictive group: patients assigned to the most restrictive transfusion policy.
[b] liberal group: patients assigned to the most liberal transfusion policy.
[c] low risk: patients younger than 50 years of age without risk factors.
[d] intermediate risk: patients from 50 to 70 years of age without risk factors.
[e] High risk includes one or more of the following risk factors:
any heart rhythm different than sinus rhythm, unstable cardiac ischaemia (by history or ECG), myocardial infarction less than 6 months, heart failure, heart valve disease, age from 70 years onwards, serious peripheral arterial disease, including large vessel surgery (aortic aneurysm, peripheral vessels), cerebral arterial disease (CVA or TIA in history), hypertension with left ventricular hypertrophy (LVH) (shown on ECG/ echocardiogram), serious pulmonary disease, expressed in polyglobulinaemia (emphysema / pulmonary fibrosis), insulin dependent diabetes mellitus.

Clinical endpoints

The proportion of transfused patients was smaller (26.4%) in the restrictive group compared to the liberal group (39.1%, p=0.001), as was the mean RBC use per patient (p=0.003) (Table 2). No difference in hospital stay (p=0.27) was noted between the groups. Mean duration of surgery and median blood loss were comparable between groups (data not shown).

Table 2. RBC use and post-operative clinical endpoints by assigned transfusion policy group

Clinical endpoints Numbers (%) or mean (SD)	**Restrictive group[a] n=299**	**Liberal group[b] n=304**	**P**	**common OR[c] (95% CI)**
N / proportion transfused patients (in %)	79 / 26.4	119 / 39.1	0.001	
RBC use (U/patients)	0.64 (1.4)	1.00 (1.6)[d]	0.003	
LOHS (days)	9.6 (5.1)	10.2 (7.4)[e]	0.27	
Hb day +1 (g/dL) (SD)	10.6 (1.6)	10.3 (1.4)	0.02	
Hb day +4 (g/dL) (SD)	10.5 (1.2)	10.5 (1.2)	0.99	
Hb at discharge (g/dL) (SD)	11.4 (1.3)	11.4 (1.2)	0.99	
Infections	16 (5.4)	31 (10.2)	0.03	2.0 (1.1-3.8)
Cardiovascular complications	30 (10.0)	27 (8.9)	0.63	0.9 (0.5-1.5)
Respiratory complications	5 (1.7)	15 (4.9)	0.03	3.1 (1.1-8.5)
Neuro-psychiatric complications	12 (4.0)	12 (3.9)	0.98	1.0 (0.4-2.2)
Haemorrhage	10 (3.3)	12 (3.9)	0.68	1.2 (0.5-2.9)
Delayed mobilisation	32 (10.7)	26 (8.6)	0.37	1.3 (0.7-2.2)
Mortality	0 (0)	3 (1.0)	0.25	
Composite complications[f]	93 (31.1)	110 (36.2)	0.18	1.3 (0.9-1.9)

[a] restrictive group: patients assigned to the most restrictive transfusion polic.y
[b] liberal group: patients assigned to the most liberal transfusion policy.
[c] to estimate complication risk, a common odds ratio (OR) is calculated.
[d] 95% CI of difference [0.12, 0.60].
[e] 95% CI of difference [-1.6, 0.4].
[f] patients could experience more than one complication
Median RBC use (IQ range) was 0.0 (0-2.0) in the liberal policy group and 0.0 (0-1.0) in the restrictive policy group

Infections occurred in 47 (7.8 %) of all patients, of which 16 patients were in the restrictive group (5.4%) and 31 patients in the liberal group (10.2%, p=0.03). Pooled risk estimates were calculated for post-operative complications, which resulted in an elevated risk of infections (common OR=2.0, p=0.03) and respiratory complications (common OR=3.1, p=0.03) in the liberal group, however both were not significant after correction for multiple testing (significance level p<0.01). Other post-operative endpoints were also not different between the groups.

