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PEER-REVIEW REPORT WITH AUTHOR'S ANSWERS

Name of journal: *World Journal of Methodology*
Manuscript NO: 100840
Title: The remarkable effects of the ionized medical water Asea® in 3 boys with Duchenne muscular dystrophy
Provenance and peer review: Invited Manuscript; Externally peer reviewed
Peer-review model: Single blind
Reviewer's code: 08027840
Position: Peer Reviewer
Academic degree:
Professional title:
Reviewer's Country/Territory: China
Author's Country/Territory: Romania
Manuscript submission date: 2024-08-27
Reviewer chosen by: Hong-Xin Jiang
Reviewer accepted review: 2024-09-24 11:13
Reviewer performed review: 2024-10-03 01:06
Review time: 8 Days and 13 Hours

SPECIFIC COMMENTS TO AUTHORS

REVIEWER: "Firstly, I would like to thank Professor Roxana-Maria Nemes for her attention to Duchenne Muscular Dystrophy (DMD), a rare disease, and for her bold and meaningful exploration of treatment options. DMD is a fatal X-linked recessive genetic disorder caused by mutations in the DMD gene that encodes for the dystrophin protein. It is characterized by progressive neuromuscular weakness and atrophy, which gradually affects the heart and respiratory muscles, ultimately leading to heart failure and respiratory failure. Currently, conventional clinical treatments are symptomatic and cannot improve the outcome of patients dying from early-onset heart failure and respiratory failure. The commonly used clinical treatment strategies include corticosteroids and supportive treatments such as vitamin nutritional support therapy. The small molecule miRNA targeted therapy against anti-atrophy protein expression is expensive and has only moderate effects."

AUTHOR'S ANSWER:
I also want to thank the reviewer for the time and patience to read our paper and for this good concise description of DMD.

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REVIEWER: "This paper reports the use of a dietary supplement to observe the corresponding indicators of rhabdomyolysis in three children, resulting in a decrease in the indicators of rhabdomyolysis. Firstly, this is a very meaningful attempt, observing the reduction of DMD rhabdomyolysis through the application of ARS, providing interesting clinical data for the clinical treatment of DMD. "

AUTHOR'S ANSWER:
I want to thank the reviewer for this appreciation on our attempt to describe the effects of ARS in these 3-case series of boys with DMD.

REVIEWER: "As a case report, Although the specific mechanism is unclear, it is not clearly related to cellular ROS damage. If one wishes to explain the mechanism of reducing DMD rhabdomyolysis through the application of ARS, simply detecting muscle indicators such as CK-MB is too simplistic. It is recommended to include indicators of the corresponding pathways in the detection indicators."

AUTHOR'S ANSWER:
I've added the following paragraphs in the Discussions section:
In vitro studies (mainly Samuelson (G.L.) (2010). White Paper on In-Vitro Bioactivity of ASEA™ Related to Toxicity, Glutathione Peroxidase, Superoxide Dismutase Efficacy and Related Transcription Factors) clearly showed that ARS is a very potent selective NRF2 activator, thus a very potent (indirect) antioxidant, by increasing (by up to 8-fold!) the cellular concentrations of *endogenous antioxidant enzymes* (**EAE**) (like *glutathione synthase*, *SOD* etc): the studies conducted *in vivo* also support this main pharmacological mechanism of ARS. That is why we've considered that the most probable explanatory hypothesis on the significant drop in all the measured rhabdomyolysis markers (CK, CK-MB, LDH, AST, ALT) is the potent NRF2-activating mechanism of ARS which strongly activates many types of EAE that all neutralize a large quantity of ROS from all the muscular cells (including the cardiomyocytes!), decreasing the chronic muscular inflammation (including the rhabdomyolysis rate).

Given that all the rhabdomyolysis labs were paid by the parents of these DMD child-patients, it would had been too expensive for those parents (given the low average monthly income of Romanians) to cover the additional labs needed for clearly demonstrating the NRF2 activating effect of ARS in vitro like the *plasmatic level of SOD*, the *total antioxidant capacity of serum*, *the*

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plasmatic level of malondialdehyde, the *intracellular level of the reduced glutathione* etc. These preliminary results on this DMD 3-case series surely deserves a future grant to extensively study more DMD patients and use an extensive panel of labs (including antioxidant markers), as also proposed later on in this section.

REVIEWER: "At the same time, as a clinical experimental treatment, the observed number of cases is too small, there is no control group, and there is no detailed explanation of the medication used in all cases. Also, when discussing the clinical efficacy and mechanism, the references cited are not appropriate and need to be revised."

AUTHOR'S ANSWER:

I've also added the following paragraphs in the Discussions section:

The main explanation of the low number of DMD patients reported here (with no control group) is that DMD is relatively rare and DMD child-patients whose parents refuse corticosteroids (but accept ARS as a compensatory adjuvant) are very rare in Romania: furthermore, very few Romanian medical doctors know about ARS and much fewer have experience in prescribing ARS as an adjuvant dietary supplement.

In the main table of this paper, we have given many details and explanations of the adjuvant medication and other non-pharmacological therapies used in all 3 DMD cases: however, we had to synthesize the huge quantity of data, so that not to overwhelm the potential readers with a very large article.

Unfortunately, the cited papers on ARS were very hard to find and to be cited here, because many references don't have DOIs (as not being published in peer-review journals).