Auto-adjusting positive airway pressure in children with sickle cell anemia: results of a phase I randomized controlled trial

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ABSTRACT

Low nocturnal oxygen saturation (SpO_2) is implicated in complications of Sickle Cell Anemia (SCA). Twenty-four children with SCA were randomized to receive overnight auto-adjusting continuous positive airway pressure (auto-CPAP) with supplemental oxygen, if required, to maintain SpO_2 ≥94% or as controls. We assessed adherence, safety, sleep parameters, cognition and pain. Twelve participants randomized to auto-CPAP (3 with oxygen) showed improvement in Apnea/Hypopnea Index (p<0.001), average desaturation events >3%/hour (p=0.02), mean nocturnal SpO_2 (p=0.02) and cognition. Primary efficacy endpoint (Processing Speed Index) showed no group differences (p=0.67), but a second measure of processing speed and attention (Cancellation) improved in those receiving treatment (p=0.01). No bone marrow suppression, rebound pain or serious adverse event resulting from auto-CPAP use was observed. Six weeks of auto-CPAP therapy is feasible and safe in children with SCA, significantly improving sleep-related breathing disorders and at least one aspect of cognition.

Key words: red cells, hemoglobinopathies, quality of life, continuous positive airway pressure, oxygen saturation.

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Introduction

Sickle cell anemia (SCA) is one of the most common inherited disorders worldwide, and migration is making the condition increasingly common in many areas of Northern Europe.[1] Individuals with SCA have a high prevalence of sleep-related breathing disorders (SRBD) related both to upper airway obstruction and low nocturnal oxygen saturation levels (SpO_2)[2,3] which has been linked to subsequent central nervous system events, and frequent episodes of acute pain.[4,5] Cognitive deficits are also common in SCA[6] but the possibility that they are related to SRBD or potentially reversible has not previously been considered although age-related cognitive decline in an SCA cohort has been demonstrated,[7] and selected aspects of cognition have improved in adults with SRBD using positive airway pressure intervention.[8] Cognitive performance could be a potential efficacy measure for interventions for SRBD in SCA. Continuous positive airway pressure (CPAP) is the gold standard therapy for Sleep Apnea.[9] Poor compliance with therapy is well-recognized, although long-term adherence has improved in recent years.[10] The introduction of auto-adjusting CPAP (auto-CPAP), in addition to advances in interfaces, improves tolerance and has fewer side effects.[11] Oxygen supplementation may also be a useful addition to auto-CPAP to reverse low nocturnal SpO_2, but a previous study showed oxygen therapy can lead to bone marrow suppression and rebound pain.[12] These adverse effects might not occur if oxygen supplementation is titrated against nocturnal SpO_2 levels as an adjunct to auto-CPAP treatment.

Design and Methods

Objectives

We conducted an *open-label* phase I, randomized controlled

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trial of six weeks' prophylactic, overnight auto-CPAP, with oxygen supplementation if necessary, to maintain mean SpO_2 ≥94% in SCA children. Aspects of feasibility (acceptance, adherence, and safety) and the effect on measures of cognitive function were explored. Specifically, we wanted to: (i) explore both child and parental acceptance of overnight intervention and adherence to therapy; (ii) demonstrate evidence of any adverse events or suppression of erythropoiesis, or rebound pain on withdrawal of therapy; and (iii) determine whether measures of cognitive function are appropriate endpoints for further investigation. We hypothesized that overnight auto-CPAP would improve cognitive function. Our primary endpoint was Processing Speed Index (PSI), the speed at which an individual can process simple information without error.

Participants

Children between four and 18 years of age with SCA, were eligible for the study, but were excluded if they had received blood transfusions or hydroxyurea in the previous 90 days; had participated in another clinical trial within the last six months; were pregnant or lactating; were previously diagnosed with neurological problems or had pre-existing medical conditions contraindicated for auto-CPAP use.[13] Written parental consent and child assent were obtained from all participants prior to enrolment. Children were randomized to receive auto-CPAP or to a control group without treatment, minimizing using the Minim computer program (Minim: allocation by minimization in clinical trials. Available from: *http://www.sgul.ac.uk/depts/chs/disciplinegroups/stat_guide/minim.cfm*), an acceptable alternative to stratified randomization[14] by important prognostic factors, i.e. silent infarct visible on T2-weighted MRI on two views, and previous adenotonsillectomy.

This study was approved by the National Research Ethics Service and registered at http://www.controlledtrials.com (ISRCTN29004071) and *www.ClinicalTrials.gov* (NCT00415727).