Table 3 shows that infections (mainly urine tract infections and wound infections) and respiratory complications occurred more often in transfused patients, respectively 66% (31 of 47) and 70% (14 of 20) of patients developing these complications had been transfused. Of the patients who developed infections, median RBC use in the restrictive group was 0.5 units (IQ range 0-2.0) and 2.0 in the liberal group (IQ range 1.0-3.0). Two patients had already been treated for a pre-existent infection (jaw and urine tract infection, one in each group).

Table 3. Infections and respiratory complications by assigned transfusion policy group in relation to RBC use (yes or no)

Clinical endpoints **Numbers of patients (n)**	**Restrictive group (n=299)** **RBC use:** **79 yes/ 220 no**	**Liberal group (n=304)** **RBC use:** **119 yes/185 no**	**P-value**
Infections (total number n=47)	**16(8/8)**	**31(23/8)**	**0.03**
Urine tract infection (UTI) (n=24)	8 (4/4)	16 (12/4)	
Wound infection (n=16)	6 (2 /4)	10 (9/1)	
Of which deep prosthetic infection (n=6)	3 (1/2)	3 (3/0)	
Pneumonia (n=1)	0	1 (0/1)	
Systemic bacterial infection (n=3)	1[a] (0/1)	2 (1/1)	
Other (localized) (n=3)	1 (1/0)	2 (1/1)	
Of which pre-existent infection (n=2)	1 (1/0) Jaw	1 (1/0) UTI	
Respiratory complications (total number n=20)	**5 (3/2)**	**15 (11/4)**	**0.03**
TACO (n=5)	2 (2/0)	3 (3/0)	
Bronchospasm in COPD (n=2)	1 (0/1)	1 (0/1)	
Respiratory insufficiency due to opiates (n=3)	0	3 (2/1)	
Pulmonary embolism (n=1)	0	1 (0/1)	
Unclassified hypoxaemia (n=9)	2 (1[b]/1)	7 (6[c]/1)	

Abbreviations: UTI= Urine Tract Infection; TACO=Transfusion Associated Circulatory Overload; COPD=Chronic Obstructive Pulmonary Disease

[a] this patient also had a deep prosthetic wound infection

[b] this case was possibly transfusion related (TACO)

[c] one case was possibly transfusion related (TRALI)

Patients with respiratory complications received a median RBC use of 1.0 unit in the restrictive group (IQ range 0-3.5) and of 2.0 in the liberal group (IQ range 2-2.75). Patients with postoperative infections or respiratory complications had significantly longer hospital stays compared to compared to patients without these complications: median hospital stay 12.0 [9.0-12.0] and 13.0 [10-17] days with infections and respiratory complications respectively, compared to 9.0 [7-10] in patients without these complications ($p<0.001$) (not shown).

Of five patients, the respiratory complications were related to a RBC transfusion and diagnosed as Transfusion Associated Circulatory Overload (TACO). Of nine patients with unclassified hypoxaemia, seven had received RBC transfusions. Detailed chart review of these seven patients further revealed two possible transfusion related cases. One 73-year old male with a history of CABG, PTCA and hypertension, who had knee surgery and one postoperative RBC transfusion, following a low Hb value of 9.2 g/dL, after which the patient developed cardiac failure (possible TACO) that responded well to diuretics (with compatible chest X-ray). The other was a 76-year old male patient with a history of CABG who received two RBC transfusions for a postoperative Hb value of 9.1 g/dL, with transient hypoxaemia, which needed oxygen support and resolved uneventfully (possible TACO or TRALI, although chest X-ray was not taken). A third 34-year old patient with a history of Still's disease, had knee surgery followed by massive postoperative blood loss of 2 litre by drains, with dyspnoea and tachypnoea and a postoperative Hb of 9.1 g/dL. After the patient received 4 RBC transfusions to compensate for the blood loss, he recovered completely. Of the remaining four transfused patients with unclassified hypoxaemia a relationship with RBC transfusion could not be found, mainly due to lack of chart information. However, in all patients hypoxaemia was mild and all patients completely recovered without additional mechanical ventilation.

