**Author's response to reviews**

**Title:** Small volume plasma exchange for Guillain-Barré syndrome in resource poor settings: a safety and feasibility study

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RESPONSE TO THE REVIEWERS COMMENTS

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Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study

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Pilot and Feasibility Studies

Dear Editor
We would like to thank you for considering our manuscript as potentially acceptable for publication in Pilot and Feasibility Studies. We also would like to thank the reviewers for their critical and useful comments that helped us to improve the manuscript. We responded point-by-point within the 'Response to Reviewers' box in the submission system and highlighted (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript.

We declare that the author list and order is the same as the first submission and we agree with the criteria for authorship as outlined in BioMed Central's editorial policies.

Reviewer #1:

This manuscript describes an important study of small volume plasma exchange for the treatment of GBS in a resource-constrained environment to determine whether it is safe and whether it is feasible to remove the proposed volume of plasma in this patient cohort. The study is already underway, having been started in March 2016. The rationale, methods and proposed feasibility outcomes are clearly described and are appropriate. I have some concerns about the safety assessments:

1. Will all GBS patients be enrolled, regardless of presence or severity of autonomic instability such as hypotension or cardiac arrhythmias. If so, what measures will be taken to ensure that they do not suffer harm?

Response: We enrolled adult patients (≥ 18-years-old) with GBS. We excluded pediatric age group, pregnant woman and patients with severe or terminal concomitant illness (page 8, line 180,184-87).

Severe autonomic instability (hypotension, cardiac arrhythmias or arrest) present on admission was not an exclusion criterion but monitored and treated before the start of SVPE. However, autonomic instability may also appear after inclusion and start of the SVPE treatment. In such patients, we followed the predefined instructions mentioned under “attempts to minimize the risks associated with SVPE”. According to these instructions, the SVPE procedure will be stopped temporarily in patients who develop hypotension (30 mmHg decrease in systolic blood pressure, systolic blood pressure < 90 or MAP < 65 mmHg). Only after management of hypotension (which can be a part of autonomic insufficiency caused by GBS, SVPE or both) we resumed the SVPE. These measures are highlighted in the new version of the manuscript (page 9,10, line 124-29)

2. It is stated that "the study will be considered safe" if patients do not develop sepsis or venous thrombosis. Exacerbation of autonomic instability is a secondary outcome measure but may severely impact safety of the procedure. How will the incidence and severity of exacerbation of autonomic instability be factored into the overall assessment of safety of the procedure?
Response: We agree autonomic instability may severely impact the safety of the procedure. Therefore autonomic instability is a major secondary outcome measure and will be analyzed as such.

In our study autonomic instability was not a primary outcome measure since it may occurs frequently in GBS (even without treatment) and is usually treatable. The protocol however defines in detail that the heart rate and blood pressure are recorded frequently and the results and interventions if needed will be reported. In the new version of the manuscript we have further emphasized the importance of monitoring and treating autonomic disability (page 9,10, line 124-29 and page 11, line 259-62).

3. It is not clearly indicated exactly how autonomic function will be assessed during the process of removal of blood, simply a comment that it will be recorded daily. Will there be continuous monitoring of BP and cardiac rhythm? If not, how frequently will these measures be recorded during and immediately following the blood removal?

Response: Monitored blood pressure and cardiac rhythm before and after each session of SVPE (12 times a day) and more frequently in case of abnormal findings or clinical features). We provide more detailed information on measuring the BP and heart rate in the new version of the manuscript (page 11, line 259-63).

4. It is stated that Hb will be measured at baseline. Will patients be excluded if there is pre-existing anemia? What is considered an acceptable Hb concentration?

Response: Lower limit of normal Hb% was considered 13 g/dL for men and 12 g/dL for women and severe anemia was considered if Hb% <8 g/dL both for men and women. Pre-existing anemia will be corrected by blood transfusion before SVPE. This is further clarified in the text with reference (page 10, line 236-39).

5. Patients will leukocytosis at baseline may have covert pre-existing infection. This may increase the likelihood of developing CVC-related infection and also exacerbation of autonomic instability. Will patients with baseline leukocytosis be excluded or investigated for covert infection?

Response: All patients with a severe concomitant disease were excluded. GBS patients with clinical or laboratory evidence for a severe infection, as may be indicated by leukocytosis, were excluded except for patients with evidence for an aspiration pneumonia. Such infections are frequent in GBS, usually mild and show a good response to treatment. During the SVPE procedure, we will treat the patient for aspiration pneumonia and look for the development of CVC-related infection. We have clarified this in the new version of the manuscript (page 10, line 231-36).
Reviewer #2: Written by: Saadul Islam and Sohail Mulla

We have provided our review primarily on the methodological rigor of the submission. Neither of us is a clinician or a statistician, so we would defer to more experienced individuals on providing a comprehensive review of the submission as it related to these matters. Nevertheless, we have made a few clinical and statistical comments for the authors to consider.

Summary

The submission was a protocol for a clinical study that aims to determine the safety and feasibility of small volume plasma exchange (SVPE) for Guillain-Barré syndrome (GBS). The investigators aim to recruit 20 adult patients with GBS from a single centre (the National Institute of Neurosciences) in Bangladesh. The patients will undergo six daily sessions of SVPE for eight days. The primary safety outcomes are the number of patients developing severe sepsis due to central line-associated blood stream infection (CLABSI) and venous thrombosis in the limb. The primary feasibility outcome is the ability to remove at least eight litres of plasma over eight days. There are multiple secondary outcomes of safety and feasibility as well, including the relative risk of CLABSI due to SVPE compared to CLABSI in a control group of at least 20 patients whom the investigators will recruit during the study period. The investigators have recruited 15 patients with GBS and 18 control cases, since March 2016.

