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TÍTOL: Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome

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Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome

1. RESUM (EN CATALÀ)

La teràpia suplementària de ferro millora la capacitat d'exercici i la qualitat de vida en malalts amb una cardiopatia congènita cianòtica i/ o síndrome d'Eisenmenger

El dèficit de ferro és una troballa comú en la cardiopatia congènita cianòtica, i pot ser la causa d'una reducció en la capacitat d'exercici. Actualment, està indicada la reposició dels dipòsits de ferro en aquest grup de malalts, éssent les evidències científiques escasses. En el present treball investiguem la seguretat i eficàcia del tractament amb ferro en malalts amb una cardiopatia congènita cianòtica. Per tal motiu, vint-i-cinc malalts amb una cardiopatia congenita cianòtica i dèficit de ferro van ser inclosos de forma prospectiva entre Agost del 2008 i Gener del 2009. El tractament utilitzat fou fumarat ferròs oral, fins a una dosi màxima de 200 mg tres vegades al dia. En l'anàlisi basal i als tres mesos de seguiment es va utilitzar el test de qualitat de vida "CAMPHOR", el test de la marxa dels 6 minuts i la prova d'esforç amb consum d'oxigen. L'edat mitja fou 39.9+/-10.9 anys, 80% dones. Catorze malalts tenien la síndrome d'Eisenmenger, sis una malaltia cianòtica complexa i cinc

circulació de Fontan. Cap d'ells va haver d'interrompre el tractament degut a efectes adversos. Després de tres mesos de tractament, l'hemoglobina (19.0+/-2.9g/dL a 20.4+/-2.7g/dL, p<0.001), ferritina (13.3+/-4.7mug/L a 54.1+/-24.2mug/L, p<0.001) i saturació de transferrina (17.8+/-9.6% a 34.8+/-23.4%, p<0.001) van augmentar significativament. També hi va haver una millora significativa en la puntuació del test de qualitat de vida (20.7+/-10.9 a 16.2+/-10.4, p=0.001) i el test de la marxa (371.7+/-84.7m a 402.8.0+/-74.9m, p=0.001). No es van evidenciar canvis significatius en els valors de consum d'oxigen (40.7+/-9.2% a 43.8+/-12.4%, p=0.15). En definitiva, la teràpia suplementària amb ferro en els malats amb una cardiopatia congènita cianòtica i dèficit de ferro és segura i millora la qualitat de vida i la capacitat funcional. En aquest grup de malalts, per tant, és aconsellable identificar el dèficit de ferro i restaurar-ne els seus dipòsits.

Paraules clau: Síndrome d'Eisenmenger, cardiopatia congènita cianòtica, dèficit de ferro, capacitat d'exercici, qualitat de vida, teràpia suplementària de ferro.

Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome

Iron deficiency is common in cyanotic congenital heart disease (CHD) and results in reduced exercise tolerance. Currently, iron replacement is advocated with limited evidence in cyanotic CHD. We investigated the safety and efficacy of iron replacement therapy in this population. METHODS: Twenty-five iron-deficient cyanotic CHD patients were prospectively studied between August 2008 and January 2009. Oral ferrous fumarate was titrated to a maximum dose of 200mg thrice-daily. The CAMPHOR QoL questionnaire, 6minute walk test (6MWT) and cardiopulmonary exercise testing were conducted at baseline and after 3months of treatment. RESULTS: Mean age was 39.9+/-10.9years, 80% females. Fourteen had Eisenmenger syndrome, 6 complex cyanotic disease and 5 Fontan circulation. There were no adverse effects necessitating termination of treatment. After 3months of treatment, hemoglobin (19.0+/-2.9g/dL to 20.4+/-2.7g/dL, p<0.001), ferritin (13.3+/-4.7mug/L to 54.1+/-24.2mug/L, p<0.001) and transferrin saturation (17.8+/-9.6% to 34.8+/-23.4%, p<0.001) significantly increased. Significant improvements were also detected in the total CAMPHOR score (20.7+/-10.9 to 16.2+/-10.4, p=0.001) and 6MWT distance (371.7+/-84.7m to 402.8.0+/-74.9m, p=0.001). Peak VO(2) remained unchanged (40.7+/-9.2% to 43.8+/-12.4% of predicted, p=0.15). CONCLUSION: Three months of iron replacement therapy in iron-deficient cyanotic CHD patients

was safe and resulted in significant improvement in exercise tolerance and quality of life. Identification of iron deficiency and appropriate replacement should be advocated in these patients.

Keywords: Eisenmenger syndrome, Cyanotic heart disease, Iron deficiency, exercise capacity, Quality of life, iron replacement therapy.

Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome

Introduction

Cyanosis is present in 10 to 20% of adult patients with congenital heart disease (CHD) and is considered a complex multisystemic disorder. Chronic hypoxia in these patients results in an increase in hemoglobin concentration (secondary erythrocytosis). This is a physiologic adaptation aimed at increasing oxygen delivery to peripheral tissues by an increase in oxygen carrying capacity and total blood volume.[1-3] The optimal hemoglobin concentration varies between patients and is modulated through the increased production of erythropoietin which depends primarily on oxygen saturation at rest and during effort.[3, 4]

Iron is a vital substrate for hemoglobin production and sufficient iron stores are necessary to achieve and maintain adequate levels of hemoglobin. Unfortunately, more than one third of patients with cyanotic heart disease are iron deficient.[5, 6] Possible causes of iron deficiency include increased iron consumption through increased erythropoiesis, inappropriate venesections, hemoptysis, bleeding from arteriovenous malformations or collateral vessels, abnormal hemostasis, limited dietary intake or absorption, and use of anticoagulants and antiplatelets. Iron deficiency has also been identified as a risk factor for cerebrovascular events.[7] Moreover, it is associated with exercise intolerance through reduced oxygen delivery and its effect on skeletal muscle cell metabolism.[8, 9] Iron deficiency may remain

undetected in cyanotic patients since common findings as microcytosis are rarely found. Increased awareness is, thus, essential and routine monitoring of the peripheral red blood cells and iron-related parameters may aid in the prompt detection of iron-deficiency anemia in patients with cyanotic heart disease.

At present, there are limited data on the management of cyanotic patients with iron deficiency. Recent guidelines recommend avoidance of inappropriate venesection and cautious treatment of iron deficient cyanotic patients with close monitoring of hemoglobin levels.[10, 11] However, data are lacking on the efficacy of iron supplementation on exercise capacity in this population. Moreover, while caution to avoid over treatment and excessive erythrocytosis is recommended, no prospective trials have addressed the safety of iron supplementation in this cohort. We aimed to investigate the safety of iron supplementation in iron deficient cyanotic CHD patients and its effect on exercise capacity and quality of life (QoL).

Methods

Study design

This was a prospective, single center, non-randomized study. The protocol closely follows routine practice in our center and was approved by the local Ethics Committee. All cyanotic patients (resting oxygen saturation of ≤90% after 5 minutes of rest) followed at our center not on iron supplements, who were able to undergo exercise testing were systematically screened between February 2008 to January 2009 for iron deficiency (Figure 1). This was defined as serum ferritin<30ug/L or serum ferritin<50ug/L and transferrin saturation<15%.[12, 13] Exclusion criteria were 1) pregnancy; 2) overt anemia (defined as hemoglobin < 11.5 g/ dl) or active bleeding; 3) known hypersensitivity to iron supplements; 4) patients who were recently initiated on advanced therapies for pulmonary hypertension and 5) patients with severe hyperviscosity symptoms at the time of screening, as classified by Perloff et al.[14] These hyperviscosity symptoms included headaches, dizziness, altered mentation, visual disturbances, parasthesia, tinnitus, fatigue and muscle aches. Patients fulfilling the above criteria and agreeing to participate constituted our study population.

Baseline assessment

Baseline pretreatment assessment included a clinical interview and physical examination. Blood tests included full blood count, transferrin saturation, ferritin, creatinine and alanine transaminase levels. All patients completed a CAMPHOR QoL questionnaire, a six-minute walk test (6MWT) and a cardiopulmonary exercise test (CPET) as described below.

Quality of Life assessment

The CAMPHOR questionnaire was used for assessing quality of life. This is a questionnaire designed specifically for patients with pulmonary arterial hypertension (PAH) and was selected because a significant proportion of cyanotic CHD patients have PAH.[15] It has been validated in patients with PAH and has a good reproducibility, excellent internal consistency and is more sensitive to changes in clinical status compared to the other non-specific QoL instruments.[16]

The CAMPHOR questionnaire addresses two components of QoL: a generic and a Health related QoL (HRQoL) component. Generic QoL refers to an individual's subjective perception of satisfaction of life in areas that he/she considers important. Completing this section of the questionnaire gives the *QoL score*. HRQoL is restricted to aspects of life which are affected by disease and are potentially modifiable with treatment. The HRQoL component of the CAMPHOR questionnaire assesses impairment and disability separately. Impairment may result from the loss of physical, psychological or physiological function and leads to specific symptoms. Completing this part of the questionnaire, thus, provides a *symptom score*. Disability is described as any restriction of lack of ability to complete tasks deemed normal. The *activity score* is obtained in this section after completing this part of the questionnaire.

The individual CAMPHOR scores are combined to provide a *total CAMPHOR score*. High scores are associated with reduced QoL.

