JOGM
Journal of Global Medicine

COMMENTARY

The hypothesis of Early Home Oxygen Therapy (EHOT) in sickle cell crisis

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The article by Omoigui [1] presents a thought-provoking perspective on the management of sickle cell crisis, focusing on the potential of a simple, yet overlooked, intervention: concentrated oxygen therapy during the 'golden half hour'. This commentary offers a constructive evaluation of the article's central thesis and its potential implications.

Core proposal and strengths

The central hypothesis is that when triggers induce haemoglobin polymerisation, resulting in sickling and increased rigidity of erythrocytes, the sickle cells formed can be reversed with early administration of concentrated oxygen. This time-dependent use of oxygen prevents reversible sickle cells (RSC) from progressing to irreversible sickle cells (ISC), thereby preventing the end-organ sequelae of sickle cell crises. While RSC can return to normal discoid on reoxygenation, repeated crises damage the cell membrane, making it impossible for the cell to return to its normal state. The author argues that this early intervention capitalises on a critical, narrow therapeutic window [1].

This approach is commendable for its focus on preventing sickle cell crisis sequelae rather than simply reactive treatment. It highlights the potential for a readily available therapy to reduce morbidity and mortality associated with the condition significantly. By focusing on the initial stages of the vaso-occlusive crisis, the article challenges the prevailing paradigm of crisis management, which often begins only after the crisis has been established and symptoms are severe.

Key considerations and areas for further investigation

While the proposal is promising, a comprehensive appraisal must address several critical limitations. These points are essential for guiding future research and clinical application. There is limited patient data, as the hypothesis has been tested only on a small sample size of seven patients over a 20-year period. In this small sample size, apart from the reduction in hospitalisations, no other objective outcome measures were presented [1]. This is insufficient data to establish a causal relationship or justify a significant change in clinical guidelines. This small data set, while useful for generating a hypothesis, highlights the need for larger, more rigorous clinical trials in different settings to validate the findings.

The safety of home oxygen use needs to be addressed. While the suggestion of using portable oxygen concentrators for home care is a potential solution, fire safety implications must be considered. In the United Kingdom, the incidence of fires secondary to home oxygen use is 0.12%, which is twice the national average of 0.06% for the general population for all causes, and fire-related deaths per year per 10,000 oxygen users is 0.36, which is about half of the deaths (0.62) in the United States [2]. Rigorous patient education and monitoring protocols would be essential to prevent misuse and ensure proper administration. This is particularly important for an at-risk population that may not always have immediate access to professional medical supervision during a crisis.

Another safety issue is the role of oxygen therapy in exacerbating ischaemia-reperfusion injury [3]. The endothelial dysfunction in sickle cell disease results in the disruption of the vascular system, leading to recurrent episodes of ischaemia-reperfusion injury in multiple organ systems [4]. In cardiovascular diseases, where oxygen has been used extensively to treat or prevent hypoxia, it often leads to hyperoxia [3]. Hyperoxia is associated with the excessive production of reactive oxygen species, and it also dampens endogenous adaptive responses to hypoxia, thereby exacerbating organ injury [3].

In other clinical conditions, such as myocardial infarction (MI) and stroke, hyperoxia has been shown to contribute to ischemia-reperfusion injury, leading to worse outcomes [5, 6]. A critical question is whether the use of oxygen, as suggested by the author [1], could have the same harmful effects, leading to poorer health outcomes in the medium to long term for patients with sickle cell disease, given the lack of available data. This is a fundamental physiological concern that requires careful study.

Health economics: a global perspective

A crucial component of any new therapy is its economic viability and potential for widespread adoption. While

specific QALY (Quality-Adjusted Life Years) and DALY (Disability-Adjusted Life Years) data for Early Home Oxygen Therapy (EHOT) in a home care setting are not yet available, the paper estimates an initial cost of $0.60–$1.00 billion if all Sickle Cell Disease (SCD) patients in Nigeria, the most endemic country, were to have home oxygen [1]. There would be a recurring cost of $85–90 million every 2–4 months, with an average annual cost of approximately $340–$350 per patient, in a country where the annual family income is less than $1,200 [1]. Nigeria is the epicentre of SCD, with the highest burden of the disease worldwide [7–9]. The average per capita healthcare expenditure in Nigeria is roughly $91 per year [10]. Additionally, there is the issue of the availability of long-term oxygen therapy in sub-Saharan Africa [11, 12].

However, in stark contrast, the costs of advanced curative therapies, such as gene therapy and bone marrow transplantation, range from $1 million to over $2.5 million per patient in advanced economies [13, 14]. While some local bone marrow transplant programs are emerging in Nigeria, they remain astronomically high for the average family, where catastrophic health spending for SCD is common.

Beyond the issue of cost, the infrastructure required for advanced treatments is severely lacking. Nigeria has less than one hospital bed per 1,000 people, a fraction of the global average. The sophisticated facilities needed for a bone marrow transplant, such as sterile environments, specialised labs and multidisciplinary teams, are minimal. While a few centres now offer this procedure, they are nowhere near the scale required to address the immense patient population [9, 15]. For gene therapy, the necessary infrastructure for production, storage and administration is almost non-existent in the country.

This immense disparity highlights the fact that even if these advanced therapies are proven to be 'cost-effective' by Western economic models, their absolute cost and the lack of a delivery infrastructure render them inaccessible to most of the population that needs them most. The article's hypothesis, if proven, offers a powerful alternative. By providing a potentially effective, low-cost intervention that can be administered in a home care setting, EHOT addresses not only a clinical gap but a profound economic and social one. It could offer a scalable solution for a global health crisis, preventing debilitating complications and improving the quality of life for millions of people.

Conclusion and call to action

Omoigui's article [1] is potentially an essential contribution to the field of sickle cell disease management. It serves as a vital call to re-evaluate our foundational assumptions about crisis management and to explore the potential of simple, non-pharmacological interventions. The concept of the 'golden half hour' provides a robust framework for future research and has the potential to be a game-changer for clinical practice. This work should stimulate a new wave of studies dedicated to validating this promising approach to reducing the profound suffering and systemic damage caused by sickle cell crises. The priorities include assessing large samples of patients with measurable objective markers, both before and after the initiation of EHOT, and determining whether EHOT needs to be universal or if it is beneficial only to a specific cohort of patients. In the medium term, if EHOT proves itself, biochemical and molecular markers of ischaemia-reperfusion injury need to be assessed to prevent unintended consequences.

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Citation: Journal of Global Medicine 2025, 5: 335 - http://dx.doi.org/10.51496/jogm.v5.335

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