Effect of incentive spirometry in prevention of acute chest syndrome during painful crisis in adult sickle cell patients

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CONFIDENTIAL

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1. INTRODUCTION AND RATIONALE

Sickle cell disease (SCD) is a common hemoglobinopathy caused by a single point mutation in the 6th position of the β-globin gene (substitution of valine for glutamic acid), which leads to the replacement of normal hemoglobin (HbA) by sickle-hemoglobin (HbS). SCD is a heterogeneous disorder, with clinical manifestations including chronic hemolytic anaemia, increased susceptibility to infections due to functional asplenism, recurrent painful vaso-occlusive episodes and chronic ischemic organ damage resulting in a diminished quality of life and early death. (1)

One of the most severe complications during vaso-occlusive painful crisis is the acute chest syndrome (ACS), occurring in 30% of all sickle cell patients at least once in their life. (2) ACS is a major cause of death in sickle cell patients and frequently develops during and shortly after the start of a painful crisis. (3) The mortality of this complication is around 4,3% and is the most frequent cause of intensive care unit (ICU) admission for sickle cell patients. ACS is defined as the presence of a new pulmonary infiltrate (on chest X-ray) in combination with clinical symptoms such as fever or respiratory symptoms in a patient with SCD. (2) Though the exact cause is unknown, several factors, such as pulmonary fat embolism, bacterial or viral infection, thromboembolic occlusion and hypoventilation due to thoracic bone infarction, have been associated with ACS.(4) Nowadays, treatment focuses primarily on antibiotic therapy and (exchange) blood transfusion. (5)

Incentive spirometry has been demonstrated to be effective as primary prevention of the development of ACS in children admitted with a vaso-occlusive painful crisis. (6) However, the effect of incentive spirometry in prevention of ACS in adult sickle cell patients during painful crisis has not been studied so far. Therefore, the aim of our study is to evaluate the efficacy of incentive spirometry on the incidence of ACS in adult sickle cell patients admitted with a vaso-occlusive painful crisis.

Since phospholipase A2 ($sPLA_2$), an inflammatory mediator, can predict ACS and has been used successfully as a screening tool for early intervention, (7) plasma levels of $sPLA_2$ will also be assessed in this study in order to related the efficacy of spirometry to this biomarker. Furthermore, serum levels of procalcitonin, which is a strong indicator of bacterial infection,(8) will be assessed at presentation in order to recognize a subgroup of infection related ACS and to assess the efficacy of spirometry in this subpopulation. In addition, PCR's on respiratory viruses (*respiratory syncitial virus, human metapneumovirus, influenza A and B, parainfluenza 1-4, adenovirus, coronavirus, parechovirus, rhinovirus* and *bocavirus*) and atypical bacteria such as *C. pneumoniae*, *C. psittaci*, and *M. pneumoniae* will performed on throat swaps taken at randomization. *L. pneumophilia* antigen will be analyzed in a urine sample.

2. HYPOTHESES

We hypothesize that incentive spirometry will reduce the incidence of ACS in adult sickle cell patients admitted with an acute vaso-occlusive painful crisis.

3. STUDY OBJECTIVES

1. To evaluate the efficacy of incentive spirometry in primary prevention of ACS in adult sickle cell patients during painful crisis.

2. To relate the efficacy of incentive spirometry to plasma levels of $sPLA_2$ and serum levels of procalcitonin.

3. To evaluate whether plasma $sPLA_2$ levels may be helpful to stratify patients in high and low risk groups and to evaluate the value of incentive spirometry in these groups to prevent ACS.

4. To evaluate whether serum procalcitonin may stratify patients with an ACS related to an infectious and non-infectious pathogenesis and to evaluate the value of incentive spirometry to prevent ACS.

5. To identify the micro bacterial organisms responsible for the development of an acute chest syndrome and to relate this with the procalcitonin plasma levels.