Six minute walk test

This test was conducted by a single operator in a 20m indoor, marked corridor,

following the American Thoracic Society guidelines.[17] Heart rate, pulse oximetry and Borg scale were recorded at baseline and 6 minutes.

Cardiopulmonary exercise testing

This was performed on a treadmill using an incremental maximal exercise protocol, which includes a stage 0 during which patients walk at a velocity of 1 mph at a 5% gradient (modified Bruce protocol). A respiratory mass spectrometer (Ultima PFX, Medgraphics Cardiorespiratory Diagnostics, St Paul, USA) was used to measure minute ventilation (VE), carbon dioxide production (VCO_2) and oxygen consumption (VO_2). Patients were encouraged to exercise to exhaustion. Peak VO_2, VE/VCO_2 slope and anaerobic threshold (AT) were measured and recorded. Peak VO_2 was expressed as the percentage of predicted for age, gender, height and weight. The VE/VCO_2 slope was obtained by linear regression of data acquired through the entire period of exercise.[18]

Iron replacement

Iron replacement consisted of oral ferrous fumarate 200mg once a day for 1 week, followed by 200mg twice daily for the next week and finally to the target dose of 200mg three times daily. This iron formulation contains 66mg of elemental iron per tablet, thus providing the recommended dose of 150-200mg of elemental iron per day for oral treatment of iron deficiency anemia in adults. Patients unable to tolerate oral therapy received intravenous iron replacement. For this purpose, patients were admitted to hospital and received a single dose of intravenous iron sucrose 200mg. Iron stores were then reassessed after 1 month and intravenous replacement repeated if found to be still iron deficient.

Follow up and outcomes

All investigations performed at baseline were repeated at the 3-month follow-up visit. Moreover, all adverse events during the 3-month follow-up period were recorded, with particular attention to hyperviscosity symptoms. Patients were also urged to report possible adverse effects of iron replacement, such as abdominal cramps, constipation, heartburn, nausea, and vomiting.

The primary measure of efficacy was change in 6MWT distance after 3 months of iron replacement. Other measures of efficacy included change in total CAMPHOR score and peak VO_2.

Statistical analysis

In order to detect a change in 6MWT distance of 35m, with a standard deviation of 67m, at a two-sided significance level of 0.05 and a power of 80% (paired comparison), 24 patients were recruited. Continuous variables are expressed as mean±SD and compared between baseline and follow-up using the Wilcoxon signed rank test. The relation between change in hemoglobin concentration and baseline hemoglobin levels was assessed using linear regression. All p-values were two-sided and a p-value of less than 0.05 was considered to indicate statistical significance. Analyses were performed using R version 2.8.1 (R Foundation for Statistical Computing, Vienna**,** Austria).

Results

A total of 123 adult cyanotic CHD patients were screened. Of these, 32 were found to be iron deficient. One patient was excluded due to pregnancy and 6 patients were not keen to participate in the study. No patients were excluded for the presence of severe hyperviscosity symptoms. Twenty-five patients were eventually recruited in the study. One patient dropped out of the study during follow-up as she underwent cardiac surgery for pulmonary artery debanding and could not attend the follow-up appointment.

The mean age of participants was 39.9±10.9 years and the majority were females (80%) (Table1). Fourteen patients (56%) had Eisenmenger syndrome, 5(20%) had a Fontan circulation, 4(16%) had double inlet left ventricle and 2(8%) had complex pulmonary atresia. A quarter of patients (n=7) had prior history of venesections, but none had been venesected in the year prior to entering the study. Prior bleeding episodes in these patients were relatively uncommon (4 had a history of hemoptysis and 1 had a spontaneous muscle hematoma).

Mean resting oxygen saturation was 80.6±5.3% and the vast majority of patients were in functional class II or more (88%). Amongst patients with Eisenmenger syndrome, 10 (71%) were on bosentan therapy (> 3 months on a stable dose). Almost one half of patients were on warfarin (44%). At screening, the majority of patients (n=22) experienced occasional symptoms of fatigue and a few have had headaches (n=12), muscle weakness (n=6) or faintness (n=5).

Average baseline hemoglobin concentration was 19.0±2.8g/dL. Average baseline ferritin, transferrin saturation and serum iron levels were 13.0±4.7ug/L, 17.5±9.3% and 12.7±6.5umol/L, respectively. Among 25 participants, only 5 patients

had microcytosis (mean corpuscular volume (MCV)<80 fl) and only 8 had hypochromia (mean corpuscular hemoglobin (MCH)<28 pg/erythrocyte).

Iron therapy

Twenty-three patients were initiated and tolerated oral iron therapy well. Two patients declined oral supplementation due to severe gastrointestinal side effects from previous treatment and opted for intravenous therapy. The mean dose of oral iron supplementation (ferrous fumarate) achieved during the study was 509±160mg/day. The two patients who received intravenous therapy iron had a single 200mg dose of iron sucrose and achieved the target range of iron stores (ferritin≥50ug/L or ferritin≥30ug/L and transferrin saturation≥15%) after 1 month. This level was maintained at 2 months, thus requiring no further intravenous supplementation.

