

Long-term oxygen therapy in children with sickle cell disease and hypoxaemia

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Received 13 April 2020

Revised 29 July 2020

Accepted 30 July 2020

ABSTRACT

Objective To evaluate the acceptability and safety profile of nocturnal long-term oxygen therapy (LTOT) in children with sickle cell disease (SCD) and chronic hypoxaemia.

Design Retrospective cohort study.

Patients, setting and intervention Children with SCD who started LTOT from 2014 to early 2019 in two tertiary hospitals in London, UK were retrospectively enrolled. Patients who started disease-modifying therapies <12 months before LTOT or while on LTOT were excluded.

Main outcome measures Minor and major adverse events during LTOT were reported. Laboratory and clinical data, transcranial Doppler (TCD) scans and overnight oximetry studies performed at steady state within 12 months before and after starting LTOT were compared.

Results Nineteen children (10 males; median age 12 years, range 6–15) were included. Nearly half of them (9/19; 47%) were on hydroxyurea at baseline. No child discontinued LTOT because of intolerance or poor adherence. No major adverse events were reported. Laboratory data did not show significant changes in haemoglobin and reticulocyte count after 1 year of follow-up. No statistically significant change in the incidence of vaso-occlusive pain events was noted (median annual rate from 0.5 to 0 episode per patient/year; $p=0.062$). Overnight oximetry tests performed while on LTOT showed improvements in all oxygen saturation parameters (mean overnight and nadir SpO₂, % of time spent with SpO₂ <90%) compared with the baseline.

Conclusion LTOT is a safe and feasible treatment option for children with SCD and chronic hypoxaemia.

INTRODUCTION

Sickle cell disease (SCD) is a hereditary blood disease with multi-organ involvement.¹ This condition affects millions of people, especially in sub-Saharan Africa, but its burden is also increasing in many western countries, in part because of the impact of recent migration.²

In patients with SCD, deoxygenated haemoglobin S (HbS) tends to polymerise damaging the red-cell membrane and making red blood cells (RBCs) rigid and sickle-shaped, causing intravascular haemolysis.³ In such conditions, RBCs tend to adhere to leucocytes and vascular endothelium, impairing capillary blood flow and causing vaso-occlusion, which in turn triggers tissue ischaemia.⁴ Repeated cycles of ischaemia, reperfusion and intravascular haemolysis induce oxidant stress and more

What is already known on this topic?

- ▶ Chronic hypoxaemia is a common complication of sickle cell disease in children and it can affect clinical outcomes. Previous small case series have reported that continuous oxygen therapy is harmful as it suppresses erythropoietic drive with a subsequent fall in haemoglobin concentration and an increase in the incidence of painful crises. This has led to a reluctance to use home oxygen therapy, but its long-term safety is not known.

What this study adds?

- ▶ This is the first study to show that the use of low-flow nocturnal long-term oxygen therapy is a safe and well-tolerated treatment option in children with sickle cell disease and chronic hypoxaemia.

inflammation that, along with other factors, cause chronic vasculopathy.⁵ Overall, these mechanisms deriving from oxygen desaturation are the main contributors to both acute and chronic manifestations of SCD and chronic hypoxaemia might therefore be expected to significantly exacerbate them.

The prevalence of hypoxaemia is high in children with SCD, with almost half of them showing nocturnal oxygen desaturation⁶ and over a third low daytime oxygen saturation (SpO₂) at steady state.⁷ Moreover, chronic hypoxaemia has been associated with an increased risk of cerebrovascular disease,^{8,9} left ventricular dysfunction¹⁰ and pulmonary hypertension,¹¹ even in young patients.

