Study Protocol

Non-invasive measurement of serum haemoglobin in a perioperative setting

Protocol Version 1.2, August 22nd, 2019

1. TABULAR SUMMARY

Aim	• Anaemic patients that otherwise undetected by pre-operative tests recommended by international guidelines • Accuracy of SpHb compared to the gold standard in a pre-operative setting
Endpoints	• SpHb measurement pre-operatively • Laboratory Hb measurement pre-operatively • *n* of detected anaemic patients • *n* of otherwise (according to pre-operative blood sampling guidelines) undetected anaemic patients
Inclusion criteria	• Age > 18 years • Patient is planned for elective surgery • Pre-operative evaluation by an anaesthesiologist • Informed consent
Exclusion criteria	• Age <18 years • Patient refusal • Emergency surgery • No central laboratory Hb-test available
Sample size	Approximately 1500 patients
Study site	Div. of General Anaesthesiology, Emergency- and Intensive Care Medicine, Medical University of Graz
Sponsor	Medical University of Graz Div. of Gen. Anaesthesiology, Emergency- and Intensive Care Medicine, Medical University of Graz, Austria Head: Prof. Philipp G. Metnitz, MD, PhD
Investigator	Gabriel Honnef, MD Div. of Gen. Anaesthesiology, Emergency- and Intensive Care Medicine, Medical University of Graz, Austria

2. SUMMARY

Knowledge of patients' serum haemoglobin (Hb) levels is of great importance in many areas of medical practice. Standard methods of measurement require direct blood sampling; they are therefore relatively invasive, costly, and time-consuming.

Non-invasive Hb measurement techniques utilizing a finger probe (SpHb) have attracted a lot of attention over the last five years. Numerous studies have compared the accuracy of these devices with central laboratory Hb data in a wide range of clinical settings: operating rooms, critical care units, emergency departments, and blood donor clinics. (1-3)

A meta-analysis of previous studies regarding SpHb measurements in perioperative and intensive care settings has revealed a mean difference between non-invasive and central laboratory Hb results of 0.10±1.37 g/dl (*n*=4425) (2) . To date, however, few studies have assessed the use of these devices in a pre-operative setting.

Such a study could be of great value, as Hb measurement plays an important role in the implementation of PBM programmes (Patient Blood Management), which in turn are associated with improved patient outcomes, fewer transfusions and lower costs. (4-7)

Various guidelines with the aim of reducing unnecessary testing have been proposed. Such guidelines prioritize the tests to be applied during preparation for minor, intermediate and major surgery, considering specific comorbidities. (8)

Our goal is to establish SpHb threshold values that can help health care provider sort out which patients would potentially benefit from central laboratory Hb testing pre-operatively and who would likely not. We also aim to compare the mean difference between these two methods in a pre-operative setting.

With reliable cut-off values, SpHb levels could serve as a pre-test for patients with a low ASA score undergoing minor to intermediate surgery—i.e., those who would normally not receive a complete lab-test before an operation. This adaptation of clinical routine could help to detect anaemia where it might otherwise be missed.

To achieve this goal, we will observe and record SpHb values from patients meeting the inclusion criteria undergoing pre-operative evaluation for plastic, trauma, orthopaedic,

urological, general and gynaecological surgery over one year by the Department of Anaesthesiology and Intensive Care Medicine at the University Medical Centre Graz.

All patients will be evaluated pre-operatively by an anaesthesiologist, utilizing both central laboratory measurements as clinical routine and non-invasive Hb measurements. Both measurements (SpHb and central laboratory Hb) will be documented, along with the normally collected patient data, using the electronic system currently in use. Median values from the two methods will be compared, and possible cut-off values calculated.

3. BACKGROUND

3.1. Patient Blood Management (PBM)

According to the World Health Organisation (WHO), patient blood management (PBM) is a "patient-focused, evidence based and systematic approach for optimising the management of patients and transfusion of blood products to ensure high quality and effective patient care". (5)

A growing number of large observational studies and randomised controlled trials suggest that avoiding unnecessary transfusion can reduce morbidity and mortality. (4, 9) The high prevalence of untreated pre-operative anaemia implies a clinically relevant potential to avoid a significant amount of transfusions each year and thereby improve outcomes. (10, 11) In the effort to reduce red blood cell transfusions and detect pre-operative anaemia, preoperative Hb measurement is essential to detect and treat anaemia early.

3.2. Non-invasive haemoglobin measurement

Haemoglobin assessment is one of the most common laboratory tests performed worldwide. The value of a reliable clinical method of measure Hb in patients undergoing major surgery is well established. (4, 10)

The gold standard of Hb measurement involves venepuncture or finger prick. These methods are invasive and costly in terms of both time and resources, not to mention the risk they pose for both patient and clinical staff. These risks include pain, nerve damage, infection and the transmission of diseases.

Non-invasive Hb measurement is performed with a finger probe to measure SpHb without blood sampling. Rad-67™ Spot-check Pulse CO-Oximeter® (Masimo corporation, Irvine,

CA) is a device based on multi-wavelength co-oximetry for the spectrophometric estimation of haemoglobin (SpHb).