The most common side effect of oral iron therapy was abdominal pain (25%) followed by constipation (17%) and diarrhea (17%) (Table 2). One patient reported a single episode of vomiting. There were no adverse effects reported by the 2 patients receiving intravenous iron. Dose reduction was required in 4 patients due to gastrointestinal side effects. No patients required discontinuation of iron or switch to intravenous treatment. Importantly, there were no cases of new or worsening hyperviscosity symptoms.

Changes in iron stores and hemoglobin concentration

Significant increase in iron stores was observed after 3 months of therapy (Table 3). Serum iron (13.0±6.5umol/L to 21.0±11.5umol/L, p<0.001), ferritin (13.3±4.7ug/L to 54.1±24.2ug/L, p<0.001), as well as transferrin saturation (17.8±9.6% to 34.8±23.4%, p<0.001) increased. A significant increase in hemoglobin concentration (19.0±2.9g/dL to 20.4±2.7g/dL, p<0.001) and MCV (86.4±9.0 to

91.7±6.7 fL, p<0.001) was also observed. This change was seen both in patients with lower (< 19.7 G/ dl, median hemoglobin level) or higher baseline hemoglobin levels (16.8±2.3g/dL to 18.7±2.7g/dL, p=0.002 and 21.2±1.2g/dL to 22.2±1.0g/dL, p=0.042 respectively). However, the magnitude of change was greater in those with lower baseline hemoglobin concentration (Figure 2). While all patients improved their hematologic parameters after 3 months, 6(25%) patients just fell short of criteria for iron repletion (mean ferritin level and transferrin saturation levels at 25.3±2.2ug/L and 28.6±22.7% respectively).

Change in exercise capacity

Iron therapy led to a significant improvement in exercise capacity expressed as 6MWT distance (371.7±84.7m to 402.8±74.9m, p=0.001) (Figure 3). A significant improvement was also observed in total exercise duration on cardiopulmonary exercise testing (409.0±167.2s to 431.8±202.8s p=0.022) (Table 3) but the increase in percentage predicted peak VO_2 was not significant (40.7±9.2 to 43.8%±12.4% of predicted, p=0.15).

Quality of life

Overall, total CAMPHOR score improved significantly after treatment (20.7±10.9 to 16.2±10.4, p=0.001) as did both health related symptom scores (8.0±4.3 to 6.0±3.8, p=0.007) and activity scores (5.6±3.9 to 4.8±3.8, p=0.025). Generic QoL showed a non significant improvement.

Discussion

Our study demonstrates that replenishing iron stores in iron deficient cyanotic adult patients with CHD leads to improvement in QoL and exercise capacity measured by exercise duration in cardiopulmonary test and 6MWT distance. This improvement occurred irrespective of baseline hemoglobin levels. Adverse effects from iron therapy were at most mild, with no new or worsening symptoms of hyperviscosity and no patients requiring discontinuation of therapy.

While the criteria for diagnosing iron deficiency anemia in non-cyanotic patients are well-established, the definition of anemia in cyanotic erythrocytotic patients remains elusive. In fact, traditional diagnostic criteria for anemia do not apply to these patients, where "appropriate" levels of hemoglobin may vary according to their oxygen saturations.[5] Also, other erythrocyte indices such as MCV and MCH are not sensitive indicators of iron deficiency in cyanotic patients.[6] Although most of iron-depleted patients in our study had normal MCV and MCH levels, a significant rise in hemoglobin was observed after iron treatment. This suggests the existence of a state of "relative anemia" in our study population and the importance of checking iron stores, rather than erythrocyte indices, to identify iron deficiency in cyanotic patients.

Systematic iron supplementation for a period of 3 months resulted in a significant improvement in exercise capacity measured by the 6MWT likely related to the increase in hemoglobin concentration. In fact, hemoglobin levels are known to related to exercise capacity in cyanotic CHD patients.[19, 20] The average increase in 6MWT distance of 31m is comparable to that seen in trials of advanced therapies for pulmonary hypertension, ranging between 16m in the trepostinil PAH study and 34m in the BREATHE-5.[21, 22]

While total cardiopulmonary exercise time increased significantly, there was

only a small, non-significant increase in peak VO_2. In this study, severe desaturation during exercise was observed and low oxygen saturation might have reduced the arterial-mixed venous oxygen difference and limited the increase in oxygen delivery (i.e. peak VO2). In fact, in the presence of left to right shunt, peak VO2 does not reflect maximal cardiac output during exercise and a prognostic value of peak VO2 in this setting is yet to be established. 6MWT distance, rather than peak VO2, has been used as an objective clinical endpoint in a previous randomized controlled study in patients with Eisenmenger syndrome.