4. STUDY DESIGN

A multicentre randomized controlled clinical trial, studying the effect of incentive spirometry on the incidence of ACS in comparison with standard care in adult sickle cell patients admitted with a vaso-occlusive painful crisis. Endpoint of the study is the development of an ACS.

5. STUDY POPULATION

5.1. Patients

Adult (≥18 years) sickle cell patients (HbSS, HbSC, $HbS\beta^0$- or $HbS\beta^+$-thalassemia) presenting with an acute painful crisis and thoracic pain without signs of an ACS will be asked to participate in this study. After informed consent is obtained, patients will be randomized for incentive spirometry (study group) or standard care (control group).

5.2. Inclusion criteria

1. High performance liquid chromatography confirmed diagnosis of HbSS, HbSC, HbSβ^0- or HbSβ^+-thalassemia genotypes.
2. Written informed consent by the patient.
3. Thoracic or back pain above the diaphragm.
4. Hospital admission due to vaso-occlusive painful crisis.

5.3. Exclusion criteria

1. Blood transfusion in the preceding three months
2. Diagnosis of ACS at presentation
3. Age < 18 years

6. STUDY PROCEDURES

6.1. Study group

Upon inclusion in the study, blood samples will be drawn via venipuncture and urine sampling will be performed according to the protocol. Chest X-ray of each patient will be taken at the emergency department (ED) and repeated on day 5 of hospital admission or sooner if clinically indicated.

Patients in the study group will be educated in the use of the spirometer (Respiflo™FS, Kendall) and the study protocol by the investigator. During admission patients have to inhale 10 times through the spirometer every 2 hours (between 8 a.m. and 10 p.m.) until at least 24 hours after the pain has subsided. If awake, patients may use the spirometry also between 10 p.m. and 8 a.m. Patients are asked to register every time they inhale through the spirometer and pain scores will be assessed (Visual Analog Scores).

Attending nurses under supervision of a specialized sickle cell nurse on the ward, together with the patient, will evaluate the spirometry protocol and pain scores daily. Patients will continue to receive the standard care as well (see below).

6.2. Control group (standard care only)

Patients in the standard care group will be evaluated equally but will receive standard care consisting of pain medication (iv/sc morphine), hydration and antibiotics in case of fever (>38.5 Celsius) according to local protocol. Oxygen therapy should be considered in case of hypoxia (blood oxygen saturation ≤ 92 %, measured with finger pulse oximeter).

6.3. Blood samples and laboratory analysis

6.3.1. Blood

Blood will be drawn at randomization:

EDTA blood (2x 4 cc)

- Hemoglobin levels, red blood cell counts, reticulocyte counts, leukocyte counts and differentiation, platelet counts will be determined with an automated cell counter.

Heparin geltube (1x 4.5 cc)

- Creatinin, ASAT, ALAT, AF, gGT, LDH, indirect bilirubin and proBNP levels will be determined according to local protocols.

Serum (1x 10 cc)

- Serum samples will be stored at -70°C for future analysis of high sensitive C-reactive protein (CRP), soluble vascular cell adhesion molecule 1 (sVCAM-1) and procalcitonin which will be determined with ELISA methods.

Citrated plasma (1x 4,5 cc)

- Citrated plasma samples will be stored at -70°C until analysis of $sPLA_{2,}$ pro-thrombin fragments (F1+2), D-dimer levels, protein S (free and total) and C activity and von Willebrand activity (vWF-Act)

6.3.2. Bacterial and viral analysis

- Throat swaps for bacterial and viral pathogens will be taken at randomization and analyzed by PCR for respiratory viruses (*respiratory syncitial virus, human metapneumovirus, influenza A and B, parainfluenza 1-4, adenovirus, coronavirus, parechovirus, rhinovirus* and *bocavirus*) and atypical bacteria (*C. pneumoniae*, *C. psittaci*, and *M. pneumonia*).

