Original Article

Supplemental oxygen therapy recommendations in patients with sickle cell disease during air travel: A cross-sectional survey of North American health care providers

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Abstract

Introduction: Air travel may expose patients with sickle cell disease (SCD) to an increased risk of disease-related complications. Several factors are felt to contribute including prolonged hypoxia, dehydration, temperature changes, and stress. The Canadian Paediatric Society (CPS) position statement, published in 2007, recommends that SCD patients use supplemental oxygen on flights. While the National Heart, Lung and Blood Institute (NHLBI) recommend that SCD patients dress warmly, stay hydrated, and move about the cabin. Other guidelines do not make specific recommendations.

Methods: A cross-sectional online survey was circulated through the Canadian Hemoglobinopathy Association (CanHaem) and American Society of Pediatric Hematology and Oncology (ASPHO) listservs to North American health care practitioners (HCPs). Participants were asked to share their air travel recommendations for patients with SCD. Similarly, a patient survey regarding experiences with air travel was circulated through the Sickle Cell Disease Association of Canada (SCDAC) and the Sickle Cell Foundation of Alberta (SCFOA) listservs and discussion boards.

Results: Although air travel is perceived to be a risk factor for sickling complications, only 18% of HCPs recommend supplemental oxygen. Most HCPs advise patients to increase hydration, carry analgesics, and wear warm clothes to prevent sickling complications. The patient survey was limited by a low response rate.

Conclusion: The majority of HCPs are not routinely recommending prophylactic oxygen to patients with SCD during air travel.

Keywords: *Air travel; Flight; Hemoglobinopathy; Oxygen; Sickle cell disease*

Sickle cell hemoglobinopathies are a group of inherited disorders resulting in the expression of abnormal hemoglobin. As opposed to the expression of adult hemoglobin (HbA), individuals with sickle cell disease (SCD) have a point mutation in the β -chain of the hemoglobin protein, leading to the production of hemoglobin S (HbS). There are variants of the hemoglobin protein that when combined with HbS are categorized as sickle cell hemoglobinopathies including but not limited to

HbSC, HbS β^0 , HbS β^+ , HbSD, and HbSE (1,2). When deoxygenated HbS polymerizes, it results in sickling, or abnormally shaped rigid erythrocytes. Sickling of erythrocytes impairs the flow of blood through micro-vasculature, causing vascular damage, tissue hypoxemia, infarction as well as reperfusion injury. Potential clinical manifestations of SCD include hemolytic anemia, vaso-occlusive pain crisis (VOC), acute chest

syndrome (ACS), priapism, aplastic crisis, splenic infarction, stroke, and life-threatening infections (3,4).

High-altitude exposure, including air travel, results in lower oxygen saturation in both paediatric and adult populations (5–10). While most commercial airplanes cruise at an altitude of 9,000 to 12,000 m, passenger cabins are pressurized to a maximum altitude of 2,400 m (11,12). Lower atmospheric pressure at higher altitudes creates a hypoxic environment (6,11). Lee et al. showed that the oxygen saturation of healthy children decreased to 94.4% during air travel. Similarly, Ward et al. showed an in-flight drop of mean oxygen saturation from 97.0 to 88.6% in adults (9). Children are thought to be more susceptible to hypoxemia due to a more compliant rib cage, fewer alveoli, smaller airway diameter, and increased sensitivity to bronchoconstriction (11,13,14). While hypoxic conditions such as these do not typically provoke complications in individuals with normal hemoglobin, hypoxic environments may trigger or exacerbate SCD complications (2). In addition to prolonged hypoxia, there are several factors that may contribute to an increased risk of SCD complications during air travel including dehydration, temperature changes, and increased stress (11–13,15–17). Previously published literature suggests that

the risk of air travel–related sickling complications is between 1.4 and 68% (15,18–20). In their 2011 retrospective study of all travel-related complications, Stajanovic et al. report a VOC risk of 36 to 60% (15). In contrast, Runel Belliard et al. reported infection as the most common complication. Of note, air travel–related complications were not the primary endpoint of these studies. Much of the literature that has specifically reported air travel–related sickling complications was published prior to the 1980s. Interestingly, there have also been case reports of patients with sickle cell trait developing complications during air travel, with the majority being splenic complications (21–24). Literature is summarized in Table 1 (18,19,21–27).

