Impact of hospitalization for vaso-occlusive crisis on health-related quality of life in children with sickle cell disease

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Abstract

Background: Sickle cell disease (SCD) is characterized by vaso-occlusive crises (VOCs), that impair the health-related quality of life (HRQoL). The aim of this study is to evaluate the impact of hospitalization for VOCs on HRQoL in children with SCD over time. **Methods:** In this longitudinal cohort study, children aged 8-18 years diagnosed with SCD at the Amsterdam UMC were included between 2012 and 2021. HRQoL was annually measured as part of standard care using the Pediatric Quality of Life Inventory. The impact of hospitalization for VOC on HRQoL was evaluated using linear mixed models 3, 6, 9 and 12 months after hospitalization. The effect of frequency of hospitalization for VOC on HRQoL was evaluated over the last 12 months. **Results:** In total , 94 children with SCD were included with a median age of 11.8 years (IQR 9-14). Thirty-seven patients (39%) had been hospitalized for a VOC. Hospitalization for VOC led to a decrease of 3.2-4.8 points in total HRQoL compared to patients without hospitalization, most pronounced 3 months after hospitalization. Recurrent admission for VOC in the last 12 months was associated with a decrease of 2.3 points in total HRQoL (p=0.04). The most affected subscale was physical functioning. **Conclusion:** The adverse effects of hospitalization for VOC in children with SCD persist up to 12 months after hospitalization. After hospitalization for VOC, extra attention and support for its negative impact on HRQoL are recommended. This study also underlines the importance of systematically measuring HRQoL allowing clinicians to intervene accordingly.

Introduction

Sickle cell disease (SCD) is the most common hemoglobinopathy affecting millions of people worldwide.[1] SCD is caused by a single point mutation in the β-globin gene. This gene mutation leads to formation of abnormal hemoglobin known as hemoglobin S (HbS). Upon deoxygenation, HbS polymerizes into long chains, thereby changing the shape of red blood cells into a stiff, sickle-shaped form causing acute and chronic complications including vaso-occlusion, chronic hemolysis, and multi-organ damage.[2] Vaso-occlusion along with impaired oxygen supply and reperfusion of injured tissues causes acute pain.[3] These recurrent and unpredictable so-called vaso-occlusive crises (VOCs), are frequently located in the chest, back or abdomen, but may affect every part of the body. In patients with SCD, the frequency of VOCs ranges between 0 to 18 VOCs per year.[4] Although VOCs are primarily managed at home with oral or suppository analgesic agents, they are the most common cause for hospitalization and emergency department visits in patients with SCD.[5-7] In some cases, VOCs are complicated by the development of an acute chest syndrome, that may be life-threatening and require admission to the pediatric intensive care unit.

Nowadays, disease-modifying therapies including hydroxyurea[8], voxelator[9] and crizanlizumab,[10,11] and curative therapies such as stem cell transplantation are becoming more available for the management of SCD. Unfortunately not all patients have access to these treatments and not all VOCs can be prevented.[12-14] VOCs have a negative impact on all aspects of patient's lives, not only physically, but also emotionally and socially.[15] As screening programs and preventative measures have led to higher survival among children with SCD, SCD has now transformed into a more chronic disease,[16,17] and more attention is required for the substantial personal and societal burden.

Health-related quality of life

Health-related quality of life (HRQoL) refers to the perceived wellbeing in physical, mental and social domains of health[18], and is a patient-reported outcome (PRO) as it is assessed by patients themselves (self-reported).[19,20] In children, HRQoL can be assessed by the caregiver (proxy-reported) as well. Validated questionnaires to systematically monitor HRQoL are called patient-reported outcome measures (PROMs). In the Emma Children's Hospital, the KLIK PROM portal (www.hetklikt.nu) is used to routinely measure HRQoL in daily clinical practice with PROMs.[21-23]

Previous research has shown that HRQoL is significantly affected in children with SCD, in both self- and proxy-reported HRQoL studies.[17,24-28] Children with SCD had a substantially lower HRQoL compared to both the general pediatric population, and other children with chronic disorders.[26,27,29-31] The painful VOC strongly affects the HRQoL more than any other SCD-related complication such as avascular necrosis or stroke.[32]This is likely due to lack of control, effective therapeutic interventions[29] and the difficulty of pain management.[33] In particular health care utilization seems to be a strong predictor for worse HRQoL in children with SCD.[34]