Limited evidence is available on safety or efficacy of long-term oxygen therapy (LTOT) for chronic hypoxaemia in patients with SCD. Few small case series^{12–14} have reported that continuous high-flow oxygen therapy is harmful as it suppresses erythropoietic drive with a subsequent fall in haemoglobin concentration and an increase in the incidence of painful vaso-occlusive pain events (VOEs).^{12,13} One of these was an adult case report,¹³ while in the other two^{12,14} neither ages of the patients nor the degree of chronic hypoxaemia was reported. In two of these studies, oxygen was provided at much higher levels than current norms.^{12,14} On the contrary, Ip *et al* observed no detrimental effects on erythropoiesis and painful crises with the use of nocturnal low-flow LTOT in six adult patients with SCD.¹⁵ Recent



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To cite: Liguoro I, Arigliani M, Singh B, *et al*. *Arch Dis Child* Epub ahead of print: [please include Day Month Year]. doi:10.1136/archdischild-2020-319347

American Thoracic Society guidelines based on very low-quality evidence offered conditional recommendation to use LTOT in children with SCD and severe chronic hypoxaemia, defined as a $\text{SpO}_2 < 90\%$ (1) for at least 5% of recording time of a continuous monitoring (eg, overnight oximetry) or (2) at least in three separate spot pulse oximetry checks.¹⁶ In summary, small case series have noted possible negative effects of continuous high-flow oxygen therapy due to the risk of suppression of erythropoiesis and rebound VOEs after withdrawal.^{12–14 17} This has led to a reluctance to use LTOT.

This is the first study that aimed to assess the acceptability and safety profile of nocturnal LTOT in a cohort of children with SCD and chronic hypoxaemia. We also described the impact of this intervention on SpO_2 parameters and clinical outcomes after 1 year of follow-up.

METHODS

This retrospective observational study was performed for quality improvement purposes. Clinical records of paediatric patients with SCD at two different tertiary hospitals (Evelina London Children's Hospital and King's College Hospital, London, UK) who started LTOT between January 2014 and January 2019 were retrospectively reviewed. Inclusion criteria for patients with SCD (HbSS or HbS/ β^0 thalassaemia) were the indication for starting LTOT obtainable from medical charts and the absence of missing values in the baseline and follow-up laboratory, clinical history data, transcranial Doppler (TCD) results and overnight oximetry studies. Patients who had concurrent CPAP with O_2 treatment, hydroxyurea (HU) or any other disease-modifying therapy (ie, chronic transfusion, experimental drugs) started within the year preceding LTOT and while on LTOT, as well as those who underwent tonsillectomy and adenoidectomy (T&A) surgery during the study period, were excluded.

Home oxygen was administered via nasal cannula or mask according to the patient's preference, at the rate of 0.5–2 L/min, through the use of an oxygen concentrator (online supplementary appendix 1). Nasal cannulae/masks were replaced every 1 or 2 weeks. Home caregivers were given appropriate education and training about the management of the equipment. Patients on nocturnal oxygen had regular follow-up appointments with the paediatric haematologists and/or paediatric pulmonologist every 3–6 months and underwent also periodical follow-up nocturnal oximetry.

Assessments

For daytime SpO_2 , overnight oximetry, TCD and laboratory data, in each participant the closest record to the beginning of LTOT and the latest (up to 14 months for TCD scans and blood tests) after starting it were compared.

A Nonin GO_2 pulse oximeter (Nonin, Plymouth, MN, USA) was used to measure daytime SpO_2 , with the value recorded after at least 2 min of stable SpO_2 readings and a clear pulsatile photoplethysmographic signal.

Nocturnal oximetry tests (Bitmos GmbH, Masimo sat 801+) were carried out over one night at the sleep laboratory of the Evelina London Children's Hospital, within 1 year before and after starting LTOT. During nocturnal oximetry, parents kept a sleep diary. Artefacts due to poor perfusion, low signal identification and movement were manually excluded, as were periods of wakefulness according to the sleep diary's records. Studies with less than 4 hours of artefact-free data were excluded. Analysis software provided standard parameters, including overnight mean and nadir SpO_2 . Oxygen flow rate was initially set at 0.5 L/

min in all patients, and then progressively titrated to have SpO_2 between 94% and 97% (online supplementary appendix 1).