Air travel complications are important to consider as air travel has become increasingly common. Furthermore, due to international migration, many patients with SCD in North America are of African, Caribbean, or Central/South American heritage (28,29). Piel et al. show that there has been a large influx of sickle cell patients and carriers from source countries including Africa and the Indian subcontinent to North America, Western Europe, and Australia from the 1960s to 2000. These factors may contribute to increased air travel. Patients and families are increasingly concerned about travel safety, in light of

Table 1. Literature summary of air travel–related complications among patients with sickle cell disease or sickle cell trait

	Type of study	Population	Outcomes
Claster et al., 1981	Retrospective study	45 patients (all SCD including variants).	Among patients with HbSS, and HbSC/Sβ ⁰ the risk of complications 13% and 35.3%, respectively.
Cooley et al., 1954	Case series	6 patients (HbAS).	All patients had splenic complications requiring splenectomy.
Doenges et al., 1954	Case series	2 patients (HbSC).	Both had splenic infarction, one requiring splenectomy.
Githens et al., 1977	Case report	11-year-old male (HbSC).	Patient had splenic complication.
Green et al., 1971	Case series	7 patients (SCD or HbAS).	Four patients had splenic complications, two had VOC, and one small bowel infarction.
Mahony et al., 1979	Retrospective study	244 patient/family interviews.	HbSC/Sβ ⁰ patients have 23% risk of complications.
Murano et al., 2013	Case report	43-year-old male (HbAS).	Patient had splenic infarction and splenectomy.
Nadesan K and Nagarathnam M., 2001	Case report	41-year-old male (HbSC).	Sudden death from pulmonary embolism on flight.
Rotter et al., 1955	Case series	6 patients (HbAS, HbSC, or HbSβ ⁰).	All had splenic complications, one splenectomy.
Runel-Belliard et al., 2009	Prospective study	42 patients (all SCD including variants).	Infection is most common complication.
Sullivan et al., 1947	Case report	18-year-old male (HbAS).	Patient had a VOC episode.
Stankovic Stojanovic et al., 2011	Retrospective study	148 patients (all SCD including variants).	Most common travel-related complication is VOC (68% risk).
Ware et al., 1998	Correspondence	73 patients (all SCD including variants).	One patient with severe HbSβ ⁺ had a bone pain crisis.

the unfortunate passing of a 10-year-old child with SCD on a trans-Atlantic flight in 2016 (30).

By reducing prolonged hypoxia, supplemental oxygen could decrease the associated risk of sickling complications. While some authors recommend supplemental oxygen during travel for a subset of patients with SCD, the publications are largely published prior to 1980. For example, Claster et al. recommended supplemental oxygen for SCD patients with an intact spleen (18) and Green et al. suggested that HbSC patients avoid air travel or use supplemental oxygen (22). Rotter et al. recommended supplemental oxygen for HbSS/S β -thalassemia patients in 1956 (23). The Canadian Paediatric Society (CPS) position statement (2007) recommends that children with sickle cell anemia have access to supplemental oxygen above 2,300 m to prevent sickling complications, emphasizing the need for supplemental oxygen among children with splenomegaly or high blood viscosity (13). While the National Heart, Lung and Blood Institute (NHLBI) guidelines (2002) state that travelling at altitudes greater than 4,500 m may induce VOC in SCD patients, dressing warmly, staying hydrated, and moving about the cabin should decrease the complication risk (31). Other commonly used guidelines including the National Center for Biotechnology Information (NCBI), and the Canadian Haemoglobinopathy Association (CanHaem) do not make any specific recommendations regarding supplemental oxygen for SCD patients during air travel.

There is a lack of research to assist clinicians in providing evidence-based advice to SCD patients and families about safe travel practices. This study was designed to determine common clinical practices of practitioners who care for patients with SCD across North America with regard to supplemental oxygen recommendations.

