Author’s response to reviews

Title: ASSESSING THE EFFICACY AND SAFETY OF MAGNESIUM SULFATE FOR MANAGEMENT OF AUTONOMIC NERVOUS SYSTEM DYSREGULATION IN VIETNAMESE CHILDREN WITH SEVERE HAND FOOT AND MOUTH DISEASE

Authors:

qui phan (phantuqui@gmail.com)
Lam Khanh (lampk@oucru.org)
Truong Khanh (truonghuukhanh@gmail.com)
Trieu Huynh (huynhtrieu82@gmail.com)
Giang Pham (chuotchui1007@yahoo.com)
Bich Nguyen (drngocbich@yahoo.com.vn)
Quyen Tran (bstranthanhquyen@gmail.com)
Vuong Thien Huynh (vuonghuynh_vn@yahoo.com)
Tien Nguyen (ntmytienmdc@yahoo.com)
Thoa le (thoalephan@gmail.com)
Nhan Le (drnhanbvhidong1@yahoo.com.vn)
Saraswathy Sabanathan (saras.whitehorn@googlemail.com)
Rogier Doorn (rvandoorn@oucru.org)
Tan Le (tanlv@oucru.org)
Toan Nguyen (toannd@oucru.org)
Laura Merson (laura.merson@ndm.ox.ac.uk)
Dung Nguyen (dungntp@oucru.org)
Ronald Geskus (rgeskus@oucru.org)
Hung Nguyen (drthanhhung@gmail.com)
Author’s response to reviews:

The Editor

BMC Infectious Diseases

Dear Editor,

Re: Assessing the efficacy and safety of magnesium sulfate for management of autonomic nervous system dysregulation in Vietnamese children with severe hand foot and mouth disease

On behalf of all the authors I would like to thank you and the reviewers for taking time to review our manuscript. The various comments were very helpful for the revision of the manuscript, which I am pleased to submit for your consideration. Changes to the manuscript are highlighted in yellow.

Below this letter I have listed the individual comments with our responses in italics. Please let me know if you need any further information.

Yours faithfully,

Dr Phan Tu Qui (Corresponding Author)
Head of Paediatric Intensive Care Unit
Hospital for Tropical Diseases
Ho Chi Minh City, Vietnam
phantuqui@gmail.com
Editor’s Comments:

1. The use of placebo controls in clinical trials remains controversial. Are parents well-informed that the trial included placebo without any treatment?

Response: At the time of recruitment to the clinical trial, for those with Stage 1 hypertension the Vietnamese national guidelines recommend no specific intervention. Supportive therapy together with close observation, including invasive blood pressure monitoring, are recommended, so that milrinone can be commenced within 1 hour if Stage 2 hypertension develops. Thus, for the majority of study participants the intervention with MgSO4 or placebo was commenced at a time when the child would not normally be receiving any antihypertensive treatment; other therapy was given in accordance with the MoH guidelines and all study participants were observed very closely to assess the safety (and potential efficacy) of intervening with an antihypertensive agent at an earlier stage than usual. For individuals presenting with Stage 2 hypertension systems were put in place to ensure that study treatment commenced within 30 minutes of admission and that milrinone was added within a further 30 minutes if there was no improvement. All the IRBs involved agreed that, provided the MoH recommended treatment was started within 1 hour (if necessary), that this time frame would be consistent with what happens in practice for severe HFMD cases.

These details were explained to the family twice – once during the initial screening/assessment prior to signing the informed consent form (ICF), and then again within 12-24 hours of enrolment, at which time the option to withdraw from the study was clearly articulated. We recognize that having a child in ICU is extremely stressful for family members and we wanted to be sure that the parent/guardian had fully understood the information presented at study enrolment. However, no child was withdrawn from the trial by the family after the second explanation. Full details of the protocol, including specific information on the consent procedure and copies of the ICF, has been published in Trials (2016) 17:98

These points have been clarified in the abstract (page 3, lines 4-8), introduction (page 5, lines 16-21), and methods (page 8, lines 4-13 and 18-22)
2. Tables 1 and 5. Please explain the numbers and percentages (in bracket). Big proportions of them are not lab-confirmed HFMD?

Response: The summary statistics in Tables 1 and 5 are absolute count (%) for categorical variables and median (range) for continuous data, as explained in the table footnotes. While the laboratory diagnostic yields for HFMD vary between studies, our study had an overall diagnostic yield of 70% (for the prospective trial participants) and 82% (for the retrospective study participants), which is within the same range as previous reports (references: PMID: 28367766, 30550944). Many factors may contribute to negative RT-PCR results, including the quality of the specimens obtained and timing in the illness evolution.

To elaborate on this we have added some text to the result sections, page 12 lines 19 now read “Enteroviruses were detected by generic RT-PCR (28) in 18/26 (70%) of the cases overall, which is within the same range as previous reports for clinically diagnosed HFMD, with EV-A71 confirmed by specific RT-PCR (29) in 9/14 (64%) MgSO4 recipients and 4/12 (33%) placebo recipients.”

3. Although the efficacy of MgSO4 cannot be demonstrated, perhaps the authors can discuss about its effects on the patients. It seems that the expected effects were not achieved.

eg. No competition with calcium ions? (Fig 3).

No influence on BP?

Effects on nitric oxide and catecholamines?