QoL and fatigue scores were not associated with the type of transfusion policy (non-significant differences in mean scores between transfusion policy groups or number of RBC transfusions, except for FSI scores measuring daily activity which showed a significant, but weak correlation $r=0.36$ ($p<0.001$) with the number of RBC transfusions at time-point T2 (4 days postoperatively). However, this association disappeared after correction for the possible confounders pre-operative FSI score (T1), duration of surgery, surgical blood loss and post-operative complications, which lowered r to 0.08 ($p=0.085$). The transfusion status (being transfused or not) was also significantly associated with the FSI score at T2, with better scores if not transfused, but also with the VAS scores at T2, the FSI score at T3 and the Fact-Fatigue score at T2 (all had significant differences in mean scores between transfused and non-transfused groups with p-values <0.001). After correction for the four possible confounders, in all cases significance was lost.

DISCUSSION

In this post-hoc analysis, we compared a restrictive transfusion policy with a liberal policy and evaluated the clinical impact on post-operative complications and well-being. The restrictive transfusion policy resulted in an absolute reduction of 0.36 RBC unit per patient and a 31% relative risk reduction of proportion of transfused patients (13% absolute decrease from 39% to 26%). This finding is in line with the findings of Carless and co-workers, who

performed a meta-analysis of 17 randomised studies on transfusion triggers in a variety of patient groups including orthopaedic surgery and found an average relative risk reduction of 37% [12]. Although we found only an absolute reduction of 5% (from 36% to 31%) in the composite postoperative complication rates, the liberal group had more often infections and respiratory complications. The majority of postoperative infections and respiratory complications occurred in transfused patients. Estimated risks for these complications were respectively doubled and tripled in the groups assigned to the liberal transfusion trigger. However, if corrected for multiple testing ($p<0.01$), the significance between the groups was lost. A decreased infection rate with a restrictive transfusion policy was also found by Carless and co-workers, who analysed four randomised studies that reported infection rate, with a pooled risk ratio of 0.76 (95% CI 0.60 to 0.76). Two of those studies used leukoreduced RBCs [12].

The finding of an increased respiratory complication rate with a liberal transfusion policy has not been reported earlier. Postoperative pulmonary morbidity has been associated with RBC transfusions in cardiac surgery [13]. In our dataset, detailed chart review of seven transfused cases with unclassified hypoxaemia revealed a possible transfusion-related complication in two, and in a third a complete recovery thanks to the transfusions. Due to lack of information (no chest x-rays) of the remaining four cases, we could not rule out a sub-clinical transfusion associated circulatory overload (TACO) or transfusion related acute lung injury (TRALI) as a possible underlying cause [14]. Despite the use of leukocyte-depleted RBCs in both groups, the patients assigned to a restrictive transfusion policy had a lower incidence of postoperative infections and respiratory complications compared to the patients assigned to a more liberal transfusion policy, which phenomenon we hypothesize to be a consequence of the transfusion policy, with no consequences on well-being. These data strongly suggest that use of a restrictive transfusion policy is important in blood management programs, and even should be the first step in implementation, aiming for improved patient outcome.

In order to evaluate whether RBC transfusions contributed to well being by separating the effects of transfusion from the effects of the need for transfusion, we correlated QoL scores to RBC use. The number of RBC transfusions and the transfusion status was, after correction for possible confounders, not associated with QoL and fatigue scores at any time-point. We may therefore conclude that the number of RBC transfusions or the transfusion status was not related to well being and functioning in the direct postoperative period. We previously showed no effect of anaemia on QoL in this cohort.

This study has some limitations. First, the study was not powered to evaluate post-operative complications, since the prevalence of these complications is low, nor was the study powered to evaluate the relationship between RBC use and postoperative functioning and well being. Second, by reassigning the randomised groups to a "liberal" and "restrictive" group, the validity of the current "post-hoc" analysis might be disputed. However, since

the allocation was still randomised, the inference and p-values are completely valid as if it were a randomised allocation from the start. Therefore, the results from this study provide a higher level of evidence than data from prospective observational studies. Third, since postoperative anaemia was only moderate in our studied patients, we cannot extrapolate our findings to patients with more severe anaemia.