Cyanotic heart disease has a significant impact on QoL. It is a chronic, multi-system disorder, associated with significant long-term morbidity impacting on many aspects of life (e.g. education, social).[24-28] However, QoL is often overlooked in routine clinical practice and even in clinical trials. QoL questionnaires/scores should be part of the routine clinical assessment of these patients, especially when assessing the effects of clinical interventions. The substantial improvement in the QoL score seen in our study is suggestive of the adverse effect of iron deficiency on cyanotic patients, which can be reversed with appropriate therapy.

Although iron replacement for iron-deficient CHD patients is currently recommended by adult congenital cardiologists and clinical guidelines,[10, 11, 29, 30] physicians may be concerned about 'over treating' these patients. This is especially true in iron deficient patients with high baseline levels of hemoglobin. The primary concern is that of a dramatic increase in red cell mass in response to iron supplementation causing severe hyperviscosity symptoms. However, there are no data to support this concern to date. In our study, short term iron replacement was not associated with new severe hyperviscosity symptoms, even in patients with high baseline hemoglobin concentration. Mild hyperviscosity symptoms are often non-

specific and rarely require treatment once iron deficiency and dehydration have been excluded. Moreover, patients with higher baseline hemoglobin concentration demonstrated a milder response to iron supplementation (Figure 2) implying the presence of an adaptive mechanism. This suggests that no iron deficient patient should be denied treatment based on their baseline hemoglobin levels alone.

In this study, iron supplementation was performed using the dose of iron recommended for non-cyanotic iron-deficient patients.[31] Despite this dose being substantial higher than that previously recommended (66mg elemental iron/day),[32, 33] no hyperviscosity symptoms occurred in our population. Moreover, 6 (25%) patients were still iron deficient at the end of the study. The optimal dose of iron, which should be safe yet effective, remains elusive and should be a topic of further investigation.

Limitations

The definition of iron deficiency is extrapolated from the non-cyanotic population, in which ferritin<30ug/L has a positive predictive value of 92-98%[12] whereas transferrin saturation<15% has a sensitivity of 80% but low specificity (50-65%).[34] Although ferritin levels in normal patients range from 40-200ug/L, some studies have shown that low normal levels (<50ug/L) can be associated with other pathologic conditions.[35] We therefore expanded our definition to include patients with a ferritin<50ug/L and transferrin saturation of <15% in an attempt to increase specificity.

Even though not all patients had pulmonary hypertension, we chose to use the CAMPHOR score to assess quality of life in this study. This score is targeted to patients with pulmonary hypertension and was, thus, designed to assess patients with

low energy levels and significant exercise limitation, which commonly affect ordinary activities.[15] Moreover, different to scores designed for congestive heart failure, the CAMPHOR score relies on the assessment of breathlessness and energy levels rather than peripheral oedema.[15] Significant exercise limitation and early onset of dyspnea are common features of PAH and complex cyanotic congenital heart disease.[18] We, thus, felt that the CAMPHOR score could be an appropriate tool in this setting compared to other non disease-specific questionnaires.

The small sample size precludes subgroup analysis to identify those patients who benefit most from iron supplementation versus those with little or no benefit. Moreover, the results of the present study refer to short term supplementation and follow-up. Longer term studies in a larger population are needed to determine the efficacy and risks of chronic iron replacement.

Finally, this was an uncontrolled prospective study. Therefore, we cannot exclude that the observed beneficial effects might reflect a placebo effect, rather than true change due to iron repletion. However, the concomitant significant improvement in objective measures such as hemoglobin exercise duration and 6MWT distance suggests otherwise. A randomized controlled study is needed to confirm the efficacy of iron supplementation therapy in this population.

Conclusion

Three months of systematic iron replacement therapy in iron-deficient cyanotic CHD patients was safe and resulted in significant improvement in exercise tolerance and QoL. Systematic screening for iron deficiency and appropriate replacement therapy should be advocated in these patients.

