Author’s response to reviews

Title: Clinical Spectrum of Rhabdomyolysis Presented to Pediatric Emergency Department

Authors:

Chun-Yu Chen (116984@cch.org.tw)
Lu-Lu Zhao (zhaolulu2001@tzuchi.com.tw)
Wen-Chieh Yang (v1004@hotmail.com)
Yu-Jun Chang (83686@cch.org.tw)
Kang-Hsi Wu (d5284@mail.cmuh.org.tw)
Han-Ping Wu (arthur1226@gmail.com)

Version: 3 Date: 24 July 2013

Author’s response to reviews: see over
July 24th, 2013

Dear Editor-in-Chief,

Enclosed you will find the revised manuscript entitled "Clinical Spectrum of Rhabdomyolysis Presented to Pediatric Emergency Department" (MS: 1185264627891119). In this revised manuscript, we have addressed the reviewers’ concerns and made the mandatory style changes to meet the style of the journal: BMC Pediatrics. We wish to thank you for allowing us to resubmit this revised manuscript and hope that you will now find it acceptable for publication in the BMC Pediatrics. I would very like to make any further revision followed by your comments and it would be highly appreciated if this manuscript could be smoothly run to publication process.

We thank for your assistance in improving our manuscript. Looking forward to hearing from you soon.

Best regards,

Han-Ping Wu, MD, PhD
Director, Department of Pediatrics
Taichung Tzuchi Hospital
Tel: +886-4-36060666 ext 3117
Fax: +886-4-36021123
Dear reviewers:

Enclosed is our revised manuscript (Clinical Spectrum of Rhabdomyolysis Presented to Pediatric Emergency Department). We appreciate the constructive comments of your review and have revised the manuscript. Below are our replies to the reviewers:

Itemized comments

Reviewer #1: Minor revisions

Q1: It may not be correct to state that the most important complication is ARF as arrhythmias, shock and DIC may be just as important. It may be commonest or best recognised.

Answer:
Thanks for your recommendation. We have revised the sentences based on your opinion in our revised manuscript.

On page 5, line 11.
As we know, ARF is the most recognized complication of rhabdomyolysis.

Q2: It would probably be more acceptable to change Acute Renal Failure to the more acceptable/current nomenclature of Acute Kidney Injury.

Answer:
Thanks for your recommendation. The term acute kidney injury (AKI) has been proposed to encompass the entire spectrum of the syndrome from minor changes in renal function to requirement for renal replacement therapy (RRT). However, in our study, we focused exclusively on patients with more severe renal function impairments (renal failure or on those who received dialysis). So, we aimed to survey the related factors and clinical spectrum in patients with more severe clinical condition as ARF than those with AKI. In addition, we compared with the previous studies which also focused on children with rhabdomyolysis and used the term of ARF as a complication. As the above reasons, we chose to use the term of ARF in our investigation.

Q3: No mention is made of family history in the paediatric patients to exclude Hereditary/Acquired which is more commonly seen in Adults.

Answer:
In our study, we excluded patients who had a documented history of muscular dystrophy or other metabolic muscle disorder. According to the medical records, we did not find any positive family history in those patients. We added the statements of family history in our revised manuscript.

On page 7, line 3.
The following information was obtained from the medical records of each patient: age, gender, family history, ........

Q4: Page 8 - spelling errors or phrase that does not make sense - 3/4 way down page - "oFor yje cause of exercise"

Answer:
Thanks for your correction. We have corrected the spelling errors in our revised manuscript.

On page 9, line 16-17.
For the 6 patients where involvement was caused by exercise, all of them were in the adolescent group.

Quality of written English: Needs some language corrections before being published.

Answer: Thanks for your recommendation. Our manuscript has been thoroughly and professionally edited by a native English speaker.
Reviewer #2:

Q1: Abstract:
The conclusions should be shortened and don't repeat those presented in “Results”. Suggest move “..not identify any reliable predictors of ARF or need for RRT” to “Results” part.

Answer:
Thanks for your recommendation. We have shortened the conclusions and removed the repeat statement presented in “Results”. And according to the professor’s suggestion, we move “..not identify any reliable predictors of ARF or need for RRT” to “Results” part.
“The incidence of ARF associated with rhabdomyolysis in our study was 8.1 % and no child needed for RRT.” was deleted in conclusions.
“We did not identify any reliable predictors of ARF or need for RRT.” was moved to “Results” part.

Q2: Results:
p. 8, last sentence of the first paragraph, “OFor yje (?) cause of exercise, all of them were in the adolescent group.” Should be revised.

Answer:
Thanks for your correction. We have corrected the spelling errors in our revised manuscript.
On page 9, line 16-17.
For the 6 patients where involvement was caused by exercise, all of them were in the adolescent group.

Q3: Discussion:
p. 11, last sentence of the first paragraph, “In patients caused by trauma, car accident was the major cause and none of these 6 patients complicated with ARF, including a 4-year-old girl with major trauma.” Suggest be moved to “Results” part.

Answer:
Thanks for your recommendation. We have moved “In patients caused by trauma, car accident was the major cause and none of these 6 patients complicated with ARF, including a 4-year-old girl with major trauma.” to “Results” part.