Intervention

Positive airway pressure therapy, with automatic adjustment of the pressure level when apnea, hypopnea, flow limitation, or snoring events were detected (REMstar® Auto M Series with C-Flex™ System, Respironics®, Murrysville, Pennsylvania, USA), was administered via a breathing circuit and a nasal or oral-nasal mask. Intervention was administered nightly for six weeks in the participant's home, along with baseline, interim, and final sleep measurements, parental questionnaires and neuropsychological assessments. Supplemental oxygen (if required) was titrated overnight two weeks after Auto-CPAP commenced via a pressure valve placed in-line with the patient circuit using the minimum flow of oxygen to maintain SpO_2 >94% and was then administered at that flow for the final four weeks using a low flow oxygen-therapy delivery system (Millennium™ M5 Respironics®). The control group received no treatment. Adherence to therapy was assessed using Encore Pro™ data management software and SmartCard™ technology (Respironics®). Adequate adherence was defined as usage for a minimum of five hours per night for at least 80% of nights. All clinical measures, with the exception of the measurements described above, were performed during planned appointments at King's College Hospital, London.

Sleep measurements

The Stardust® II sleep diagnostic device (Respironics®) was used to measure sleep parameters in all participants at baseline and at the close of the study. Those who had auto-CPAP were assessed the night following the last night of intervention. In addition, participants on auto-CPAP had a repeat study two weeks after commencement of therapy to identify those requiring supplemental oxygen.

Laboratory investigations

Venipuncture for full blood count and liver function tests was taken at baseline, two weeks after randomization (treatment arm only), and at the end of the study, to determine whether the intervention caused erythropoietic suppression.[15] Data were also used to explore whether auto-CPAP would reduce markers associated with inflammation and hemolysis.

Serious adverse events and adverse events

A detailed list of expected (serious and non-serious) adverse events was defined (*Online Supplementary Appendix 1*). Participants recorded all painful episodes on a daily basis for eight weeks (two weeks prior and six weeks post randomization). The effect of treatment on pain was measured by the number of days with pain using the pain documented in the two weeks prior to randomization and the final two weeks of intervention or control.

Measurement of cognitive function

Neuropsychological assessments were administered to all participants at baseline and 6-week follow-up by the same assessor, who was blind to participant allocation. This assessment included five tests from the Wechsler Intelligence Scale for Children (WISC-^{IV}UK):[16] Matrix Reasoning, is a measure of general intelligence; Digit Span, measuring short-term and working memory; Coding and Symbol Search (which together yield the Processing Speed Index - PSI), and Cancellation. PSI and Cancellation scores reflect visual attention skills under time pressure.

Sample size

The aim of this phase I trial was to produce data to inform power calculations suitable for further controlled trials. A change in PSI score of 15 points is clinically significant.[17] The sample size was calculated using unpublished data from the East London Cohort,[18] in which SCA children had a mean PSI of 85 (SD 13). Using this cautiously large standard deviation, a sample size of 12 in each group would have 80% power to detect a PSI change of 15 points using a two-group t-test with a 0.05 significance level.