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TABLES AND FIGURES

Table 1. Baseline clinical characteristics

Clinical characteristics	n=25
Age, yrs	39.9±10.9
Female gender, n (%)	20 (80)
New York Heart Association	
Class I, n (%)	3 (12)
Class II, n (%)	17 (68)
Class III, n (%)	5 (20)
Diagnoses	
Eisenmenger syndrome, n (%)	14 (56)
Ventricular septal defect, n	10
Patent ductus arteriosus, n	2
Atrioventricular septal defect, n	1
Truncus arteriosus, n	1
Fontan circulation, n (%)	5 (20)
Double inlet left ventricle, n (%)	4 (16)
Pulmonary atresia with ventricular septal defect, n (%)	2 (8)
Past history	
Thrombosis^{+}, n (%)	1 (4)
Venesection, n (%)	7 (28)
Hemoptysis, n (%)	4 (16)
Bleeding$^{\#}$ (others), n (%)	1 (4)

Menorrhagia, n (%)	0 (0)
Vegetarian diet, n (%)	0 (0)
Medications	
Advanced therapy for pulmonary arterial hypertension, n (%)	10 (40)
Warfarin, n (%)	11(44)
Furosemide, n (%)	3 (12)
Digoxin, n (%)	2 (8)
Beta-blockers, n (%)	4 (16)
Symptoms associated with hyperviscosity	
Headache, n (%)	12 (48)
Faintness, n (%)	5 (20)
Altered mentation, n (%)	0 (0)
Visual disturbance, n (%)	2 (8)
Parasthesia, n (%)	2(8)
Tinnitus, n (%)	2 (8)
Fatigue, n (%)	22(88)
Muscle weakness, n (%)	6 (24)

All patients with hyperviscosity symptoms had mild symptoms except for 3 patients: 2 had moderate fatigue and 1 patient with moderate symptoms of muscle weakness.

+ cerebrovascular accident

spontaneous hematoma

Table 2. Adverse events during iron treatment

Adverse events	
Hyperviscosity symptoms[†]	
New and persistent n (%)	0 (0)
Worsening symptoms n (%)	0 (0)
Adverse effects of iron therapy	
Constipation n (%)	4 (17)
Vomiting n (%)	1 (4)
Abdominal pain n (%)	6 (25)
Diarrhea n (%)	4 (17)
Patients needing to discontinue treatment n (%)	0 (0)
Patients needing to reduce iron dose n (%)	4 (17)

†: headaches, dizziness, altered mentation, visual disturbances, parasthesia, tinnitus, fatigue or muscle aches

Table 3. Test results before and after iron therapy

Tests conducted	Baseline	End of study (3 months)	P value
Laboratory tests			
Hemoglobin, g/dL	19.0±2.9	20.4±2.7	<0.001
Packed Cell Volume	57.1±9.7	61.4±8.2	<0.001
Red blood cell count, $x10^{12}$/L	6.7±0.9	6.7±0.9	0.44
Mean cell corpuscular volume, fL	86.4±9.0	91.7±6.7	<0.001
Mean corpuscular hemoglobin, pg	29.0±3.5	30.7±2.9	<0.001
Mean corpuscular hemoglobin concentration, g/dL	33.3±1.0	33.3±1.0	1.00
Ferritin, ug/L	13.3±4.7	54.1±24.2	<0.001
Serum iron, umol/L	13.0±6.5	21.0±11.5	<0.001
Transferrin saturation, %	17.8±9.6	34.8±23.4	<0.001
Creatinine, umol/L	77.8±14.3	76.9±15.1	0.77
Alanine transaminase, IU/L	25.6±11.3	26.3±12.3	0.30
Six minute walk test			
Walk distance, m	371.7±84.7	402.8±74.9	0.001
Starting heart rate, beats/min	81.4±13.5	79.6±13.1	0.10
Peak heart rate, beats/min	100±19.4	98.6±17.5	0.45
Pre-test Borg score	0.4±1.0	0.7±1.7	0.80
Post-test Borg score	4.2±2.4	4.3±2.7	0.94
Post-test oxygen saturation, %	69.4±10.0	66.8±9.3	0.17
Cardiopulmonary exercise testing			
Peak VO_2, ml/kg/min	13.9±2.9	14.6±3.9	0.18
% predicted peak VO_2	40.7±9.2	43.8±12.4	0.15
VE/VCO_2 slope	53.6±3.6	53.1±17.0	0.64

Respiratory exchange ratio at peak	1.0±0.1	0.9±0.1	0.15
Total exercise duration, s	409.0±167.2	431.8±202.8	0.022
Peak exercise oxygen saturation, %	65.5±12.4	62.9±12.7	0.23
Peak heart rate, beats/min	134.6±25.6	136.0±23.3	0.94
Heart rate reserve, beats/min	52.8±18.1	53.5±27.0	0.89
CAMPHOR questionnaire[+]			
Symptom score	8.0±4.3	6.0±3.8	0.007
Activity score	5.6±3.9	4.8±3.8	0.025
QoL score	7.1±5.5	6.0±5.1	0.12
Total score	20.7±10.9	16.2±10.4	0.001

Peak VO_2 indicates peak oxygen consumption; QoL, Quality of Life

[+]*CAMPHOR questionnaire scores: improvement is reflected by reduction in scores*

Figure 1.