Page 9, line
For the traumatic causes, traffic accidents (n = 6, 100%) were the major cause and none of these 6 patients were complicated with ARF, including a 4-year-old girl with major trauma.

Q4: Table 1. Suggest add a column of “total” and for each item, just keep one line (of “yes” and delete the redundant line)

Answer:
Thanks for your recommendation. We have adjusted the Table 1, according to Professor's concise suggestion.

Quality of written English: Needs some language corrections before being published

Answer:
Thanks for your recommendation. Our manuscript has been thoroughly and professionally edited by a native English speaker.
Q1: Major comments
This is a retrospective case series of a pediatric population presenting at the emergency department of a university hospital. The authors collected 37 children in 6 years. This number is rather small for such a long period and for a condition that is not so extremely rare. The detection of the patients was performed via ICD9 codings. One may wonder if this approach is effective in detecting this condition. So how representative is this small population for the condition of rhabdomyolysis in children? The authors don’t either mention how many patients were screened. The results section doesn’t comprise a clear baseline description of the study population. The results section doesn’t comprise all the parameters mentioned in the methods section. The English language needs revision (see below).

Answer:
Thanks for your recommendation. In our study, we included only children who presented to pediatric emergency department (ED) with rhabdomyolysis and initial CPK levels > 1000 IU/L. Other children with rhabdomyolysis who did not visit pediatric ED or were not diagnosed at pediatric ED were excluded. In addition, we think children with rhabdomyolysis who suffered from mild symptoms and signs may not choose pediatric ED for treatments and first visited the outpatient clinics. The patients with outpatient clinics care were also excluded. Due the relative strict inclusion and exclusion criteria, we had a small population for the condition of rhabdomyolysis in children presenting to the ED. We described the screening process and comprised a clear baseline description of the study population in the Methods and Results sections. Besides, all the parameters mentioned in the Methods section were comprised in the Results section.

Q2: Minor comments
Introduction
§ Line 10: ‘Previous studies reported that CK levels greater than 1000 U/mL sent to the emergency department (ED), the prevalence of ARF was 5%’; this sentence is incomprehensible and must be rephrased

Answer:
Thanks for your recommendation. We have rephrased the sentence. Page 5, line 11-13
In a larger study of 191 children with a CK level greater than 1000 U/mL who were
sent to the emergency department (ED), the prevalence of ARF was 5%.\textsuperscript{11}

**Q3:** Line 12: ‘However, the related researches about rhabdomyolysis in children presented the pediatric ED are still rare’; better presented to the pediatric ED?

**Answer:**
Thanks for your correction. We have corrected the sentence according to the professor’s suggestion. Page 5, line 13-15

“However, after the search of the related literature, it would appear that research discussing rhabdomyolysis in children that also presented to the pediatric ED is still rare.”

**Q4:** Methods

§ How many patients were screened, how many were excluded and what percentage of the population was finally included?

**Answer:**
Thanks for your recommendation. We have described the screening process in the methods section. Page 6, line 10-16
We reviewed 445 medical charts of all eligible patients during a 6-year period from January 2006 to December 2011. Four hundred and eight patient charts were excluded (for having initial serum CK levels < 1000 U/L or showing a documented history of muscular dystrophy or other metabolic muscle disorder, a history of myocardial infarction, a history of chronic kidney disease, rhabdomyolysis that developed after admission to the hospital due to a coexisting condition or iatrogenic complication, or ages greater than 18 years). In total, 37 (8.3%) of the 445 patients were included into this series.

**Q5:** Results

§ Since the authors don’t mention how many children presented during the study period at the emergency department, it is impossible to know the incidence of rhabdomyolysis in children.

**Answer:**
Thanks for your recommendation. We have mentioned the number of children presented during the study period at the emergency department in the results section. Page 9, line 2
During the 6-year study period, about 165,000 children presented to our pediatric ED.

Q6: Line 13: ‘Of the cause of exercise, all of them were in the adolescent group.’; must be reformulated

Answer:
Thanks for your correction. We have corrected the spelling errors in our revised manuscript.
On page 9, line 16, 17.
For the 6 patients where involvement was caused by exercise, all of them were in the adolescent group.

Q7: Line 21: the authors should mention units when reporting levels of lab-values

Answer:
Thanks for your recommendation. We have mentioned units when reporting levels of lab-values.

Q8: Line 24: ‘The serum level of myoglobin was checked less than half of patients in our study’; must be in half of our study

Answer:
Thanks for your correction. We have corrected the sentence according to the professor’s suggestion on page 10, line 11-12.

The serum level of myoglobin was checked in half of our study patients.....

Q9: Line 26: ‘Analysis of differences in laboratory values between those with ARF and without ARF revealed that only BUN and Cr were significant factors.’; what do the authors mean by this phrase? instead better state that BUN and Creatinine are significant higher in the ARF group compared to the non-ARF group

Answer:
Thanks for your recommendation. We have corrected the sentence according to the Professor’s suggestion on page 10, line 10, 11.
BUN and Creatinine were significantly higher in the ARF group compared to the non-ARF group.

