Author’s response to reviews

Title: Chronic complications and quality of life of patients living with sickle cell disease and receiving care in three hospitals in Cameroon: a cross-sectional study

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Version: 1 Date: 17 Feb 2017

Author’s response to reviews:

Manuscript ID: BHEM-D-16-00029

To the Editor-in-chief,

BMC Hematology

Dear Editor,

Thank you for the opportunity given to revise our manuscript entitled, “Chronic complications and quality of life of patients living with sickle cell disease and receiving care in three hospitals in Cameroon: a cross-sectional study”. I am writing to submit the revised version for consideration for publication in BMC Hematology.

We are grateful to the reviewers for their constructive comments. We have addressed their queries and have used the “track changes” option of MS Word to modify the paper so as to account for their comments and suggestions.

We hope that you will find this revised version suitable for publication.
Responses to reviewers’ comments

REVIEWER 1

The manuscript by Andong et al. presents a cross sectional survey of selected chronic complications of sickle cell disease in both adults and children in Cameroon. The study also included instrument measurement of quality of life. The important finding is that older age, avascular necrosis and stroke were associated with poor quality of life. This study provides important information for improving outcomes with implementation sickle cell disease treatment in Cameroon. There is limited data on sickle cell disease in Africa, and this adds novelty and importance to these results. There are opportunities to strengthen the presentation of these results.

Major points:

1. Methods, Page 4, line 86: Should the questionnaire be included as a supplemental appendix with the manuscript. The outcome measures (leg ulceration, AVN and stroke) are clearly mentioned in the manuscript, however, it is not clear how such events were defined. How was stroke defined? How were painful sickle cell crises defined for the yearly number of events? Self reports? Combination of self report and hospital records? Outside medical records? Is there any data on chronic kidney disease, as this is a key chronic disease complication?

We have added the questionnaire as supplementary file in the submission

Each chronic complication was recorded based on a combination of self-report from the participant, the medical reports, and the physical examination. We explained to each participant what stroke was for example, and if yes or no he/she had such event in the past or during the study period. We then went on to do a physical examination guided by the complications we
were looking for and finally we looked into the medical records to confirm and check the laboratory and radiography results.

Stroke was defined as any sudden onset neurological dysfunction (mainly one side body weakness) that resolved or not, in the absence of trauma.

Painful sickle cell crises were defined as any bony painful event, for which a medical consultation was done or not, when there was no recent history of trauma.

We did not have any report of chronic kidney disease, either self reported or recorded in the medical file.

We have added these definitions in the methods section.

2. Methods: Style point. Please also present the information regarding ethical study approval to the methods section, especially procedures for minors, IRB approval.

Thank you. We have included ethical approval statement in the methods section.

3. Results, page 5, line 104: Did the 7 subjects out of 182 who did not participate in the study refuse participation? If yes, this should be made clear in the text.

Two participants died during the study period and 5 refused to participate. This is shown in figure 1 and is referred to in the text.

4. Results, page 5, line 107: What percentage of subjects were less than 18 years of age? This is important because it gives the reader a sense of how many consents were by proxy by parents. Prior studies in other areas of Africa have shown the SCD age distribution is heavily skewed towards younger subjects due to different patterns of mortality (Aliyu et al. Am JHematol. 2008 Jun;83(6):485-90 and other examples).

Out of the 175 participants 89 (50.9%) were below 18 year of age. But since adulthood in Cameroon is defined as from 21 years, we added in the results the number of participants aged below 21 years instead, because they are the one whose consents were obtained from parents or guardians.
5. Results, page 5, line 108: How was the diagnosis of SCD made when only 33% had qualitative hemoglobin electrophoresis results? Perhaps this should be clarified with specific criteria used in the methods section.

SCD had been diagnosed in all patients based on electrophoresis. The 33% are those who were able to find their results and show us for details on percentages of HbS, F, C, A2 and A. We have added a statement in the methods.

6. Results, page 6, line 121: How were subjects determined to have opioid tolerance? What were the daily doses of opioids (in morphine equivalents)?

To determine if a subject had opioid tolerance we asked them if they were taking any narcotic, if they were dependent and if they required higher doses at each time to relief pain. Daily doses were not recorded.