MATERIAL AND METHODS

A literature review using PubMed, TRIP database, and Medline (Ovid) search engines was conducted using the following search criteria: ([sickle cell or sickle] and [air travel or flight or airplane or altitude]). Two investigators independently reviewed abstracts and reference lists. Clinical practice guidelines from the CPS, NHLBI, NCBI, CanHaem, and the British Thoracic Society were reviewed.

Following the review of literature, two descriptive cross-sectional online surveys were designed. In the first survey, North American health care practitioners (HCPs) providing care to paediatric or adult patients with SCD were asked to share opinions on air travel as a risk factor for sickling complications, and air travel-related recommendations. Nonidentifiable demographic data were collected including but not limited to province/state of practice, altitude of their centre, and size of patient population. Two investigators were involved in the design of

survey questions which were peer-reviewed by seven practitioners, including paediatric hematologists, a nurse practitioner, and multiple registered nurses at the Stollery Children's Hospital, to ensure content and face validity. There were three versions of the survey before distribution. The online survey was pilot tested by the same seven practitioners to ensure branching logic and functionality was appropriate. Following survey design, ethics approval for the survey and study was obtained from the University of Alberta Research Ethics Board. The survey was distributed to North American HCPs from March 2017 to May 2017. The survey was circulated through CanHaem and the American Society of Pediatric Hematology and Oncology (ASPHO) forums and listservs.

A similarly structured survey was designed for patients and families affected by SCD. Through the use of open- and close-ended questions, participants were asked to share their experiences with air travel and supplemental oxygen. No identifiable information was collected. Survey questions were designed by two investigators, and peer-reviewed by seven practitioners to ensure content and face validity. The survey was also reviewed by three families (as content experts) who attend the Stollery Children's Hospital comprehensive sickle cell clinic, for clarity and readability. Content experts ensured that the topic was completely explored from a patient perspective. The survey was circulated from June 2017 to September 2017 through the Sickle Cell Disease Association of Canada (SCDAC) and the Sickle Cell Foundation of Alberta (SCFOA) forums and discussion boards.

Study data were collected and managed using REDCap (Research Electronic Data Capture) data tool hosted by the Women and Children's Health Research Institute (WCHRI). REDCap is a secure, web-based application which supports data collection and analysis (32). Branching logic was employed; thus, the number of responses for individual questions is variable. Data were analyzed using descriptive statistics.

RESULTS

A total of 81 HCP responses were collected. Due to inconsistencies in the data, two responses were excluded. Seventy-five per cent (n=81) of the survey respondents were paediatric providers. Table 2 highlights the respondent demographics.

Appraisal of air travel-related risks

HCPs were asked to share their opinions regarding air travel-related risks in SCD, more specifically whether air travel is a risk for developing VOC, splenic complications, ACS, or cerebrovascular accident (Figure 1). While 61% (n=79) and 37% (n=79) of HCPs felt that air travel was a risk factor for VOC and ACS, respectively, there was no consensus on other complications. A large proportion of HCPs were unsure regarding air travel-associated risks,

ranging from 22 to 42% (n=79). Among those who believed air travel was a risk for splenic complications, the majority (56%, n=16) indicated that children are at higher risk.

Air travel recommendations

HCPs were asked to share their clinical practices regarding supplemental oxygen recommendations (Figure 2A). The majority of HCPs (82.1%, 95% confidence interval [CI]: 71.7, 89.8) do not recommend supplemental oxygen use during air travel. Over 90% of the HCPs working at large centres (>100 patients), did not recommend oxygen (n=79). Among the 14 respondents that recommend oxygen, 50% do so for all patients, 36% for only HbSS/Sβ⁰ patients, 7% for HbSS/Sβ⁰/SC patients only, and the remaining 7% for HbSS/Sβ⁰/Sβ⁺ only (Figure 2B). While 40% (n=10) of the adult providers advised the use of oxygen, only 16% (n=62) of the paediatric providers had the same recommendation. In regards to country of practice, 8% (n=52) of the American HCPs and 36% (n=28) of the Canadian providers recommended oxygen. As depicted in Figure 2A, while most HCPs did not recommend supplemental oxygen, they advised patients to increase hydration (94%, n=79), carry analgesics (92%, n=79), and wear warm clothes (83%, n=79).