While research has been conducted on the impact of VOC on HRQoL of pediatric patients with SCD, no studies have evaluated the cumulative longitudinal effect of hospitalization on HRQoL. Longitudinal analyses allow us to evaluate the impact of hospitalization on HRQoL over time. Therefore, the aim of this study is to identify the longitudinal impact of hospitalization for VOC on HRQoL in children with SCD with real-world data, up to one year after hospitalization. Identifying the impact of hospitalization allows healthcare providers to provide adequate psychosocial support as part of interdisciplinary pain management to improve HRQoL.

Methods

In this retrospective cohort study, patients aged between 8 and 18 years with a confirmed diagnosis of SCD, who received care at the Emma Children's Hospital, Amsterdam University Medical Centers (Amsterdam UMC) were eligible for enrollment. As part of standard care procedures, children routinely filled out PROMs prior to the regular visits through the online KLIK PROM portal (https://www.hetklikt.nu/). The answers were returned to the clinician and discussed during consultation. One of the measures is the Pediatric Quality of Life Inventory 4.0 Generic core scales (PedsQL^{TM} 4.0). Every child (and/or the parent) was requested to complete the PedsQL at least once a year. Patients were included in this study if they had filled out at least two PedsQLs between January 2012 and September 2021. Data of patients were excluded if patients were on a chronic transfusion therapy or if permission for use of data for research purposes had been denied. This project was reviewed by the Medical Research Ethics Committee of the Amsterdam UMC, and conducted according to the Declaration of Helsinki.

Study measures

Demographics and disease-related characteristics including age, gender, SCD genotype, medication use, and hospitalization for VOC were collected from the electronic health records (EHR). Details of hospitalization

for VOC one year prior to HRQOL measurement were collected from the EHR as well including length of stay (LOS), analgesic use and complications during hospital admission such as development of acute chest syndrome. With this information, the severity of each hospital admission was scored as mild (1 point), moderate (2 points) or severe (3 points). Mild severity was defined as a LOS shorter than 4 days; moderate severity was defined as a LOS between 4 through 6 days; and severe was classified as the presence of an acute chest syndrome independent of LOS, or a LOS more or equal to 7 days.

Self-reported HRQoL was collected by completion of the PedsQL through the online KLIK PROM portal. The PedsQL consists of 23 items covering the following 4 subscales: physical, emotional, social and school functioning.[30,35] The questions address the preceding week and could be answered with the following options: never (0), almost never (1), sometimes (2), often (3) and almost always (4). The answer '0' is converted into the score of 100, '1' into 75, '2' into 50, '3' into 25 and '4' into 0. Then, a mean score was computed for each of the 23 items, and transformed to a scale that ranges from 0 to 100. Both a total score as well as a score for each HRQoL subscale was calculated. A psychosocial score was created from the emotional, social and school functioning subscales of the PedsQL. A weighted average of the different PedsQL subscale scores was calculated to derive the total HRQoL score. The higher the calculated scores, the higher the perceived HRQoL.[36] Previous studies confirmed the validity and reliability of the PedsQL^{TM} for the measurement of HRQOL in the Dutch population.[30] To evaluate the reliability of the PedsQL versions in our study population, we calculated internal consistency estimates (Cronbach's α). Estimates of 0.70 or greater were considered good, while estimates between 0.60 and 0.70 were considered moderate and estimates below 0.60 were considered poor.[37]

Statistical analyses

All data was transformed and analyzed in the Statistical Package for the Social Sciences (SPSS) version 28.0. Descriptive data were generated for all variables to describe the study population and its characteristics. Categorical variables were presented as absolute numbers with corresponding percentages. Means and standard deviations (SDs) were calculated for continuous variables that were normally distributed. Medians with interquartile ranges (IQRs) were calculated for values that were not normally distributed. The period of follow-up was expressed in patient-years by summarizing the duration of follow-up in days for all patients divided by the number of days in a year (365.25). Baseline characteristics and mean HRQoL scores were compared between the hospitalization and no hospitalization for VOC group using the chi-squared test or the unpaired t-test. For analysis purposes, genotype was categorized in two groups: a clinically mild (HbSC and HbSß+-thalassemia) and clinically severe genotype (HbSS and HbSß0-thalassemia).