In conclusion, a restrictive transfusion policy was not associated with a higher complication rate, moreover, this policy might even result in less infections and respiratory complications, with no consequences on well-being. QoL scores were not associated to the number of RBC transfusions or to the transfusion status, suggesting that these were not of influence on well being and functioning in the direct postoperative period in moderately anaemic patients.

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APPENDIX

Transfusion policies from the original study protocol

Hb values were originally in mmol/L (e.g. 4.0 / 5.0 / 6.0 mmol/L) which is common use in the Netherlands

Protocol A: New, uniform transfusion policy (all participating hospitals)

Low risk group (patients younger than 50 years of age)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥6.4 g/dL:	0 RBC	If Hb	≥6.4 g/dL:	0 RBC
	4.8 - <6.4 :	1 RBC		5.6 - <6.4:	1 RBC
	<4.8:	2 RBC(s)		<5.6:	2 RBC(s)
Intermediate risk group (patients from 50 to 70 years of age)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥7.2 g/dL:	0 RBC	If Hb ≥	8.1g /dL:	0 RBC
	6.4 - <7.2:	1 RBC		7.2 - <8.1:	1 RBC
	<6.4:	2 RBC(s)		<7.2:	2 RBC(s)
High risk group[a] (see below)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥8.9 g /dL:	0 RBC	If Hb	≥9.7 g /dL:	0 RBC
	8.1 - <8.9 :	1 RBC		8.9 - <9.7:	1 RBC
	7.2 - <8.1 :	2 RBC(s)		8.1 - <8.9:	2 RBC(s)
	<7.2:	3 RBC(s)		<8.1:	3 RBC(s)

[a]High risk includes one or more of the following:
- any heart rhythm different than sinus rhythm.
- unstable cardiac ischemia (by history or ECG)
- myocardial infarction less than 6 months
- heart failure
- heart valve disease
- age (from 70 years onwards).
- serious peripheral arterial disease, including large vessel surgery (aortic aneurysm, peripheral vessels).
- cerebral arterial disease (CVA or TIA in history)
- hypertension with left ventricular hypertrophy (LVH) (shown on ECG/ echocardiogram)
- serious pulmonary disease, expressed in polyglobulism (emphysema / pulmonary fibrosis).
- insulin dependent diabetes mellitus.

Protocol B: Standard care transfusion policies

***Hospital number 1 (University Medical Center):**

- Peri-operative transfusion policy (day 0):

  if Hb between 8.1 and 9.7 g /dL and dependent on blood loss: 1-2 RBC(s).

- Post operative transfusion policy (from day 1) :

  if Hb <9.7 g /dL : 2 RBC(s), independent of age, risk status

***Hospital number 2 (general hospital):**

- Peri-operative transfusion policy (day 0):

  I keep Hb >6.4 g/dL in case of age < 60 years and ASA[a] class 1

  II keep Hb >8.1 g.dL in case of age ≥ 60 years and ASA[a] class 1, 2, 3

  III keep Hb >9.7 g/dL in case of ASA[a] class 4 or serious cardiopulmonary disease

[a]American Society of Anesthesiologists

- Post operative transfusion policy (from day 1):

  I keep Hb >9.7 g/dL in case of co-morbidity as: IC / CCU admission, uremia, serious heart-, lung- or vessel disease:

  II If no co-morbidity exists, the transfusion trigger is age-dependent:

Age (years)	**Hb (g/dL)**
>70	10.5
50-70	9.7
25-50	8.9
<25	8.1

***Hospital number 3 (general hospital):**

- Peri-operative transfusion policy (day 0):

  if Hb <9.7 g/dL and dependent on (expected) blood loss: 2 RBC(s)

- Post operative transfusion policy (from day 1):

  I Patients with cardiac history:

  - if Hb <9.7 g/dL: 2 RBC(s)

  II Patients without cardiac history if symptomatic (nausea, dizziness, tachycardia, general malaise, paleness):

  - if Hb 7.2 g/dL – 8.1 g/dL: 2 RBC(s)

  III If Hb ≤7.2 g/dL 2 RBC(s)