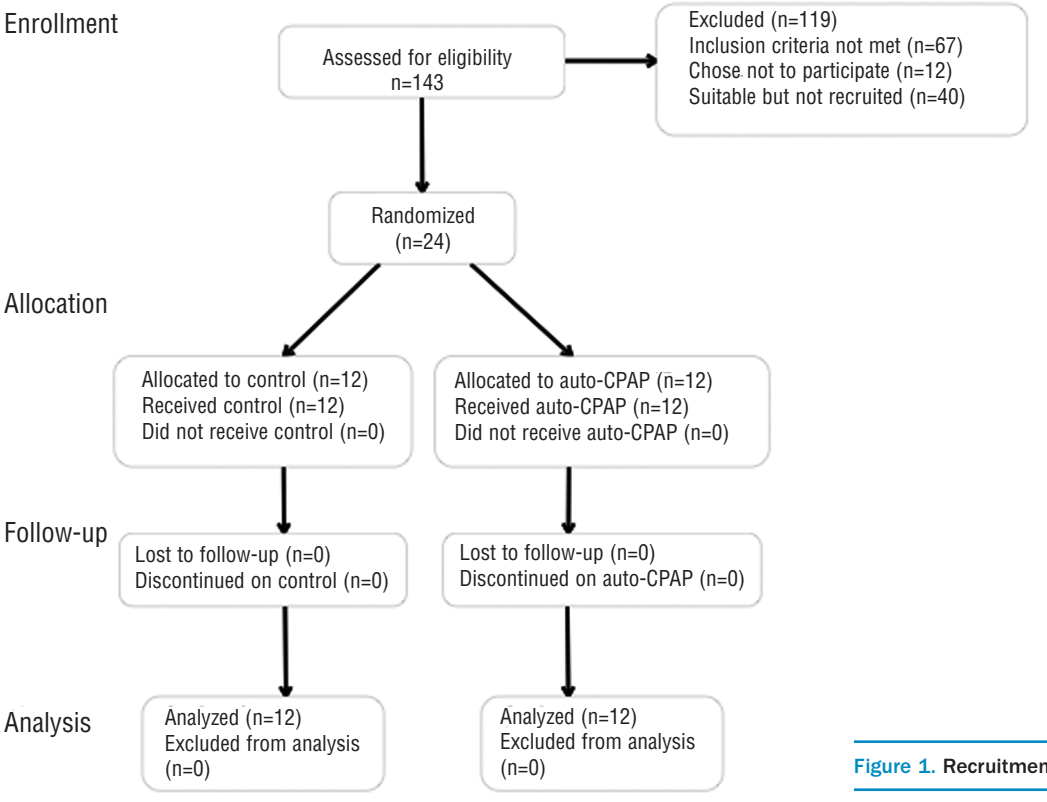

Figure 1. Recruitment flow chart.

Statistical methods

Selected neuropsychological, clinical, sleep, hematologic and biochemical measures were stratified by treatment group, and presented at baseline and after six weeks follow-up using appropriate summary measures: mean (*SD*) for continuous outcome variables, or incidence rate for pain events. For continuous outcomes, baseline group differences were examined using t-tests. The group difference in change between baseline and follow-up for each continuous outcome was assessed by linear regression using final value as the outcome, adjusting for baseline value, including an indicator for treatment group. Changes between baseline and interim sleep studies were assessed using paired t-tests. Group difference in number of pain events at baseline and after intervention was assessed using exact Poisson regression, with group differences presented as incidence rate ratios. In this phase I trial, no adjustments were made for multiple comparisons.[19] There were some mild departures from normality among continuous variables, but robust assessment was not possible with our small sample, and analyses were performed on untransformed data. A single variable (serum erythropoietin) was severely non-normal. We transformed this variable (natural logarithm) for group comparisons. Statistical significance was assumed at $p<0.05$ but confidence intervals and p values are presented to clarify the exact strength of statistical relationships. All analyses were performed using Stata statistical software (Version 10, StataCorp LP, College Station, Texas, USA).

Results and Discussion

Participant flow

We screened 143 patients routinely attending the SCA clinic at King's College Hospital; 67 were ineligible, a further 12 chose not to participate. From the remaining 64, the first 24 were enrolled into the study, 12 receiving auto-CPAP and 12 controls. All randomized participants completed the trial. Primary endpoint analysis was planned as intention-to-treat, and provided complete information for this endpoint. Secondary endpoints were analyzed among participants with complete information (Figure 1).

Baseline data

Mean age at entry was 11.2 years (SD 3.1) and 11.3 years (SD 3.4) for treatment and control groups, respectively (age difference, *t* test $p=0.98$). Five out of 12 boys received auto-CPAP and 8/12 boys were in the control group (sex distribution, Fisher's exact test $p=0.41$). Four participants had prior adenotonsillectomies; 2 in each group. One 6-year old participant could not tolerate MRI and was assumed to have no infarct and one had silent infarction (both controls). There was evidence of SRBD in both groups, with high mean Apnea/Hypopnea Index (AHI). Among the outcome variables at baseline, statistically significant group differences were found only in Digit Span, $p=0.03$ (Table 1). A practical proxy for SCA severity – mean days in hospital – did not differ between groups: treatment group 6.8 days (SD 8.6 days), control group 5.1 days (SD 9.0 days; *t* test $p=0.65$), nor did the mean emergency department attendances: control 1.6

Table 1. Mean (Standard Deviation) summaries for neuropsychological (WISC-IV), clinical and laboratory measures by treatment group before and after intervention, with formal assessment of group differences.