7. STATISTICS

The non-parametric Mann-Whitney U (or when necessary Kruskal-Wallis) test will be applied for between group comparisons. Spearman rank correlation analysis will be used to study the relationship between different laboratory results. Two-tailed p values ≤0.05 are considered statistically significant. We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0,5. Failure is defined as the development of an Acute Chest Syndrome as defined in the protocol at page 3, line 11. If the true relative risk of failure for experimental subjects relative to controls is 0,3. We will need to study 32 experimental subjects and 32 control subjects to be able to reject the null hypothesis that this relative risk equals 1 with

probability (power) 0,8. To correct for dropouts the study population will set at 35 subjects per treatment arm. The Type I error probability associated with this test of this null hypothesis is 0,05. We will use a chi-squared statistic to evaluate this null hypothesis. The sample size was calculated using Stata/SE, version 10.1 (sampsi program, StataCorp LP, Texas, USA).

8. STUDY ORGANISATION

This project will be carried out by the Department of Hematology, Academic Medical Center (Amsterdam, the Netherlands) and the Department of Hematology, Erasmus Medical Center (Rotterdam, the Netherlands) and the Department of Internal Medicine Slotervaart Hospital (Amsterdam, the Netherlands).

9. ETHICAL AND REGULATORY STANDARDS

9.1. Ethical principles

This protocol is in accordance with the principles laid down by the 18th world medical assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989) World Medical Assemblies.

9.2. Laws and regulations

This protocol is in accordance with laws and regulations of the country in which the study is performed.

9.3. Informed Consent

The informed consent document will be used to explain in simple terms, before persons are entered into this study, the nature, scope and possible consequences of the study. The participant will give consent in writing. The signature of the investigator and participant must confirm the participant's consent. The investigator is responsible to see that informed consent is obtained from the participant and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedure. The signed informed consent forms remain with the investigator.

9.4. Ethical review

Before start of the study, the study protocol and/or appropriate documents will be submitted to the ethical review committee (ERC), in accordance with local legal requirements. Only after approval will

the study begin at the investigative site. The ERC will also be informed of all amendments and if necessary approval must be sought for ethical aspects.

9.5. Confidentiality

All patient names will be kept secret to anyone other than the investigator. Participants will be numbered consecutively in the order in which they are included in the study, the next participant receiving the next available number. The number allotted to them during the study will identify patients throughout documentation and evaluation. The participants will be told that all study findings will be stored on computer and handled in strictest confidence.

10. OWNERSHIP OF DATA

The CURAMA study group, which is a collaborative effort between the Department of Vascular Medicine, Academic Medical Center (Amsterdam, the Netherlands), the Department of Internal Medicine Slotervaart Hospital (Amsterdam, the Netherlands), the Department of Internal Medicine, Sint Elisabeth Hospital (Curaçao, Netherlands Antilles), Red Cross Bloodbank Foundation Curaçao (Curaçao, Netherlands Antilles), the Laboratory of Clinical Thrombosis and Hemostasis in the Department of Internal Medicine, Academic Hospital Maastricht (Maastricht, the Netherlands), the Department of Clinical Chemistry (Groningen, the Netherlands) and the department of Hematology, Erasmus Medical Center (Rotterdam, the Netherlands), has the ownership of all data and results collected during this study. CURAMA is embedded in the Antillean Institute of Health Research. In consequence, the study group reserves the right to use these data, either in the form of case record forms, or in the form of a report, with or without comments or with or without analysis, in order to submit them to health authorities. The final publication of the study results will be written by the Study Coordinator(s). The manuscript will be sent to a peer reviewed scientific journal.
Authors of the manuscript will include the study coordinator(s), clinicians who referred a significant number evaluable patients, and others who have made significant scientific contributions.

11. CLINICAL STUDY REPORT

It is our intention that the findings of the study be published in scientific journals and presented at scientific meetings. The responsibility for presentations and/or publications belongs to the investigators.

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