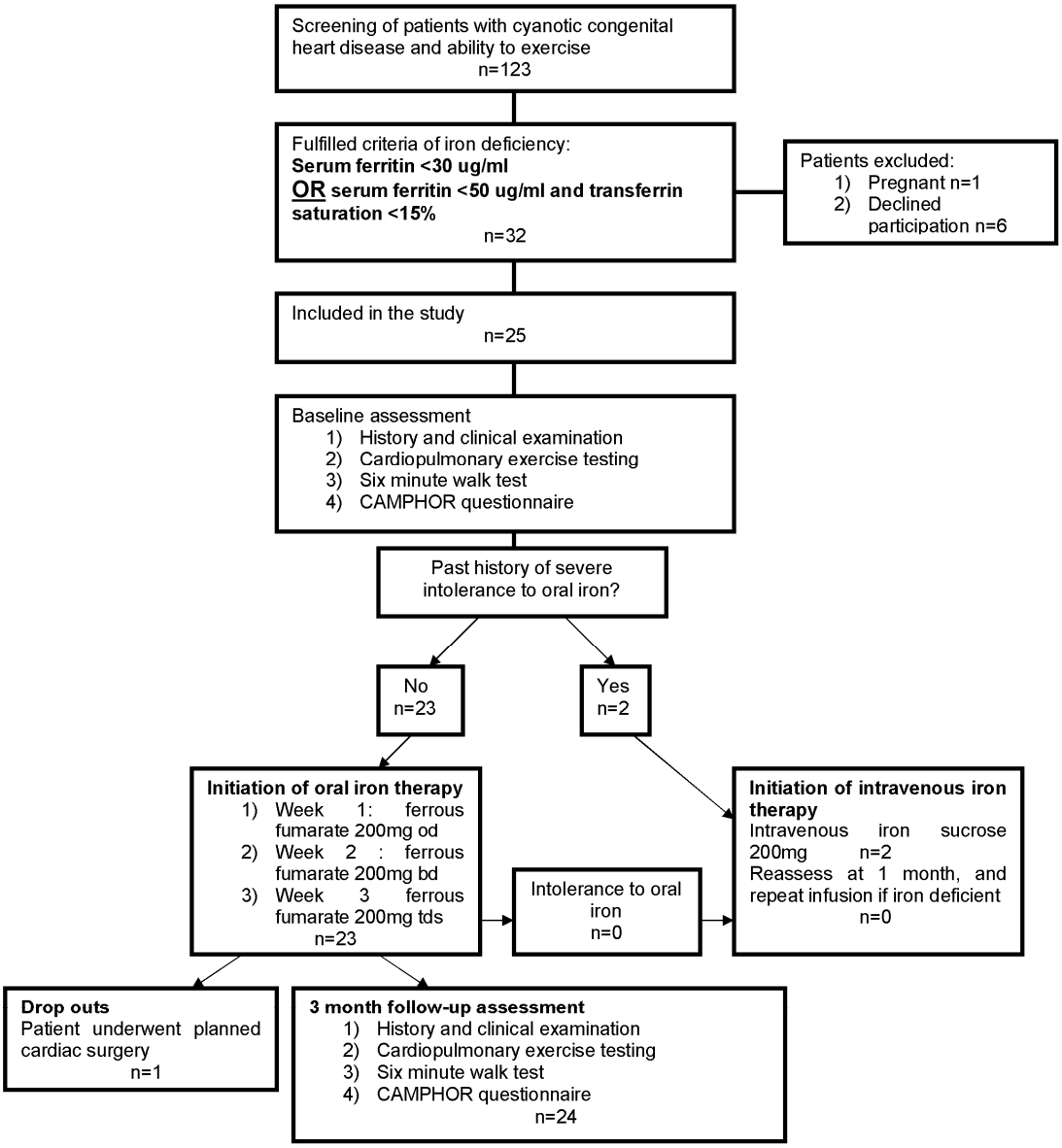

Screening of patients with cyanotic congenital heart disease and ability to exercise
n=123
Fulfilled criteria of iron deficiency:
Serum ferritin <30 ug/ml
OR serum ferritin <50 ug/ml and transferrin saturation <15%
n=32
Patients excluded:
1) Pregnant n=1
2) Declined participation n=6
Included in the study
n=25
Baseline assessment
1) History and clinical examination
2) Cardiopulmonary exercise testing
3) Six minute walk test
4) CAMPHOR questionnaire
Past history of severe intolerance to oral iron?
No
n=23
Yes
n=2
Initiation of oral iron therapy
1) Week 1: ferrous fumarate 200mg od
2) Week 2 : ferrous fumarate 200mg bd
3) Week 3 ferrous fumarate 200mg tds
n=23
Intolerance to oral iron
n=0
Initiation of intravenous iron therapy
Intravenous iron sucrose 200mg n=2
Reassess at 1 month, and repeat infusion if iron deficient
n=0
Drop outs
Patient underwent planned cardiac surgery
n=1
3 month follow-up assessment
1) History and clinical examination
2) Cardiopulmonary exercise testing
3) Six minute walk test
4) CAMPHOR questionnaire
n=24

Figure 2.