7. Discussion, page 7, line 144: A point is made about the late diagnosis of SCD. What is the consequence of a late diagnosis in Cameroon where most subjects are not treated with specific therapies (prophylactic antibiotics, vaccinations, hydroxyurea)?

The consequences are multidimensional. First of all the individual will have a poor health and consequently a poor quality of life. Secondly the whole family will be affected both economically and psychologically. Finally this will affect the country’s economy as a whole in terms of fewer days at work or school by the patient and their care givers. We have added a statement in the discussion section.

8. Discussion, page 8 line 178: Based upon the above critiques, other limitations are present: establishing a valid SCD diagnosis and self-reports of chronic complications.

Thank you. We have expanded the limitations to account for this comment.

Minor points:

1. Page 7, discussion, line 141: Suggest adding something to the effect that the standards of care were established in developed countries. Implementation of these standards may or may not be feasible in developing countries like Cameroon. Perhaps the authors could even make a statement about what degree of implementation would be realistic.
Implementation of these standards of care is quite feasible in a country like Cameroon if the disease burden is understood and made a priority by stakeholders. As from 2015, the Mother and Child Center of the Chantal Biya’s Foundation which is a major pediatric hospital in Yaoundé the country’s capital started newborn screening. This strategy can therefore be generalized to other reference hospitals and made compulsory for every newborn.

2. Page 8, discussion, line 161: Are the authors able to distinguish tropical leg ulcers from SCD leg ulcers? Are tropical leg ulcers observed in the general population in Cameroon?

The authors could not distinguish between tropical leg ulcer and SCD leg ulcer. Reports on skin ulcers in Cameroon are from endemic Buruli ulcer areas (Trellu LT et al. PLoS Negl Trop Dis. 2016; 10: e0004385.). We did not find any report from a city like Douala.


Reference 9 has been replaced by the suggested one.

Thank you

REVIEWER 2

In this manuscript, the authors attempt to describe the clinical features and quality of life scores for a small cohort of patients with sickle cell disease at three centers in Cameroon. The topic is an important one as some patients in low and middle income countries do survive childhood, and few studies have described the long term sequelae of living with sickle cell disease in this setting. Quality of life receives little attention for people living in sub-Saharan Africa in general, and more data on this aspect of health is welcomed. While the clinical question, particularly in a cohort of patients in Africa, is of merit, the manuscript and message could be considerably improved if the authors address the following comments.

Major Comments:

1. Abstract: The authors' aims are stated in the abstract, but the introduction does not provide a focused background to chronic complications of sickle cell disease or quality of life. The description of Methods is vague and it is not clear how the participants were selected from these 3 centers or how the questionnaires were assessed. The SF-36 should be introduced to
the reader in the Methods section of the Abstract for those not familiar with what this test is. The results should begin with the number of patients and basic demographics. In the Conclusions, the authors state that care is sub-optimal, though the study does not appear to attempt to evaluate or report the delivery or quality of clinical care. Overall, the use of English language and grammar could be improved. Additional comments below from the main text should be cross-checked upon revision of the abstract.

Thank you, we have modified the abstract to account for the comments

2. As a whole, the Background text could benefit from improved citation of biomedical literature rather than third party summaries of the medical literature. For instance, the fact that SCD is often associated with chronic complications could be supported with reference to either an excellent review article about the chronic complications of sickle cell disease as a whole (for example Thein MS et al. Sickle cell disease in the older adult. Pathology. 2016 Nov 30, or Ballas SK et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. Scientific World Journal. 2012;2012:949535) or individual references regarding specific chronic complications.

We have reviewed the background and have changed the citation accordingly.

3. Background, line 56, the authors state that the WHO has "placed SCD in the 4th position of public health priorities" with citation #3 identified as the source. I am not familiar with the WHO ranking public health priorities or that SCD is among the top 5 priorities. If so, this should be more clearly stated and appropriately referenced.

We agree with the reviewer that this information is confusing. Because we could not retrieve it from the website, we have deleted.

4. The authors should include comment on the existing literature regarding QoL in SCD, as this is a large part of this study. A brief introduction with appropriate references to what we know about QoL in SCD (outside of Cameroon) would help to set the stage for the rest of the text.

The only study we were able to lay hands on was that done in Jamaica which we mentioned.