	Control		Treatment		Group difference (Treatment *vs.* Control)		
	Baseline	Follow-up	Baseline	Follow-up	Baseline *p* value	Change Diff (95% CI)	*p* value
Neuropsychological measures							
Processing Speed Index[1]	90.0 (13.8)	97.5 (17.3)	92.6 (15.5)	96.6 (17.8)	0.67	-2.9 (-14.5 to 8.7)	0.61
Coding	8.4 (2.6)	9.6 (3.4)	8.8 (3.5)	9.3 (3.5)	0.74	-0.7 (-2.2 to 0.9)	0.38
Symbol Search	8.0 (3.4)	9.5 (3.4)	8.5 (3.0)	9.3 (3.6)	0.70	-0.4 (-3.1 to 2.3)	0.76
Cancellation	10.4 (2.0)	9.9 (1.9)	10.0 (3.1)	12.3 (2.3)	0.75	2.6 (0.8 to 4.3)	0.01
Matrix Reasoning	8.6 (3.3)	8.3 (3.1)	8.4 (3.9)	8.9 (2.9)	0.91	0.8 (-1.3 to 2.8)	0.45
Digit Span	7.4 (2.8)	9.3 (3.6)	10.3 (2.9)	9.5 (3.0)	0.03	-1.9 (-4.4 to 0.7)	0.15
Clinical measures							
Systolic blood pressure (mmHg)	116.1 (13.8)	109.0 (11.0)	108.3 (11.3)	110.8 (13.1)	0.15	4.3 (-6.1 to 14.7)	0.40
Mean daytime oximetry (SpO_2)	95.3 (3.1)	94.0 (3.2)	94.2 (3.3)	95.0 (3.8)	0.41	1.8 (-0.6 to 4.1)	0.13
Pain days per person per week[2]	2.1	1.5	2.3	0.8	0.72	0.5 (0.20 to 1.07)	0.07
Hematologic measures[3,4]							
Hemoglobin [g/dL]	7.8 (1.1)	8.1 (1.0)	8.1 (1.4)	8.4 (1.5)	0.52	0 (-0.5 to 0.5)	0.99
Red blood cell count [1012]	2.9 (0.6)	3.0 (0.5)	2.7 (0.5)	2.8 (0.5)	0.51	-0.1 (-0.3 to 0.2)	0.69
Reticulocyte count [10^9/L]	357.2 (121.2)	428.3 (80.0)	340.1 (93.8)	338.6 (98.4)	0.71	-72.5 (-145.1 to 0.1)	0.05
Erythropoietin (logged)[5]	2.07 (0.44)	1.98 (0.33)	2.00 (0.19)	1.97 (0.22)	0.72	0.12 (-0.24 to 0.29)	0.83
White blood cell count [10^9 /L]	10.9 (2.1)	11.7 (1.9)	13.0 (3.4)	12.1 (3.0)	0.09	-0.8 (-2.9 to 1.3)	0.44
Biochemical measures							
Lactate dehydrogenase [IU/L]	601.7 (163.6)	573.7 (127.1)	552.6 (111.2)	548.6 (104.9)	0.42	-9.4 (-98.2 to 79.4)	0.83
Aspartate transaminase [IU/L]	58.7 (19.9)	51.3 (15.1)	56.6 (24.8)	48.3 (10.6)	0.82	-3.0 (-14.2 to 8.3)	0.59

[1]Processing speed Index (PSI) was constructed from two subscales: coding (measured a child's ability to decipher a code and copy the correct symbols in a controlled period of time) and symbol search (deciding if target symbols appear in a row of symbols and marking YES or NO accordingly); [2]Pain was measured as the number of pain days per person per week during the two weeks before the intervention period started and the last two weeks of the intervention period. Diary data were available for 8 participants in each group. The group difference in baseline incidence rates and at follow-up was assessed using exact Poisson regression, and presented as an incidence rate ratio (95% confidence interval); [3]Interim laboratory values were available after two weeks' treatment in 8 patients on auto-CPAP: interim hemoglobin [g/dL] 8.08±1.89, red blood cell count [10^{12}] 2.73±0.70, reticulocyte count [10^9/l] 344.09±91.82, erythropoietin (logged) 2.07±0.32. Examination of the means found no significant differences. The Ethics Committee would not approve collection of equivalent interim data in the control group; [4]In the 3 patients on supplementary oxygen from weeks 3-6, final laboratory values were hemoglobin 6.97±0.31 [g/dL] count [10^{12}], reticulocyte count 417.07±52.01 [10^9/L], erythropoietin (logged) 2.15±0.19 compared with hemoglobin [g/dL] 8.91±1.38, red blood cell count 2.34±0.13 [10^{12}], reticulocyte count 312.39 ± 97.72 [10^9/L], erythropoietin (logged) 1.90±0.19 for the 9 patients on auto-CPAP alone; [5]For baseline and final erythropoietin, N=10 in each group except for baseline treatment where N=6.