Patients with reported symptoms of sleep-disordered breathing (eg, loud snoring, witnessed apnoeas, restless sleep and mouth breathing) also underwent a cardiorespiratory sleep study at baseline (SOMNOtouch device; SOMNOmedics, Germany) to evaluate the presence of obstructive sleep apnoea. Hypercapnia was evaluated through nocturnal capnography at baseline (TCM 4/40 monitoring system; Radiometer).¹⁸

Clinical and laboratory data

Information on participants' demographics and medical history was taken from medical records. A history of asthma was defined according to the evidence of a physician's diagnosis of asthma from medical records. A VOE was identified as an episode of acute pain that lasted at least 4 hours for which there was no explanation other than vaso-occlusion and that required hospital admission with administration of parenteral analgesics.¹⁹ The annual rate of VOEs was defined as the average number of events per patient/year requiring hospital admission and was calculated for the year preceding and following the beginning of LTOT.

TCD imaging was used in all examinations, following strict protocols.¹⁸ The transducer orientation was optimised at every 2 mm interval in each vessel to ensure that the highest, audible Doppler frequency signal was obtained. The highest time averaged mean of the maximum velocity (TAMMV) measured in selected arteries were used for comparisons.¹⁸

Laboratory data at steady state, performed on the same day of TCD scans, before and after initiating LTOT were collected (Hb, reticulocyte count, white blood cell count, neutrophil count, platelet count, lactate dehydrogenase (LDH), aspartate aminotransferase (AST) total bilirubin and % fetal Hb).

Statistical analysis

Statistical analyses were performed using GraphPad Prism V.7.04 for Windows (GraphPad Software, La Jolla, CA, USA, www.graphpad.com). Continuous variables were expressed as mean (SD) or median (IQR 25th–75th). All variables were analysed for normality distribution (D'Agostino-Pearson omnibus normality test). Differences between groups were evaluated either by Wilcoxon matched-pairs signed-rank test and paired t-test as appropriate. Fisher's exact test was used to compare frequencies and percentages. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Twenty-six children and adolescents with SCD were commenced on LTOT between 2014 and 2019. Of these, seven patients were excluded for not matching inclusion criteria (figure 1), leaving 19 HbSS subjects (10 boys, 53%, median age when starting LTOT 12 years; range 6–15) in the final study population.

Nine out of nineteen patients (47%) were on HU at baseline, having started this therapy a median time of 2 years before (range, 1–6 years). Eleven children (58%) had a previous history of asthma. No child suspended LTOT during study period, except for one who discontinued after 10 months in light of marked improvements at overnight oximetry. Complete baseline clinical and demographic characteristics of our cohort are shown in table 1. Baseline cardiorespiratory sleep study results were available in 13 out of 19 patients (68%). Of these, 11 patients had an apnoea/hypopnea index (AHI) < 1 , whereas the other two had an AHI respectively of 2.10 and 2.38.

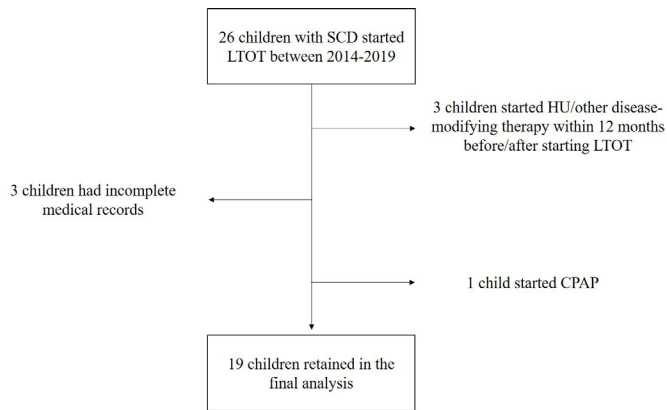


Figure 1 Figure 1 Study population. CPAP, continuous positive airway pressure; HU, hydroxyurea; LTOT, long-term nocturnal home oxygen therapy; SCD, sickle cell disease.