Factors influencing supplemental oxygen recommendations

Among practitioners that recommend oxygen, there were numerous patient and flight factors that influenced

Table 2. Demographic information of all survey respondents

Characteristic	n (%)
Scope of Practice	n=81 (%)
Paediatrics	62 (77%)
Adult	10 (12%)
Both	9 (11%)
Country of Practise	n= 81 (%)
Canada	28 (35%)
USA	52 (65%)
Size of Center	n=80 (%)
<25 patients	9 (11%)
25–50 patients	8 (10%)
51–100 patients	16 (20%)
>100 patients	47 (59%)
Altitude of Center	n=75 (%)
<100 m	44 (59%)
100–500 m	17 (23%)
500–1,000 m	9 (12%)
>1,000 m	5 (7%)
Role on Health Care Team	n=81 (%)
Medical Doctor	73 (90%)
Nurse	7 (9%)
Nurse practitioner	1 (1%)

recommendations. For patients with a prior history of air travel-related complications, all HCPs would recommend oxygen. In terms of flight factors, length of flight (>6 hours) was the only factor that clearly influenced recommendations.

Patient experiences

In a separate survey, patients were asked to share their experiences with air travel. A total of 18 patients or families completed the survey, 17 were evaluable for analysis. Fifty-nine per cent (n=17) of the patients (95% CI: 36.0, 78.4) had an air travel-related complication with VOC being the most frequent. Admission to hospital was required for three patients (30%, n=10). While 31% (n=17) of the respondents had been advised to use supplemental oxygen during air travel, three patients (18%, n=17) had used oxygen on at least one flight, and only one patient (6%, n=17) routinely used oxygen. Commonly identified barriers included cost of the oxygen tanks, being unsure about the process of acquiring oxygen tanks, and air-line or airport challenges. Despite having access to oxygen, one patient had a pain crisis during a 4-hour flight; however, they were not hospitalized.

DISCUSSION

Survey data reveal that although most practitioners in this survey do perceive air travel as a risk, especially for vaso-occlusive pain crises, the majority do not recommend oxygen as a prophylactic measure. HCPs who participated in this survey state warm clothes, hydration, and analgesic medications are adequate preventative measures during air travel, which are the recommendations outlined in the NHLBI guidelines (31). A 2014 review article published by Lantos et al. makes similar recommendations and further encourages HCPs to provide travelers with a letter outlining their diagnosis, treatment, and previous complication history (12). In contrast, the CPS recommends the use of supplemental oxygen for children flying at altitudes greater than 2,300 m. Despite CPS recommendations,

Figure 1. Air travel risk and recommendations for patients with sickle cell disease. (A) Risk assessment, in terms of VOC (vaso-occlusive crisis), SC (splenic complications), ACS (acute chest syndrome), CVA (cerebrovascular accidents), of air travel in the SCD as appraised by health care practitioners (HCPs) survey participants, n=79.

Figure 2. (A) Percent of HCP respondents recommending various preventative measures to any of their sickle cell patients, n=79. (B) Among HCP respondents recommending oxygen, recommendations differ depending on the subset of the sickle cell disease patient population, n=14.

paediatric providers in this study were not more likely to recommend the use of supplemental oxygen. However, Canadian HCPs were more likely to recommend oxygen when compared to their American colleagues. Although the CPS statement was reaffirmed in 2018, much of the literature recommending supplemental oxygen was published prior to the 1980s. Since the 1950's the airline industry has made numerous adaptations including cabin pressurization to an altitude of 1,800 to 2,400 m (33). As well, there have been advances in the medical management of SCD with the introduction of hydroxyurea (33,34). How these changes in practice have affected air travel-related complications is not well defined.