To assess the impact of the occurrence of hospitalization for VOC on HRQoL over time, linear mixed model (LMM) analysis was used. The dependent variables were HRQoL scores (both the total and the subscale scores), and the independent variable was hospitalization for a VOC. In all analyses, patients were considered as non-hospitalized if they had not been admitted to the hospital in the last 12 months. Sensitivity analyses were performed to determine whether the time period between hospital admission and HRQoL measurement, affected HRQoL. For this, the analyses were repeated for the time periods 3, 6, 9 and 12 months after hospitalization. The impact of frequency of hospital admission in 12 months on HRQoL was evaluated using LMM analyses as well. To assess the impact of the severity of a hospitalization for VOC on HRQoL over time, a subanalysis with LMM was performed within the hospitalization group using the calculated severity score. All analyses were adjusted for age and SCD genotype. The estimates of the LMM analyses were reported as regression coefficient (β). Significance levels were set at 5% and all estimates were reported with 95% confidence interval (CI).

Results

In total, 94 patients met the inclusion criteria and were enrolled in the study as shown in **Fig. 1.** The total follow-up duration was 451 patient-years with a median follow-up time of 4.0 years (IQR 2.0 - 6.0). The included patients completed the PedsQL 455 times in the period January 2012 through September 2021. This is 237 times by patients in the non-hospitalized group, and 218 times by patients in the hospitalized group (**Supplemental Fig. S1).** The median number of PedsQL completions per patient was 4 (IQR 3 - 6).

Table 1 shows the baseline characteristics of the study population. The median age of first completion of the PedsQL was 11.8 years (IQR 9.3 - 14.1) and 64% of the patients was male. There were 37 patients who had at least one hospitalization for a VOC, while the remaining 57 patients had no hospitalization for a VOC prior to measurement of the HRQoL. Patients with HbSS/HbSβ^0were more prevalent in the hospitalized group compared to the non-hospitalized group (89% vs 42%, $p<0.01$) and a larger proportion of patients used hydroxyurea (78%) compared to the non-hospitalized group (32%).

There were 37 patients with a total of 122 hospitalizations for VOC. Out of these 37 children, 22 children (59.5%) had been admitted more than once during follow-up. The median admission rate of these children was 4 times (IQR 2 - 6). Intravenous morphine was administered in 62% of the hospitalized patients for the median period of 3.0 days (IQR 0.0 - 5.0). About one-third of the cases (36%) required oxygen support, while blood transfusion was administered in 16% of the cases, mainly because of a decrease in Hb level to below 5.6 g/dL. During four hospitalizations (3%), three patients developed an acute chest syndrome. Admission to the pediatric intensive care unit occurred in three hospitalizations (3%).

In this study, the Cronbach's α for the total HRQoL score was for all versions greater than 0.8, and therefore good. For the subscales, Cronbach's α scores for the version 8-12 years version were moderate/good ranging from 0.64-0.74, except for school functioning ($\alpha = 0.49$). For the 13-18 years version, Cronbach's α scores were moderate/good ranging from 0.62-0.78. The mean total HRQoL score from the completed PedsQLs was significantly lower in the group with hospitalization (75 points, SD $\pm$ 1.5) compared to the total HRQoL score from the group without hospitalization (80 points, SD $\pm$ 1.3) (**Table 2)** .

Impact of occurrence of hospitalization for VOC

The impact of occurrence of hospitalizations in the last 3, 6, 9 and 12 months on HRQoL is shown in **Table 3** . There is a trend showing that the negative effect of hospitalization for VOC diminishes over time for all subscales **(Fig. 2)** . The decrease of the total HRQoL and all subscales scores were most pronounced 3 months after hospitalization with decreases between 3.3 and 5.8 points, except for physical functioning. The impact on physical functioning was most pronounced 6 months after hospitalization with a decrease of 6.1 points. Most affected were the total HRQoL and the subscale physical functioning.