Children were commenced on a median 0.5 L/min of supplemental oxygen (range, 0.2–2 L/min). Minor adverse effects related to the use of LTOT were reported in 4/19 children (21%), who complained of intolerance for nasal prongs or nasal dryness at some point of the follow-up period. No major adverse event was observed.

Blood test results and VOs

Reported blood test results were performed at steady state at a median time interval of 5.5 (range 1–10) months before and 9.5 (range 5–14) months after starting home oxygen (table 2). Hb level and reticulocyte count were not affected, while significant decreases were shown in mean LDH (from 994 ± 473 to 756 ± 329 U/L; $p=0.001$) and AST values (from 61 ± 19 to 52 ± 12 U/L; $p=0.012$) after initiating LTOT (table 2).

Moreover, after 1 year of LTOT, the median annual rate of VOs requiring hospitalisation did not significantly change

Table 1 Baseline characteristics of 19 patients with SCD who started nocturnal home oxygen

Variable	n (%)
N. of patients	19
Males	10 (53%)
Median age at starting home oxygen (IQR 25th–75th)	12.0 years (7.5–13.0)
Hb type—SS	19 (100%)
HU treatment at baseline	9 (47%)
Previous surgery for T&A	10 (53%)
Chronic asthma	11 (58%)
Nocturnal enuresis	6 (31%)
Indication to start home oxygen:	
≥5% of time continuous SpO ₂ monitoring <90% alone*	12 (63%)
≥5% of time continuous SpO ₂ monitoring <90% AND daily spot SpO ₂ <90%*	3 (16%)
At least three daily spots† SpO ₂ <93% AND concerns about severity of SCD-related manifestation	4 (21%)

*Consistently with the criteria indicated for SCD paediatric patients by the American Thoracic Society Guidelines for home oxygen therapy in children.¹⁶

†On three different occasions.

Hb, haemoglobin; HU, hydroxyurea; SCD, sickle cell disease; T&A, tonsillectomy and adenoidectomy.

Table 2 Effect of long-term nocturnal oxygen therapy (LTOT) on laboratory tests of 19 children with SCD and chronic hypoxaemia

	Before LTOT Mean±SD	After LTOT Mean±SD	P value
Hb g/L	76±9	77±9	0.471*
Ret ×10 ⁹ /L	305±103	278±93	0.323†
HbF %	5.9±3.7	5±2.9	0.104*
WBC ×10 ³ /L	11.9±3	11.4±3.3	0.400†
N ×10 ³ /L	5.9±2.9	4.9±2.6	0.143
PLT ×10 ⁶ /L	374±96	381±143	0.721†
LDH U/L	994±473	756±329	0.001*
AST U/L	61±19	52±12	0.012†
Total bilirubin μmol/L	62±24	62±42	0.371*

*Wilcoxon matched-pairs signed-rank test.

†Paired t-test.

AST, aspartate aminotransferase; Hb, haemoglobin; HbF, fetal haemoglobin; LDH, lactate dehydrogenase; N, neutrophil count; PLT, platelet count; Ret, reticulocyte count; SCD, sickle cell disease; WBC, white blood cell count.

(from 0.5 (IQR 0–2) to 0 episode per patient/year (IQR 0–0); $p=0.062$) (figure 2).

Nocturnal oximetry

All patients underwent an overnight oximetry at baseline (range, 0–3 months before LTOT) and while on oxygen therapy (range, 9–12 months after starting LTOT). Nocturnal oximetry results comparing baseline tests off-oxygen and follow-up tests on oxygen supplementation are shown in table 3. Children on LTOT showed a significant increase of median overnight and nadir SpO₂ ($p<0.001$ and $p<0.001$, respectively), as well as a marked reduction of per cent time spent with SpO₂ <90% ($p<0.001$) (table 3). The proportion of children with at least 5% of time of nocturnal SpO₂ monitoring <90% passed from 79% (15/19) at baseline to 16% (3/19, $p<0.001$) with the intervention, while the number of children with spot daytime SpO₂ <90% decreased from 3 to 1.