The usefulness of continuously measuring SpHb in a perioperative setting has previously been described. Several studies have shown that SpHb can help to estimate Hb values in various settings and to reduce unnecessary red blood cell (RBC) transfusions. It is also useful for Hb trend monitoring during surgery. (2, 12-14)

A meta-analysis by Kim et. al showed that the overall pooled random-effects mean difference (non-invasive vs. central laboratory) and SD were 0.10 ± 1.37 g/dL (-2.59 to 2.80 g/dL, I = 95.9% for mean difference and 95.0% for SD). (2)

In a pre-operative setting SpHb could act as an additional tool to reduce unnecessary testing without the cost of overlooking anaemic patients.

4. AIM OF THE STUDY

This studies aim is to evaluate the accuracy of non-invasive Hb measurement in a pre-operative setting and its possible role in a PBM approach to detect anaemic patients before surgery.

We will compare SpHb to the gold standard and seek to establish cut-off values that could be used to identify patients that need laboratory Hb measurement irrespective of physical status preoperatively.

4.1. Research questions

Research question 1: Can we use non-invasive Hb measurement as a pre-test to detect patients that are anaemic but would normally not get a central laboratory test?

Research question 2: Can we establish cut-off values for SpHb in a pre-operative setting?

Research question 3: How accurate is SpHb in a pre-operative setting for patients undergoing different kinds of surgery compared to the gold standard?

4.2. Hypotheses

Null Hypothesis h01a: SpHb measurement adds no benefit to the pre-operative evaluation of patients undergoing surgery.

Alternative Hypothesis ha1a: SpHb measurement is an easy and safe way to detect anaemic patients in a pre-operative setting who would normally be missed by clinical routine.

Null Hypothesis h02b: SpHb measurement cannot detect anaemic patients that would normally be missed by pre-operative evaluation recommended by current guidelines.

Alternative Hypothesis ha2b: SpHb measurement can detect anaemic patients that would normally be missed by pre-operative evaluation recommended by current guidelines.

Null Hypothesis h03a: The accuracy of non-invasive Hb measurement in a pre-operative setting is inferior to its already proven accuracy in other settings.

Alternative Hypothesis ha3a: The accuracy of non-invasive Hb measurement in a pre-operative setting is non-inferior to its already proven accuracy in other settings.

5. METHODS

This study is planned to be carried out as a prospective application study in a pre-operative clinic. Adult patients planned to undergo pre-operative examination and evaluation by an anaesthesiologist for elective surgery are to be included (see paragraph 5.1. for full inclusion and exclusion criteria).

Included patients will be evaluated by an anaesthesiologist according to national and international guidelines as it is routine at the pre-operative clinic. In addition, all included patients will have their Hb measured non-invasively by a trained health care provider. SpHb values will be recorded in the documentation software already in use at the clinic.

5.1. Inclusion and exclusion criteria

Inclusion criteria

- Age ≥ 18 years
- Patient planned for elective surgery
- Patient undergoing pre-operative evaluation by an anaesthesiologist
- Informed consent

Exclusion criteria

- Age < 18 years
- Patient refusal

- Emergency surgery
- No central laboratory Hb test available

5.2. Data acquisition

Routine documentation of the anaesthesiologic evaluation will be performed by clinical staff in the pre-operative clinic using the software solution already in clinical use.

Study relevant data including SpHb, invasively measured Hb and general patient information, will be extracted from the hospital's documentation programme already used in the pre-operative clinic.

5.3. Data management and Confidentiality

All study related data will be collected in a Microsoft Excel® data sheet. Individual patients will be represented by single data lines only.

Datasets will be encoded by numeric identifiers (pseudonymisation) already in use at the institution (admission number).

All analyses will be performed, using this pseudonymized dataset, in IBM SPSS Statistics® 23 provided by the Medical University of Graz.

6. STATISTICAL CONSIDERATIONS

6.1. Sample size

The sample size was calculated based on a two-sided confidence interval with a confidence level 1-α of 95%, an expected proportion of 0,85 and a distance of proportion to limit of 0,05.

With a prevalence of 14,1%(11) in a pre-operative setting for anemia the sample size needed was calculated to be 1392.

6.2. Statistical analyses

Mean differences and standard deviation (SD) will be calculated. Accuracy (trueness and precision) of non-invasive Hb measurement will be compared with its gold standard using linear regression analysis and Bland-Altman-analysis.

Potential SpHb cut-offs to reliably non-invasively detect anaemia as defined by the gold-standard will be tested using receiver-operating characteristics (ROC) analysis.

The theoretical number of patients with anaemia that would remain undetected by strict application of existing guidelines concerning preoperative laboratory measurements will be expressed as a total amount within the patient cohort and as an incidence per 100.000 patients.