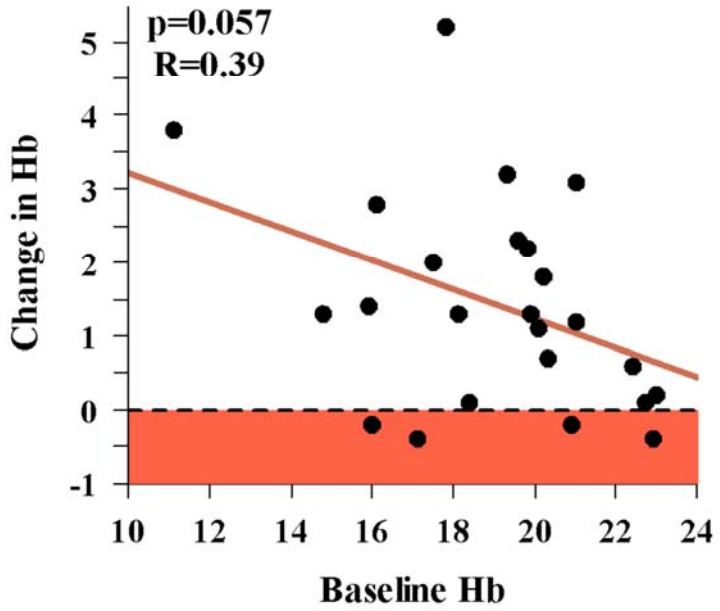
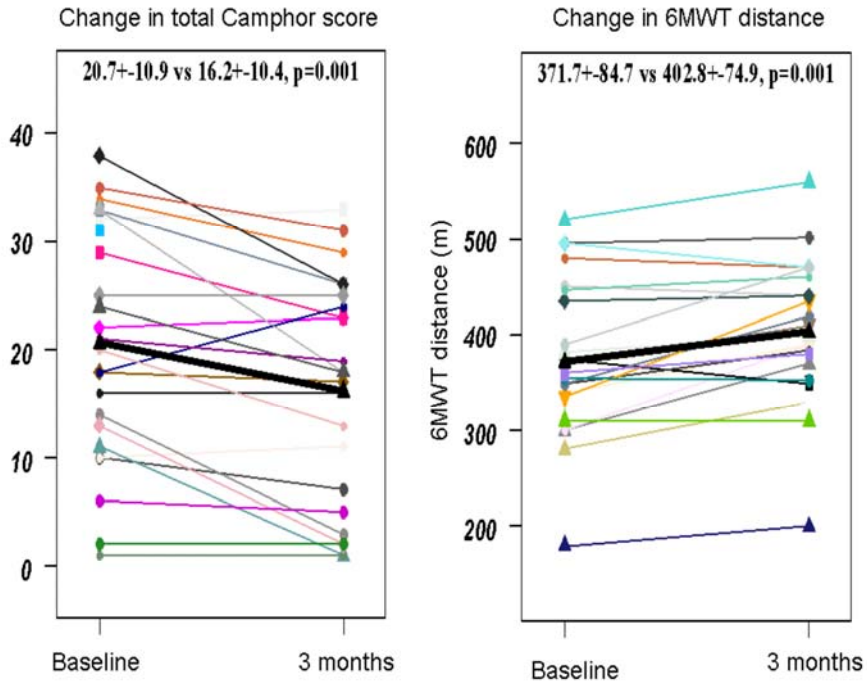

p=0.057
R=0.39
Change in Hb
5
4
3
2
1
0
-1
10
12
14
16
18
20
22
24
Baseline Hb

Figure 3.



High CAMPHOR scores reflect worse QoL

Figure Legends

Figure 1: Study Protocol. The study protocol is presented demonstrating the screening, recruitment, initial assessment and final assessment after 3 months of iron therapy.

Figure 2: Change (increase) in hemoglobin concentration over baseline hemoglobin levels. The change (increase) in hemoglobin levels after three months of iron replacement for all patients is shown. The increase is observed in patients of varying baseline hemoglobin levels. There is a trend towards a greater magnitude of increase in those who started with lower baseline hemoglobin and less in those who started at higher levels. This may suggest an adaptive mechanism.

Figure 3: Improvement in six minute walk test distance and total CAMPHOR scores. The improvement in total quality of life (QoL) scores on the CAMPHOR disease-specific questionnaire is shown with the mean±SD depicted at the top of the figure. The improvement in six minute walk test distance is similarly displayed on the right.