Response: While we were not able to demonstrate a clear effect on blood pressure (SBP, MAP) with the infusion regimen we used, we did see a reciprocal effect on plasma Ca levels, as shown in Figure 3 and referred to in the section on therapeutic monitoring. In this respect the colour coding for Figure 3 appears to have caused some confusion, so this has been changed.

We performed serial plasma and urine catecholamine measurements as part of the RCT, but had not included them in the previous submission. However, we have now included this information in the supplementary material.

Additional text has been added to the methods (page 9, line 6-8, and page 11, line 8-10), results (page 13, line 10-18), and discussion (page 15, line 20) and the catecholamine data are presented in Supplementary Figure 1.
Reviewer 1

1. Study design was not clear. Rationale: hypothesize early use of MgSO4 (when hypertension due to ANS dysregulation first becomes apparent), might control cardiovascular instability more effectively and prevent progression to severe disease. This refer to the use of MgSO4 in the earlier stage of the disease rather than the more severe form of HFMD. Therefore, the definition was not clear.

Response: Please see response to Editor’s Comment 1 above. According to the Vietnamese MoH guidelines for HFMD, although patients who present with ANS dysregulation are all considered to be severe, hypertension is classified into two categories. Patients with Grade 1 hypertension (defined in accordance with the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents) should be closely observed in an HDU/ICU setting with general supportive care, but antihypertensive treatment is not recommended unless Grade 2 hypertension develops or there are specific severe features. In the trial we randomised the majority of patients to MgSO4 or placebo at the Stage 1 hypertension level, i.e. at an earlier stage in the illness evolution than currently recommended by the guidelines, to see if progression to Stage 2 hypertension could be prevented.

These points have been clarified in the abstract (page 3, lines 4-8) and introduction (page 5, lines 16-21).

2. The study was designed to be a randomized, double-blind, placebo-controlled trial, but a retrospective "observational cohort" was also reviewed while waiting for ethical approval and funding. Both of these are indeed two separate studies, thus by combining these two together, it was quite confusing.

Response: MgSO4 was being used as second line therapy (ie. after failure of milrinone for Stage 2 hypertension) in the PICU at HTD while the study protocol was being developed and ethical approvals were being sought to intervene at an earlier stage (Stage 1 hypertension) of the ANS dysregulation. This process took more than a year and by the time the RCT commenced the regional epidemic of HFMD was coming to an end. Therefore, after stopping the RCT on the grounds of futility, we went back to the files of the patients who had received open label MgSO4 in the preceding years, to review the safety and efficacy of this novel treatment when used as part of clinical care. Carrying out formal research during an epidemic of potentially serious disease is very difficult and we feel that all information that is available on a potential therapy should be made publicly available so that others may decide whether to consider using this treatment if/when the next epidemic of severe HFMD occurs.
3. The sample was said to be 190, and this was mentioned only at the discussion section. However, at the end there was only 26 patient were recruited. The reason given was because of the drop of cases of HFMD after 2014, and this was described as “futile”. The study power was too small to be able to draw any meaningful conclusion for this current RCT.

Response: We did not describe the full details of the original sample size calculation for the RCT as these have already been published with the full trial protocol (Trials. 2016;17:98.). Actually, the sample size of 190 is mentioned in the introduction (page 7, line 2) and the reference is provided. Also we state clearly in the discussion section that, given the small number of patients enrolled in the RCT and the low event rate, no conclusions can be drawn on efficacy.

2. Study control was inappropriate with a placebo. This is a serious study bias, and it was ethically incorrect to randomize to a placebo when the hypertension needs an anti-hypertensive to optimize the blood pressure.

Response: Please see the response above to Editor’s Comment 1. The majority of these children did not have hypertension severe enough to warrant intervention with any drug at the time of randomization. The study was conducted in full compliance with ICH-GCP, after detailed review by three Ethics Committees, including the ECs of the Vietnamese Ministry of Health, the study hospital, and the Oxford University Tropical Research Ethics Committee.

Simon Nadel (Reviewer 2):

1. The levels of serum Mg in the control patients reported appear to be very high - much higher than would be expected in patients untreated with Mg and it is not clear why this should be unless they had received supplemental Mg. Maybe the authors could explain this.

Response: Actually, none of the Mg levels in the placebo recipients were high., We feel that the colour coding for Figure 3 has caused confusion here, so this has been changed.
2. Also, the dose used in this study was 30-50mg/kg per hour for 72 hours, where most paediatricians are used to a dose of 40mg/kg repeated once or twice only (for acute asthma). It may be useful for the authors to explain the dose used in this study more explicitly so clinicians can understand the dosing and safety concerns.

Response: For acute asthma, MgSO4 is used intermittently as an emergency intervention. However, occasionally it is used continuously for severe asthma (eg in adults MgSO4 has been used continuously at 2 gm per hour for 1-3 days). In HFMD, ANS dysregulation typically persists for 2-3 days, and since we aimed for stable blood pressure control over this period we elected to use the regime that we are familiar with for neonatal tetanus, another condition where ANS dysregulation persists for some time.

An additional sentence has been added to the introduction (page 5, line 9-10) clarifying the time period during which ANS dysregulation typically persists, when we wished to have stable blood pressure control. Additional text has also been added (page 6, line 8) giving the details of the MgSO4 regimen used at our hospital for neonatal tetanus.