In our study, both HCPs and patients indicated that there is an increased risk of air travel-related complications, especially VOC. Although most HCPs are recommending conservative measures like hydration, staying warm, and carrying analgesic medication, a high proportion of patients are reporting complications. While the risk of air travel-related complications, in previously published literature ranges from 1.4 to 68%, our patient survey reveals that 59% of the patients had experienced at least one complication in their lifetime. Of note, most of these events were mild to moderate, and did not require hospitalization. In 2016, a 10-year-old child with SCD suffered a fatal complication aboard a trans-Atlantic flight while travelling to Nigeria to visit family (30). While the cause of death was not determined, the patient was known to have SCD. This tragic case brought attention to the risk of air travel in the SCD patient population, worrying families. Although many of the case reports and series that describe air travel-related complications have been published over 30 years ago, air travel safety is still an active concern that should be addressed by HCPs.

Lack of current research in face of multiple advances in medicine and aviation make it difficult for HCPs to adequately appraise the risk and counsel their patients about this topic. While many HCPs in our survey did acknowledge the risk of VOC and ACS with air travel, 20 to 40% of the HCPs were unsure as to whether air travel did increase the risk. The lack

of clarity among HCPs on this issue could be confounded by the lack of recent literature. Further, the CPS and NHLBI, two commonly used guidelines, make conflicting recommendations in regards to supplemental oxygen. A lack of consensus among commonly used guidelines regarding the use of supplemental oxygen also poses a challenge to HCPs in counselling their patients about the risks and prophylactic measures to prevent sickling complications during air travel.

Study limitations

Although survey results provided valuable information regarding common clinical practices, data collected from a cross-sectional survey have limitations. Data collected represent opinions and beliefs of HCPs, which influence their clinical practice. As such, this study does not carry the power to be able to change current practice. Further, due to survey distribution through forums with a large proportion of mixed practitioners, the response rate is inaccurate and unable to be ascertained. The ASPHO forum is open to all paediatric HCPs, and not limited to those involved in the care of SCD patients. Additionally, selection and nonresponse bias is difficult to eliminate from online surveys and the sample size was limited. As there were only 18 patient participants, selection bias may have been accentuated in the survey. Given the sample size, statistical analysis was limited to descriptive statistics.

Future directions

While our survey data reveal common clinical practices and patient experiences, it lacks the power to change clinical practice. Further characterization of air travel complications as well as the benefit of oxygen as a prophylactic measure is required to inform evidence-based guidelines. Our data suggest that air travel-related complications are a concern for patients. A larger review of patient experiences would help further characterize air travel-related adverse events. These data would help further guide HCPs as they make recommendations for safe air travel.