Impact of frequency of hospitalization for VOC

The results for the impact of frequency of hospitalization in the last 12 months are shown in **Table 4** . There was a significant decrease in total HRQoL of 2.3 points for every additional hospitalization over a period of 12 months. The most affected subscales were physical functioning and school functioning. For every hospitalization, a decrease of 2.7 points in physical functioning and 2.6 points in school functioning was observed.

Impact of severity of hospitalization

Out of 37 children who had been admitted at least once for a VOC during follow-up, 15 children (41%) experienced a hospitalization classified as severe. Approximately one third of the patients had a hospitalization

classified as mild (32%). Although not significant, the severity of the hospitalization had a little negative effect on HRQoL at 3 months, which disappeared after 3 months. **(Supplemental Table S2)** .

Discussion

In the first decade of life, VOCs are the most common complication of SCD,[38] and associated with an impaired HRQoL.[39,40] Generally, SCD is associated with a high health care utilization including emergency room visits and hospitalizations due to VOCs.[41] With age, the frequency of hospitalization for VOC increases.[39,42]This study shows that occurrence of hospitalization for VOC has a negative effect on total HRQoL, evident up to 12 months after hospitalization in children with SCD. This effect was most pronounced if HRQoL was measured closely after hospitalization and decreased over time independently of the frequency of hospitalization. As the number of hospitalization increases, the negative effect on total HRQoL significantly increases as well.

Our study is in line with previous research involving the impact of hospitalization for VOC on HRQoL in children with SCD.[43] Brandow et al. prospectively found a decrease in HRQoL after hospitalization for VOC, but this effect seemed to disappear after one week.[43] The authors compared HRQoL during hospitalization for VOC with control patients in steady state. The discrepancy with our study could be attributed to the cross-sectional design of their study and the comparison with a separate control group. Instead, we used repeated measures over time to compare HRQoL between patients and within patients with and without hospitalization for VOC. Using repeated measures in the same patients allows us to monitor changes of HRQoL over time, while controlling for factors that cause variability. In our longitudinal analyses, although the effect of occurrence of hospitalization on HRQoL was greatest after 3 months, this effect was not significant most probably due to lack of power. Nevertheless, the trend up to 12 months is evidently present, and decreasing over time.

In addition, previous studies have showed an inverse correlation between self-reported HRQoL and the frequency of hospitalizations and emergency department visits, comparable to our study.[44-48] As the effect of frequency of hospitalization on HRQoL in our study does not look clinically relevant, it will become relevant as healthcare utilization increases with age. Accordingly, Campball et al. reported the higher the frequency of VOCs, the lower the self-reported total HRQoL in children with SCD.[42]

Dampier et al. found in regression models that mainly occurrence of pain-related acute care visits was responsible for negatively affected HRQoL subscales.[17] All HRQoL subscales are found to be affected in patients with SCD compared to healthy norms,[24,44,49] but the subscale physical functioning seems to be the most affected across previous studies.[25,39] This is line with our study, reinforcing the fact that hospitalization has a negative impact mainly on the physical functioning lasting for months. School functioning was only significantly affected after 12 months, so it seems that the effect of hospitalization on school functioning only manifests over time. Even though the reliability of the PedsQL for school functioning was poor in our study, hospitalization for VOC does result in school absenteeism, which in turn can lead to poor school performance or academic functioning.[50-53] As a matter of fact, the frequency of hospitalization has been reported to be a predictor of poor HRQoL with regard to school functioning in children with SCD.[50]

In several studies, SCD severity and complications were associated with worse HRQoL.[54] In the association between hospitalization for VOC and HRQoL, the severity of hospitalization has not been taken into account before. According to our subanalysis, severity of hospitalization could have affected total HRQoL, but only until 3 months after hospitalization. After this time, severity does not seem to affect the total HRQoL score. However, these results were not significant, as this analysis was conducted within a subgroup of patients with 45 completed PedsQLs.

Strengths and limitations

An important strength of this study is its longitudinal nature with data covering the last 10 years with at least two measurements of HRQoL per patient. Also, our study population with SCD is closely monitored at our SCD comprehensive care center, as each patient is requested to annually fill out PROMs before a regular visit as part of standard care.