Table 2. Mean (Standard Deviation) summaries for sleep measures by treatment group before, at baseline, and during auto-CPAP intervention.

	Control	Treatment		Comparison of Interim with baseline for auto-CPAP		
	Baseline	Baseline	Interim	Difference	t(11)	*p*
Apnea/Hypopnea Index (respiratory events per hour of sleep)	19.1 (8.7)	24.1 (10.0)	2.4 (1.5)	-21.6	8.0	<0.001
Desaturation Index (respiratory events per hour of sleep >3%)	15.5 (12.6)	16.1 (11.2)	7.1 (5.0)	-9.1	2.7	0.02
Mean overnight oximetry (SpO_2)	92.5 (5.1)	91.0 (5.4)	93.7 (3.8)	2.7	2.7	0.02

attendances (SD 1.7), treatment 1.5 attendances (SD 1.4; *t* test p=0.90).

Auto-CPAP adherence and 2-week sleep indices

Participants in the treatment group adhered to therapy. The range of usage was 5.9-9.6 hours per night (overall mean 7.2 h). Auto-CPAP was used for ≥5 h for 467/504 treatment nights (92.7%). The child with the poorest compliance registered ≥5 h per night for 35/42 nights (83%). There was a 10-fold reduction in AHI after two weeks of therapy, a reduction in desaturation index and improvement in the mean overnight SpO_2 (Table 2).

Serious adverse and adverse events

There was no evidence of bone marrow suppression during treatment with auto-CPAP alone or with oxygen supplementation (Table 1). In the control group, pain days per person per week reduced from 2.1 prior to randomization to 1.5 during the final two weeks of the study and from 2.4 to 0.8 in the treatment group (mean difference 0.5, 95% CI 0.2 to 1.1; p=0.07).

Outcomes

Outcome data are presented in Table 1. The primary outcome, PSI, increased in both groups and there was no statistically significant difference between treatment and control groups. Using a second measure of processing speed and attention (Cancellation) the improvement was more pronounced in the auto-CPAP group. Pain diary data were available for 8 children in each arm and there was a

trend for a greater reduction in pain days per week in participants on therapy (Table 1).

Auto-CPAP therapy in children with SCA appears feasible and safe, with acceptable compliance levels.[20] SRBD was common in this study group and was significantly improved by auto-CPAP. Diary documentation revealed a reduction in pain days during treatment. There was no evidence of rebound pain after treatment cessation or erythropoietic suppression. There is encouraging preliminary evidence of treatment efficacy using cognitive function endpoints, with a single measure of processing speed and attention (Cancellation) showing greater improvement among participants receiving treatment. It is possible that the attention component of this endpoint shows greater sensitivity to reversal of SRBD, perhaps due to the effect of hypoxemia on frontal lobe functioning,[21] which could be important in improving educational outcomes in SCA.

We did not select children presenting to clinic with prior evidence of SRBD, and baseline sleep studies were not scored prior to randomization, but compared with the general pediatric population,[22] mean AHI and desaturation index were elevated at baseline, and mean overnight SpO_2 was low. Interim sleep studies showed that in participants receiving auto-CPAP, AHI normalized and mean overnight SpO_2 improved. These results suggest this type of therapy is effective in children with SCA. Further research should also examine the wider context of the healthcare and social costs of SCA, including endpoints such as number of emergency department visits, hospital admissions, as well as improved school attendance and performance.

Authorship and Disclosures

MJM: design of protocol, ethics committee approval and project management of the study, responsible for sleep diagnostics and intervention: data acquisition, scoring and contributed to manuscript preparation; RSB: data manager and statistician, and contributed to manuscript preparation; AMH: contributed to protocol preparation, responsible for neuropsychological assessment and scoring, contributed to manuscript preparation; IRH: statistician, contributed to protocol preparation and contributed to manuscript preparation; SEH: physician responsible for supervising medical and neurological examinations, contributed to and commented on manuscript; MCD: physician responsible for supervising medical and neurological examinations, contributed to and commented on manuscript; FJK: design of protocol, ethics committee approval, trial registration, physician responsible for supervising medical and neurological examinations and contributed to manuscript preparation; DCR: design of protocol, physician responsible for supervising medical and neurological examinations and contributed to manuscript preparation.

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