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Hydroxyurea Improves Oxygen Saturation in Children with Sickle Cell Disease

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Keywords

Sickle cell disease; Children; Hydroxyurea

Dear Editor

Oxygen desaturation is a common in patients with sickle cell disease (SCD) and is associated with several complications. Nocturnal desaturation is significantly associated with a higher rate of pain crises, and central nervous system event ¹⁻². Daytime desaturation is a risk factor for overt stroke and associated with abnormal transcranial doppler velocities ^{3,4}. Kirkham et al reported a hazard ratio of 5.6 [1.8–16.9] of increased risk for a CNS event in patients with mean nocturnal SpO₂ less than 96% ¹, demonstrating the clinical relevance of even a modest drop in oxygen saturation. Oxygen desaturation has also been associated with elevated tricuspid regurgitant jet velocity (TRV) and diastolic dysfunction ^{5,6}. Despite these important associations, no consensus exists on its management. A single case series reported resolution of chronic hypoxemia in three patients with hydroxyurea⁷ We would like to report our findings on improvement in oxygen saturation after treatment with hydroxyurea.

Thirteen children with HbSS/S β 0 thalassemia, ages 5-21 years, were prospectively treated with hydroxurea for 12 months, for an elevated TRV on echocardiograms. Informed consent was obtained and patients were started on hydroxyurea at 20 mg/kg/day. Dose was escalated every 8 weeks till a maximum tolerated dose or total dose of 30 mg/kg/day was reached. Labs were monitored monthly, and clinic visits every 2 months. Oxygen saturation was recorded in clinic by spot pulse oximetry. Hydroxyurea was continued for 12 months. The study was approved by the Institutional Review Board. Our results (Table 1) show that hydroxyurea significantly increased fetal hemoglobin and MCV and significantly decreased reticulocyte count, WBC and LDH. There was no significant change in the TRV.

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Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the patient.

Conflict of Interest

The authors declare that they have no conflict of interest.

Hydroxyurea significantly increased oxygen saturation from a baseline of $95.15 \pm 2.4\%$ to $98.4 \pm 1.26\%$ ($p=0.0009$) at six months post treatment. This effect was sustained at 12 months post treatment ($p=0.0003$). There was a strong positive correlation between increase in oxygen saturation and fetal hemoglobin ($R=0.86$), a weaker correlation between oxygen saturation and hemoglobin ($R=0.48$) and a moderate inverse correlation between oxygen saturation and reticulocyte count ($R=0.52$).

Our results show that hydroxyurea increases oxygen saturation in children with SCD. The increase in saturation was strongly correlated with increase in fetal hemoglobin. The cause of oxygen desaturation in SCD is likely multifactorial. It is partly caused by a rightward shift in the oxyhemoglobin dissociation curve, because of the properties of sickle hemoglobin in solution⁸. Oxygen desaturation is also directly correlated with hemoglobin and inversely correlated with reticulocyte count⁹. Hydroxyurea increases fetal hemoglobin, hemoglobin and decreases reticulocyte count. Fetal hemoglobin has a higher oxygen affinity, than hemoglobin S or A, due to its lower affinity for 2,3 DPG, and hence alters the shape of the oxygen dissociation curve moving it towards the left, hence increasing oxygen saturation. Our study is one of the few studies reporting this important effect of hydroxyurea. As oxygen desaturation is associated with several complications, treating patients with oxygen desaturation with hydroxyurea, may help alleviate some of these complications. A larger study is needed to conclusively answer this important question.

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Table 1
Effect of Hydroxyurea on Clinical and Laboratory Parameters at six and twelve months post treatment

	Baseline Mean $\pm$ SD N=13	6 month Follow up Mean $\pm$ SD N=11	P value	12 month Follow up Mean $\pm$ SD N= 9	P value
O2 saturation	95.1 $\pm$ 2.4	98.4 $\pm$ 1.26	0.0009*	98.8 $\pm$ 1.26	0.0003*
Hemoglobin	8.12 $\pm$ 1.59	8.99 $\pm$ 1.70	0.21	9.37 $\pm$ 1.69	0.09
Retic count	12.42 $\pm$ 5.77	5.75 $\pm$ 3.66	0.004*	6.23 $\pm$ 2.50	0.007*
MCV	80.96 $\pm$ 11.67	101.23 $\pm$ 14.08	0.0008*	102.01 $\pm$ 15.27	0.001*
LDH	650.33 $\pm$ 253.33	391.7 $\pm$ 131.58	0.008*	428.55 $\pm$ 173.55	0.03*
WBC	11.8 $\pm$ 3.4	7.8 $\pm$ 4.40	0.02*	7.75 $\pm$ 4.24	0.025*
Platelet count	410.61 $\pm$ 98.90	338.90 $\pm$ 135.66	0.14	375.88 $\pm$ 78.20	0.39
Fetal hemoglobin %	6.06 $\pm$ 2.9	17.61 $\pm$ 9.65	0.001*	18.71 $\pm$ 7.68	0.0001*
TRV (ml/sec)	2.76 $\pm$ 0.27	2.71 $\pm$ 0.37	0.97	2.59 $\pm$ 0.17	0.1

* P 0.05