There are also limitations that should be taken into account when interpreting the data. First of all, patients with SCD who have mainly VOCs managed at home, are not taken into account in the analyses, while these VOCs burden patients as well. This also applies to patients with other SCD-related complications such as chronic pain, that may have a harmful effect on aspects of HRQoL. We did exclude patients on a chronic transfusion therapy as they were more likely to have less hospitalizations for VOC, while carrying the burden of frequent blood transfusions. Second, the PedsQL was found to have moderate/good reliability for all subscales, except for school functioning. Therefore, the PedsQL results for school functioning should be interpreted with caution. Third, patients without hospitalization completed the PedsQL more often than the hospitalized patients. Hospitalized patients may experience a higher disease burden or stress causing them to have less time for completion of PedsQLs. Another explanation is, when a patient is hospitalized, while having a visit scheduled at the outpatient clinic, this visit is not automatically rescheduled to after hospitalization.

Half of the eligible patients (or caregivers) did not give consent to use the HRQoL data for scientific research. Moreover, not all children were able to fill out the PedsQL regularly. For instance, children and/or caregiver(s) who lack digital literacy, did not complete the PedsQL via the online platform. However, we are facilitating and offering technical support at the outpatient clinic for these patients and their caregivers to overcome this problem. All of the above could have caused selection bias of the study population affecting the generalizability. In addition, our dataset was too limited to include socio-economic status in our analyses. Considering that socio-economic status is a well-known potential confounder of HRQoL, this may have caused a bias as well.

Based on findings of this study, there are some implications for clinical practice and recommendations for future research. Because of the negative impact of both the occurrence and frequency of hospitalizations for VOC on HRQoL, it is important to focus on the prevention of VOCs and the usage of disease-modifying drugs. In case of hospitalization, close monitoring and psychosocial support aimed at all aspects of HRQoL, but in particular physical functioning (e.g. by offering physiotherapy), should be considered. After frequent hospitalizations, there should be sufficient attention for school functioning as well. Furthermore, the KLIK PROM portal is an important tool in clinical practice to assess the need for extra psychosocial support in patients with SCD. SCD-specific symptom list in addition to the generic PROMs evaluating aspects of HRQoL could increase the reliability making research more replicable and easily comparable in this patients with SCD. Ultimately, a mixed-methods study should be performed to provide in-depth insights into how HRQoL is affected by hospitalization for VOC. This could allow healthcare providers to identify and better respond to the needs of children with SCD, who have been hospitalized for VOC, and customize their care.

Conclusion

In conclusion, this study showed that the negative impact of hospitalization in children with SCD persists at least up to 12 months. Health care providers should focus on the prevention of VOCs, but in case hospitalization for VOC occurs, optimal attention and guidance is recommended for the after effects of hospitalization for VOC. This study underlines the importance of measuring HRQoL in children with SCD systematically to identify timely impaired HRQoL and to intervene accordingly. Future research should focus on how hospitalization for VOC affects HRQoL and whether this effect persists beyond 12 months. This may help healthcare providers develop standardized yet tailored interventions to target specific aspects of functioning such as physical functioning, improving HRQoL of pediatric patients with SCD.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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Legends

Figures:

Figure 1. Flowchart study population selection and classification.

Figure 2. The negative effect of occurrence of hospitalization on HRQoL 3, 6, 9 and 12 months after hospitalization, diminishes over time.

Tables:

- Table 1. Baseline characteristics of the study population.
- Table 2. Mean HRQoL scores of the study population as measured by PedsQL.
- Table 3**.** Results of impact of occurrence of hospitalization for VOC on HRQoL scores in the last 3, 6, 9 and 12 months adjusted for age and genotype.
- Table 4. Results of impact of frequency of hospital admissions for VOC on all HRQoL scores in the last 12 months adjusted for age and genotype.

Supplemental figures and tables:

Supplemental Figure S1. Distribution of completed PedsQLs among the hospitalized patients and the non-hospitalized patients.

Supplemental Table S2. Results of the effect of severity of hospitalization for VOC in the last 3, 6, 9 and 12 months on HRQoL scores adjusted for age and genotype.

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