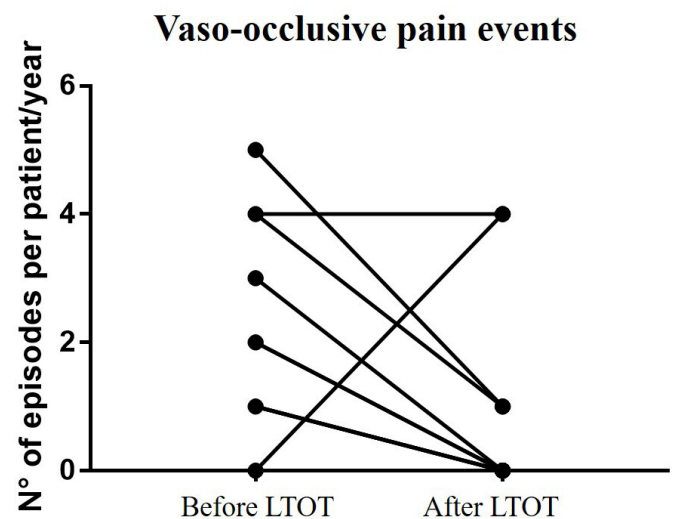


Figure 2 Number of vaso-occlusive pain episodes (VOEs) in 19 children with sickle cell disease in the 12 months before and after starting long-term nocturnal home oxygen therapy (LTOT).

Table 3 Effect of long-term nocturnal home oxygen therapy (LTOT) on overnight oximetry of children with sickle cell disease

	Baseline* Median (IQR 25th–75th)	1 year after LTOT† Median (IQR 25th–75th)	P value (Wilcoxon matched-pairs signed-rank test)
Daily SpO ₂ %	92 (91.5–92.5)	95 (93–95)	<0.001
Mean overnight SpO ₂ %	91 (89.5–92)	95 (93–96)	<0.001
Nadir overnight SpO ₂ %	81 (79–84.5)	87 (85–90)	<0.001
% time SpO ₂ <90%	12.3 (4.7–56)	0.8 (0–2.4)	<0.001

*Oximetry studies recorded off oxygen supplementation.

†Oximetry studies recorded while on oxygen supplementation.

LTOT, long-term nocturnal oxygen therapy; SpO₂, oxygen saturation.

Transcranial Doppler

TCD scans were recorded at a median time interval of 5.5 (range, 1–10) months before and 9.5 (range, 5–14) months after starting home oxygen. Significant decreases in right middle cerebral artery (from 127±16 to 119±20 cm/s; $p=0.034$), right posterior cerebral artery (from 84±18 to 72±16 cm/s; $p=0.042$) and right distal internal carotid artery (from 113±38 to 97±23 cm/s; $p=0.039$) TAMMV were recorded after starting LTOT. No significant differences were shown for other velocities (online supplemental table 1).

DISCUSSION

This is the first study to show that the use of nocturnal LTOT is a safe and well-tolerated treatment option in children with SCD and chronic hypoxaemia, with only a few minor adverse effects reported.

Two previously published case series raised concerns regarding erythropoiesis suppression when administering continuous high-flow oxygen for several days in patients with SCD.^{12 14} On a pathophysiology perspective, oxygen supplementation might inhibit the hypoxia-inducible transcription factors, which increase the production of erythropoietin in kidney and liver and enhance erythroid progenitor maturation and proliferation in the bone marrow.²⁰ However, a previous study showed that erythropoietin levels remained stable in non-hypoxic adults randomised to receive oxygen during a painful crisis.²¹ In our study population, there was some decrease of reticulocyte levels with LTOT, although it was not significant and it did not affect Hb concentration. Similarly, a retrospective observational study of six adults with SCD undergoing LTOT at 1–2 L/min did not show any detrimental effect on erythropoiesis at a 6-month follow-up,¹⁵ and a randomised crossover trial comparing 1-week nocturnal auto-adjusting CPAP versus nocturnal home oxygen therapy in children and adults with SCD did not report significant changes in Hb level with home oxygen.²² These findings suggest that, when using nocturnal LTOT at low-flow oxygen rates, compensatory mechanisms neutralise the negative impact of oxygen supplementation on erythropoiesis, resulting in a preservation of baseline Hb levels in patients with SCD.