Q10 § The authors mention in the methods section also treatment characteristics (fluid administration, bicarbonate administration), there is no mention of any of this in the results section

Answer:
Thanks for your recommendation. We have stated the treatments in the Result section on page 9, line 18-19.

All cases received a large amount of fluid administration within the first 24 hours, but no one required bicarbonate therapy.

Q11 § Line 23: how do the authors explain that the peak level of CK and myoglobine is higher in the non-ARF group compared to the ARF group (table 4)

Answer:
Thanks for your recommendation. There are some possible reasons that lead to the peak level of CK and myoglobine is higher in the non-ARF group compared to the ARF group in our report. First, the small sample size was included in ARF group (3 patients). Second, the laboratory data were not regularly followed up in some patients, lead to the definite peak data were difficult to record. Third, the pathophysiology of rhabdomyolysis is heterogeneous. First, there was a small sample size included in our study which only contained 3 patients with ARF. Second, the laboratory data were not regularly followed up in all patients, and this may lead to the difficulty in determining the definite peak data. Third, the pathophysiology of rhabdomyolysis is heterogeneous and this may cause the different appearance of laboratory data based on different etiologies of rhabdomyolysis. Based on previous studies, Watemberg et al found no relationship between CK level and risk of renal failure. Fernandez et al found there was no difference in peak CK levels between the ARF and the non-ARF groups. Finally, the definite relationship between peak CK or myoglobine and ARF caused by different etiologies of rhabdomyolysis is not clear enough. Therefore, we added the statements in the Discussion section in our revised manuscript.

Discussion
Q12 § Line 13: This sentence should be rephrased: ‘In our series, infections
accounted for the major etiology caused rhabdomyolysis (59.5%), especially in patients was 9 years or younger,…'

Answer:
Thanks for your suggestion. The sentence was rephrased on page 11, line 14-17.

In our series, infections accounted for more than half (59.5%) of the causes of rhabdomyolysis, followed by trauma (16.2%) and exercise (16.2%). In patients that were 9 years old or younger, infections was the most common cause of rhabdomyolysis and accounted for 19 of 21 patients in this age group.

Q13: The authors mention the month distribution of rhabdomyolysis in their results section. Why is this mentioned and since this is included, how do they explain the peak distribution in may?

Answer:
In our revised manuscript, we have deleted Figure 1 and omitted the related statements. As the same opinion as yours, the other reviewers have suggested that Figure 1 should be deleted and comments in results section need to be deleted. So, we have deleted the related part in the Results section. Thanks for your recommendation.

Q14: Line 21: ‘In patients caused by trauma, car accident was the major cause and none of these 6 patients complicated with ARF, including a 4-year-old girl with major trauma.’ Should also be rephrased.

Answer:
Thanks for your recommendation. The sentence was rephrased on page 12, line 3-5.

In these 6 patients that presented with rhabdomyolysis caused by trauma, traffic accident was the major cause and none of these 6 patients were complicated with ARF.

Q15: The authors do not address in their conclusion the weak points of their study; retrospective case series, small sample size…

Answer:
Thanks for your recommendation. We have addressed the limitation of our study in conclusion section on page 14, line 12-18.
The present study has a number of limitations. First, in a retrospective single center review of medical records, some details of history and physical examinations may not be rigorously documented. Second, the relatively small sample size may fail to address definitely predictive factors of ARF. Finally, the laboratory data were not regularly followed up in some patients and the definite peak data was therefore difficult to record. These limitations may have led to some bias in analyzing the clinical spectrum of rhabdomyolysis in children who presented to the ED.

Q16 The tables are instructive, but the authors should put percentages between brackets to enhance readability (table 2)

Answer:
Thanks for your recommendation. We have put percentages between brackets to enhance readability (table 2).

Q17 Figure 1: how do the authors explain the peak prevalence in May since they spend a figure to his item?

Answer:
In our revised manuscript, we have deleted Figure 1 and omitted the related statements. As the same opinion as yours, the other reviewers have suggested that Figure 1 should be deleted and comments in results section need to be deleted. So, we have deleted the related part in the Results section. Thanks for your recommendation.

Q18 Figure 2: very difficult to read, too much information, maybe better in bar graph?

Answer:
Thanks for your recommendation. We have adjusted the Figure 2 according to the professor’s suggestion.
Reviewer #4:

Major revision:

Q1- the authors reported in the methods section that .....amount of fluid administered within the first 24 hours.... will be reported. However, there are no data in the results section on the therapy of these children. This should be specified and in the discussion section the available therapy should be detailed more, so that it might be understandable to non-confident readers.

Answer:
Thanks for your recommendation. We have added the statements of treatments in the Result and Discussion sections.

Q2- Figure 1 should be deleted and comment in results section deleted.

Answer:
Thanks for your recommendation. We have deleted the Figure 1 and comment in results section according to the professor’s suggestion.

Q3- Figure 2 is not easily understandable. Please, make it clearer or delete.

Answer:
Thanks for your recommendation. We have adjusted Figure 2 to make it clearer. (New Figure 1)