7. ETHICAL CONSIDERATIONS

7.1. Potential risks and benefits

SpHb measurement, the only protocol-based procedure to be performed in patients included into this study, is a non-invasive application with no known potential to harm included patients. Venepuncture and laboratory measurement of haemoglobin concentration are part of the current routine practice in the preoperative clinic in question; patients are therefore not expected to directly benefit from the participation in this study.

Findings from this study, however, might lead to a better understanding of how non-invasive Hb measurement could be used in the future. Current supranational guidelines do not recommend Hb measurement for every patient undergoing specific surgery. With this clinical practice, health care providers might miss some anaemic patients, who might then be treated inappropriately.

The prevalence of pre-operative anaemia varies largely between different patient groups depending on age, comorbidities, planed surgery, etc. Lasocki et al. found that 14,1% of patients (*n*=1534) planned to undergo major elective hip, knee or spine surgery ware anaemic. After surgery, the number of anaemic patients increased up to 85,8%. In PBM vs. non-PBM centres, preoperative anaemia was less frequent (8,0% vs. 18,5%). (11)

As undetected anaemia represents a major problem in clinical routine, (6, 10, 15, 16) SpHb measurement could work as a pre-test in this scenario, to help health care providers in their decision-making process.

7.2. Informed consent and withdrawal

Patients undergoing pre-operative evaluation by an anaesthesiologist will be informed about the aim, intervention and protocol of this study ahead of preoperative assessment and asked to sign a consent form. Patients my refuse usage of their data at any given time-point without specification of reason in accordance with Austrian and European legislation.

8. SCHEDULE

Milestone	To be completed by
Ethics committee approval	08/2019
Acquisition of SpHb devices	09/2019
Start of patient recruitment	09/2019
Finish of patient recruitment	09/2020
Statistical analysis	10/2020
Manuscript preparation and publication	12/2020

9. REFERENCES

1. Ribed-Sanchez B, Gonzalez-Gaya C, Varea-Diaz S, Corbacho-Fabregat C, Perez-Oteyza J, Belda-Iniesta C. Economic Analysis of the Reduction of Blood Transfusions during Surgical Procedures While Continuous Hemoglobin Monitoring Is Used. Sensors (Basel). 2018;18(5).
2. Kim SH, Lilot M, Murphy LS, Sidhu KS, Yu Z, Rinehart J, et al. Accuracy of continuous noninvasive hemoglobin monitoring: a systematic review and meta-analysis. Anesth Analg. 2014;119(2):332-46.
3. Lamhaut L, Apriotesei R, Combes X, Lejay M, Carli P, Vivien B. Comparison of the accuracy of noninvasive hemoglobin monitoring by spectrophotometry (SpHb) and HemoCue(R) with automated laboratory hemoglobin measurement. Anesthesiology. 2011;115(3):548-54.
4. ESA. Practical Implementation Guide for Hospitals to support Patient Blood

Management (PBM) in the EU. 2017.
5. WHO. World Health Organization - Global Forum for Blood Safety: Patient Blood Management - Concept

paper. 2011.
6. Kotze A, Harris A, Baker C, Iqbal T, Lavies N, Richards T, et al. British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia. Br J Haematol. 2015;171(3):322-31.
7. Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, Swain SG, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion. 2017;57(6):1347-58.
8. NICE. Routine preoperative tests for elective surgery. 2016.
9. Perel P, Clayton T, Altman DG, Croft P, Douglas I, Hemingway H, et al. Red blood cell transfusion and mortality in trauma patients: risk-stratified analysis of an observational study. PLoS Med. 2014;11(6):e1001664.
10. Musallam KM TH, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. . Preoperative anaemia and

postoperative outcomes in non-cardiac surgery: a retrospective cohort study. . The Lancet. 2011.
11. Lasocki S, Krauspe R, von Heymann C, Mezzacasa A, Chainey S, Spahn DR. PREPARE: the prevalence of perioperative anaemia and need for patient blood management in elective orthopaedic surgery: a multicentre, observational study. Eur J Anaesthesiol. 2015;32(3):160-7.
12. A.A. Khalafallah CRC, M. Thomas, C.M. Chilvers, M. Sexton, M. Vialle, I.K. Robertson. Usefulness of non-invasive spectrophotometric haemoglobin estimation for detecting low haemoglobin levels when compared with a standard laboratory assay for preoperative assessment. BJA. 2015.
13. Adel A, Awada W, Abdelhamid B, Omar H, Abd El Dayem O, Hasanin A, et al. Accuracy and trending of non-invasive hemoglobin measurement during different volume and perfusion statuses. J Clin Monit Comput. 2018;32(6):1025-31.
14. Pulak Panda MS. Accuracy of haemoglobin estimation by non-invasive Pulse

Co-oximetry method: A prospective observational study

among Neonates, Children and Young Adults. JMR 2018; 4(1): 10-15

January- February. 2018.

15. Clevenger B, Richards T. Pre-operative anaemia. Anaesthesia. 2015;70 Suppl 1:20-8, e6-8.

16. Munoz M, Gomez-Ramirez S, Campos A, Ruiz J, Liumbruno GM. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus. 2015;13(3):370-9.