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References

1. Forget BG, Bunn HF. Classification of the disorders of hemoglobin. Cold Spring Harb Perspect Med 2013;3(2):a011684.
2. Bunn HF, Forget GRH. Human Hemoglobins. Philadelphia: WB Saunders CO, 1974.
3. Archer N, Galacteros F, Brugnara C. 2015 clinical trials update in sickle cell anemia. Am J Hematol 2015;90(10):934–50.
4. Ballas SK, Lief S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol 2010;85(1):6–13.
5. Lee AP, Yamamoto LG, Relles NL. Commercial airline travel decreases oxygen saturation in children. Pediatr Emerg Care 2002;18(2):78–80.
6. Ward MP, Milledge JS, West JB. High Altitude Medicine and Physiology. Chapman and Hall Medical, New York, 1995.
7. Nishi S. Effects of Altitude related hypoxia on aircrews in aircraft with unpressurized cabins. Mil Med 2011;176(1):79–83.
8. Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxaemia in young Kenyan children with acute lower respiratory infection. BMJ 1993;306(6878):612–5.
9. Reuland DS, Steinhoff MC, Gilman RH, et al. Prevalence and prediction of hypoxemia in children with respiratory infections in the Peruvian Andes. J Pediatr 1991;119(6):900–6.
10. Nicholas R, Yaron M, Reeves J. Oxygen saturation in children living at moderate altitude. J Am Board Fam Pract 6(5):452–6.
11. Samuels MP. The effects of flight and altitude. Arch Dis Child 2004;89(5):448–55.
12. Willen SM, Thornburg CD, Lantos PM. Travelers with sickle cell disease. J Travel Med 2014;21(5):332–9.
13. Lang M; Canadian Paediatric Society, Community Paediatrics Committee. Air Travel and Children's Health Issues. Paediatr Child Health 2007;12(1):45–50.
14. Poets CF, Samuels MP, Southall DP. Potential role of intrapulmonary shunting in the genesis of hypoxic episodes in infants and young children. Pediatrics 1992;90(3):385–91.
15. Stankovic Stojanovic K, Lionnet F, Girot R, Lescure FX, Pialoux G, Le Loup G. The risk of going abroad in sickle cell disease: A study of 148 adults. Trans R Soc Trop Med Hyg 2011;105(6):310–4.
16. Sommet J, Missud F, Holvoet L, et al. Morbidity among child travellers with sickle-cell disease visiting tropical areas: An observational study in a French tertiary care centre. Arch Dis Child 2013;98(7):533–6.
17. Runel-Belliard C, Lesprit E, Quinet B, Grimpel E. Sickle cell children traveling abroad: Primary risk is infection: Table 1. J Travel Med 2009;16(4):253–7.
18. Claster S, Godwin MJ, Embury SH, Francisco S. Risk of Altitude Exposure in Sickle Cell Disease. 1981. <<http://pubmedcentralcanada.ca/pmc/articles/PMC1273254/pdf/westjmed00219-0022.pdf>> (Accessed July 22, 2017).
19. Mahony BS, Githens JH. Sickling crises and altitude. Occurrence in the Colorado patient population. Clin Pediatr (Phila) 1979;18(7):431–8.
20. Ware M, Tyghter D, Staniforth S, Serjeant G. Airline travel in sickle-cell disease. Lancet 1998;352(9128):652.
21. Murano T, Fox AD, Anjaria D. Acute splenic syndrome in an African-American male with sickle cell trait on a commercial airplane flight. J Emerg Med 2013;45(5):e161–5.
22. Green RL, Huntsman RG, Serjeant GR. The sickle-cell and altitude. Br Med J 1971;4(5787):593–5.
23. Rotter R, Lutgens WF, Peterson WL, Stock AE, Motulsky AG. Splenic infarction in sickleemia during airplane flight: Pathogenesis, hemoglobin analysis and clinical features of six cases. Ann Intern Med 1956;44(2):257–70.
24. Cooley JC, Peterson WL, Engel CE, Jernigan JP. Clinical triad of massive splenic infarction, sickleemia trait, and high altitude flying. J Am Med Assoc 1954;154(2):111–3.
25. Nadesan K, Nagaratnam M. Sudden death during long distance air travel in an Hb S/C disease patient. J Clin Forensic Med 2001;8(3):151–5.
26. Sullivan BH. Danger of airplane flight to persons with sickleemia. Ann Intern Med 1950;32(2):338–42.
27. Doenges JP, Smith EW, Wise SP, Breitenbucher RB. Splenic infarction following air travel and associated with the sickling phenomenon. J Am Med Assoc 1954;156(10):955–7.
28. Piel FB, Tatem AJ, Huang Z, Gupta S, Williams TN, Weatherall DJ. Global migration and the changing distribution of sickle haemoglobin: A quantitative study of temporal trends between 1960 and 2000. Lancet Glob Heal 2014;2(2):e80–9.
29. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. Lancet 2013;381(9861):142–51.
30. Family fundraising after death of Canadian girl, 10, on transatlantic flight. CBC news Toronto, Dec. 29, 2016 <https://www.cbc.ca/news/canada/toronto/family-fundraising-girl-dies-flight-1.3914779>
31. National Heart Lung and Blood Institute. Division of Blood Diseases and Resources. The Management of Sickle Cell Disease, 4th edn. Bethesda: National Heart Lung and Blood Institute, 2002.
32. Harris PA, Taylor R, Thielke R, Payne J, Nathaniel Gonzalez JGC. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42(2):377–81.
33. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med 1995;332(20):1317–22.
34. el-Hazmi MA, Warsy AS, al-Momen A, Harakati M. Hydroxyurea for the treatment of sickle cell disease. Acta Haematol 1992;88(4):170–4.