5. In the Methods section, the authors identify three institutions in Cameroon and Figure 1 identifies 182 "eligible patients" but it is not clear what defines eligibility. Anyone presenting
to the center on a particular day? Are there only 182 patients cared for between these 3 institutions? It would be helpful to describe the size and capacity of the sickle cell center at each of the three settings. Additionally, it would be helpful to understand these centers in respect to geography, economy, population, and health care resources. I see on a map that these centers are opposite corners of the country. Does this change the patient population?

Both in patients and outpatients were recruited and anyone coming for their monthly meeting. Of the 3 centres just 1 (Laquintinie hospital) has a specific sickle cell center. In the other centers patients were recruited as outpatient and inpatient in all the different wards. These three hospitals are all located at the coastal regions (Littoral and South-West) of Cameroon. We have added these information in the methods section.

6. The authors describe a "cross sectional study" over 5 months. More details about how the study was actually performed is required. How were the patients identified and approached? Was this in a sickle cell clinic? A general clinic? An inpatient setting? Or more than one setting? How many patients were recruited from each hospital/center?

Participants were recruited at 3 different hospitals. Douala Laquintinie hospital is a sickle cell clinic with outpatient and inpatients services. This centre equally host the monthly meetings during which participants were also approached. The other two centres had a haematology consultation unit where patients were recruited but they didn’t have a special unit for SCD patients. We have added the details in the methods section.

7. The authors refer to their sample size calculation with a reference from a manuscript from Jamaica. Did they just assume the sample size and study design were the same? A more statistically appropriate description of sample size and power would be helpful. A sample size of 110 is necessary to detect what type of difference in QoL between these groups of patients? The study only has 9 patients from a rural area. Does the sample size require equal numbers in each group? Was sample size calculated before the study was performed? If this is merely a convenience sample that was obtained during a specific time frame, this should be stated without trying to identify a sample size that is not relevant for this particular study.

This study was a MD thesis, and as a prerequisite the sample size was stated in the protocol before the study was carried out. The minimum sample size was calculated with reference to the Jamaican study, but because we had just 9 participants from rural origin, urban/rural difference could not be ascertain. We agree with the reviewer that a formal sample size estimation was not necessary. For these reasons, we have removed data on sample size calculation from the methods section.
8. The data collection tools are a critical aspect of this manuscript and are not well described. How was the data regarding history of chronic complications elicited from patients/guardians? What questions were asked? What definitions were used for "heart disease" or "avascular necrosis of the hip"? How many different investigators performed these questionnaires? Were these asked of the patients or was the medical record used? Do these centers have comprehensive medical records with such data?

For heart disease every patient underwent a physical examination to look for a murmur; we also checked results heart ultrasound whenever available. Avascular necrosis of the hip was evaluated by asking the participant directly and confirming with medical records. Only one investigator administered the questionnaire to all participants. The centres used had comprehensive medical records. The detailed questionnaire is submitted with the revised version of the manuscript. We have added these details in the methods section.

9. The description of the patients would be improved with evaluation of additional, more common sickle cell complications, such as acute chest syndrome or respiratory disease? Why don't they ask questions about number of hospitalizations or number of How was the list of complications selected? The data collection tool should be added as supplementary material.

We did not include the acute chest syndrome amongst the chronic complications. We are submitting the detailed questionnaire as a supplementary file with the revised version of the manuscript.

10. Methods, line 76 states that only children above 5 were included. Were specific ages used as inclusion/exclusion criteria? Stroke can certainly occur before age 5. The comment that stroke can happen "as early as age 5" should be reworded. The authors should clearly state the inclusion/exclusion criteria for these patients and why patients less than age 5 were excluded.

Patients less than 5 years were excluded based on other studies that reported chronic complications starting averagely at the age of 5 years. We have added the inclusion and exclusion criteria in the methods section.

11. More information about the SF-36 should be included either here or above. What is the total score? What is a good score or bad score? From my reading, it appears a score of 50 is normal, above 50 is better than normal and less than 50 is less than normal? Based on the data, it appears this cohort has a good quality of life? Has this tool been translated into
French and/or local languages? In which language was it administered? Has it been validated in that population? If translated, has the translation been confirmed to be correct?

The questionnaires were translated in French to better communicate with the French-speaking participants. Therefore the tool was administered either in English or French depending on the participant’s first language. We have provided a description of the questionnaire in the methods section. To the best of our knowledge, this tool has not been specifically validated for our population.