Strengths

* First study to evaluate the safety and feasibility of SVPE in a low-resource setting.

* Background incidence of CLABSI will be measured in a control group without GBS who will undergo CVC in the same ICU and HDU during the same period as the GBS patients.

* Strict inclusion and exclusion criteria, including pre-specified diagnostic criteria of the outcomes.

* Primary and secondary outcome measures of feasibility and safety are defined a priori.

* Strict aseptic measures will be taken to minimize contamination and infection.

* Stopping rule is in place.

* Quality control of fresh frozen plasma will be done.

* Baseline measurements of CBC and Hepatitis B, C and HIV to be done intermittently.

* Comprehensive list of parameters for SVPE, hemodynamic and autonomic status, infection, and sepsis will be documented to measure safety. A combination of clinical, imaging, biochemical and microbiological data will be collected and analyzed for safety parameters.
Different neurological examinations will be done to assess clinical, functional and sensation status.

Strong data management protocol, including having an independent DSMB.

CONSORT diagram depicting protocol and operation of the trial provided.

Illustration and description of the SVPE kit and procedure provided.

SPIRIT 2013 checklist adhered to and provided.

Weaknesses (in no particular order)

The title of the paper indicates "low-income countries," which seems inconsistent with the fact that the authors are conducting the study in a single country.

Response: We modified our title as “Small volume plasma exchange for Guillain-Barré syndrome in resource poor settings: a safety and feasibility study” (page 1, line 5-6).

The authors state, in the discussion section, that SVPE "may represent an effective treatment for GBS." They repeat this statement a few times throughout the paper. Is this assertion based on previous data or the results of the study? If it is the latter, that would not be appropriate, since the authors do not designate any effectiveness outcomes in their trial.

Response: SVPE is based on the same principle, that is removal of plasma from the patients as standard plasma exchange (PE), one of the established effective treatments for GBS. However the technique of SVPE is different. The effectiveness of standard PE in GBS has been described in a Cochrane review [Chevret S, Hughes RA, Annane D: Plasma exchange for Guillain-Barré syndrome. The Cochrane database of systematic reviews 2017, 2:Cd001798.]. Therefore we expect SVPE to be as clinically effective as standard PE provided it is feasible and safe. In the manuscript we do not state that SVPE is effective in GBS. We only point at the possibility that SVPE is effective in GBS because of the similarities with standard PE. In the study one of the secondary outcome measures is clinical improvement indicating that the study will provide some first evidence for the efficacy of SVPE although an independent and properly designed study is required to demonstrate this.

The authors include a questionnaire (Appendix 1C) to measure healthcare personnel's acceptability and satisfaction. It is unclear if the authors have evidence of the psychometric properties (e.g. validity, reliability) of this questionnaire in previous settings. If not, would the authors consider generating some evidence within this study? If that is not feasible, that is a potential limitation that the authors need to acknowledge.

Response: We appreciate your concern and our limitation of not having evidence of the psychometric properties (e.g. validity, reliability) of this questionnaire in previous settings. We
indeed considered generating some evidence within this study. We acknowledged this limitation in the discussion section. (page 16, line 382-84).

* The authors indicate that SVPE is available at a relatively low cost, i.e. 500 USD. We wondered if the authors are able to provide a breakdown of the cost, so that readers are able to fully appreciate the cost efficiency of this intervention.


* The authors should consider collecting recent history of antibiotics as part of their baseline data collection, since that would influence the risk of infections observed in the study. Also, we are not sure if GBS is a recurrent condition; if so, would a previous history of GBS need to be documented? Further, any other condition that might influence the risk or symptoms of GBS would be worth collecting.

Response: Thank you for this suggestion but unfortunately we could not collect reliable evidence of recent history of antibiotics in the SVPE treated patients with GBS. In the far majority GBS is a monophasic disease and there are now risk factors known that can be used the risk for developing GBS.

* While we appreciate the authors enrolling a control group of patients, we wondered if they would be able to leverage any existing data sources (e.g. national database) to obtain relevant information as well.

Response: Unfortunately no such databases or registries are available in Bangladesh. Therefore we included the control group to be able to estimate the background incidence of infections in this particular hospital were the SVPE study is conducted.

* The authors indicate having recruited 15 patients, but it is unclear if between the time of submitting the protocol and now, whether they have been able to recruit more participants. If so, they should update the manuscript. If not, should they be concerned about not recruiting a sufficient amount of patients? Should attainment of the recruitment goal not be a feasibility outcome?

Response: We have completed recruitment of 20 patients with GBS for SVPE.

* Do the authors expect any loss to follow-up? If so, they should indicate strategies to deal with this in the analyses.

Response: We do not expect loss of follow-up. Instead based on our previous experience patients with GBS in Bangladesh are very cooperative.

* It was unclear if patients' data was encrypted. The authors should clarify.
Response: Thank you for pointing us at this omission. Indeed, the data indeed were encrypted and we have specified this in the new version of the manuscript (page 13, line 312-13).

* While we appreciate the study has received ethics approval, we wondered what would happen if the study is terminated prematurely for safety reasons, and participants receiving SVPE are unable to afford the standard treatment.

Response: We planned to include GBS patients for SVPE who cannot afford IVIG or standard PE, who are >90% as per our prospective cohort study. Fortunately we have completed the SVPE study and we attained the safety and feasibility endpoints. We look forward for the RCT of the SVPE efficacy trial.