Supplementary oxygen therapy may theoretically increase oxidative stress as well, as largely demonstrated in subjects treated with hyperbaric oxygen therapy.²³ However, SCD is intrinsically linked to multiple sources of pro-oxidant processes with consequent chronic and systemic oxidative stress. Due to the complex pathophysiology of these processes, it would be difficult to disentangle the oxidative stress due to LTOT from that triggered by other causes.^{24–26}

We documented only a few minor adverse effects in children with SCD undergoing nocturnal LTOT (ie, dry nose or throat, noise disrupting sleep), whereas there were no serious adverse event related to this intervention. Although we were not able to

document the daily adherence to nocturnal LTOT in our cohort, there were no cases of premature suspension of the intervention for patients' refusal.

Our data showed that oxygen supplementation improved overnight oxygen saturation in patients with SCD. We hypothesised that this could result in decreased rates of HbS polymerisation that could have a positive impact on vasculopathy and clinical outcomes, as suggested by the improvement of some TCD parameters and spot daytime SpO₂ values. Larger prospective studies are needed to prove this hypothesis. We noted no statistically significant changes in the incidence of VOEs or in the variation of haemoglobin concentration, and this further supports the safety of LTOT in children with SCD. In previous case series, rebound painful crisis on interruption of oxygen therapy was noted,¹² while other studies did not demonstrate any effect.^{21 27 28} Therefore, despite our encouraging preliminary findings, the evaluation of the impact of LTOT on VOE incidence warrants further and more robust confirmation in larger prospective studies. Encouragingly, our results also suggested that LTOT might lead to reduced haemolysis, with reduced LDH and AST levels, which could potentially offer long-term benefits.

Strength and limitations

All the children were assessed in a highly specialised hospital setting before starting nocturnal LTOT; therefore, we could extract detailed and reliable baseline data from hospital software. The exclusion of patients who started disease-modifying drugs over the course of the study period limited the confounding effect of HU on oxygen saturation clinical outcomes.^{29 30} However, the dose of HU and adherence to this therapy, which might have affected the outcomes, were not documented through the study. Among the other limitations, the retrospective design of the study prevented us from performing an advanced stratified analysis according to age or other baseline factors. However, due to the complete lack of evidence regarding the safety of LTOT in children with SCD, this design could be considered acceptable. It was not possible to formally measure the day-by-day adherence to nocturnal LTOT, but few complaints and an overall good adherence were reported during follow-up visits. Follow-up was limited to 12 months after starting LTOT, which prevented us from evaluating long-term clinical outcomes and side effects. Finally, this study was not designed to establish whether the positive effects of LTOT on oxygen saturation and clinical outcomes persist when the intervention is stopped.

Future directions

Beneficial effects of LTOT in terms of VOEs and haemolysis need to be confirmed in larger prospective studies with longer follow-up. Such studies should also evaluate which are the subgroups of patients with SCD and chronic hypoxaemia that

are most likely to benefit from LTOT according to baseline characteristics and duration/modalities of intervention.

Conclusions

In conclusion, over 12 months, LTOT was shown to be a safe and feasible intervention in children with SCD and chronic hypoxaemia, with some possible beneficial clinical effects.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BPDJ received educational grants from Novartis Plc, AstraZeneca, Cycliceron and Bluebird bio.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplementary information. Deidentified participant data may be available on reasonable request from IL.

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