12. What type of gel electrophoresis was used? HPLC? Are quantities of HbS, HbF, and HbA2 known? If so, this data would be helpful.

We did not get the details of the gel types used for the Hb electrophoresis, and we did not focus on the percentages of each type of Hb.

13. Are there laboratory data available for these patients? A table summarizing available laboratory data, particularly hematology data (Hb, MCV, HbF, etc), would improve the quality of this manuscript.

Sorry, we did not record laboratory data.

14. Results, line 110. What does it mean that vaccinations are or are not up to date. If full vaccine data is available, this should be presented in its entirety. For example, what percentage of patients have received pneumococcal vaccination, Haemophilus influenzae, type B, polio, Hepatitis B, etc. The comment that 59% of patients do not have vaccines "up to date" is not meaningful on its own.

The four required vaccines in sickle cell disease that were sought were: pneumococcal vaccine, meningococcal vaccine, Typhim V and Hepatitis B vaccine. If the participant was not up to date with anyone of these it was recorded as such but details for each of the vaccines was not kept as record.

15. How were the chronic complications defined? The text (lines 116-120) select random data points that are not of great interest and difficult to follow. The authors should more clearly summarize the important findings in this section.
We have provided a definition of chronic complications in the methods section (definition of terms and variables).

16. Why is a systolic murmur mentioned (line 120)? Was this identified by physical exam? Or by report from parents? It is not clear if these data were collected by extracting medical records, by asking the patients, by examining the patients or a combination of these methods. This should be more clearly defined.

Every participant underwent a multisystem physical examination. We have added the detail in the method section.

17. The QoL data (page 6, line 122-135) needs to be more clearly summarized. How many total sections were there and how is the score calculated? Is the total score just the physical component score plus the mental component score?

Yes the totals core is a combination of all sub scores. We have provided a description of the QOL data calculation in the method section.

18. When it says that "holding every else constant" it is not clear what variables are included in the multivariable model. Variables not present in the tables have been mentioned in the results section. Please be more explicit about what variables have been included in your multivariable model.

Three separate multiple linear regression models were set up to screen for factors associated with the three QoL scores: total QoL score, PCS and MCS. The variables included and retained for each model are presented in Table 3 under the heading of each component score. The regression approach has also been included in the data analysis sub-section in the methods. We have provided a description of the multivariate model in the method section (statistical analysis).

19. Overall, with significant revision, the Discussion should be restructured to highlight the important findings of this study and succinctly pass along the primary message of the research to the reader. In its current form, the Discussion is too verbose with too many stated comparisons to literature that is not entirely relevant to the current work.

We agree with the reviewer. We have reviewed and amended the discussion.
Figures/Tables

1. Figure 1 mentions 2 participants that died during the course of the study. I believe this study was a cross-sectional analysis with data collected at a single time point. How was this possible for a patient to die during the study?

Inpatients were included in our study. QOL questionnaire was administered only after a painful episode. So while waiting to administer the QOL questionnaire some of the patients died and therefore the data already collected were excluded.

2. Table 3 is not helpful. Summarize this data in the text, particularly the number of patients taking hydroxyurea. What are the "vasodilators" and what was the indication for their use?

Considering that you meant figure 2, we have deleted it and summarized the data in the text.

3. Figure 4 - does not add much value to the manuscript, but makes sense that agreement between the total score and the individual scores would be better than the agreement between the mental and the physical.

Thank you for the comment and we appreciate your interest to look into details.

Typographical and Grammatical Mistake

1. In the abstract, the 2nd sentence of the background does not make sense. There is an extra verb. Possible rewording could be: "Most developed countries have reduced applied these recommendations with success, whereas their implementation in sub-Saharan African countries has been hindered by lack of information about the burden of the disease."

This has been rectified.

2. In the final sentence of the conclusions, the word new-born should not be hyphenated. This is typically a single word written "newborn."

This has been rectified.

3. Line 74, there is a superfluous "a" in the sentence that reads, "which has a the main sickle cell center…"
It has been rectified

4. On line 128, the second sentence says "Holding every else constant…” and it should read "Holding everything else constant…”

It has been corrected

5. The second sentence of the discussion is improper English and ought to be improved. It seems like the author means to communicate that chronic complications are common even though the population is young (median age 16 yo).

It has been corrected

Thank you