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CORRESPONDENCE

Letter to the editor: Episodic-precipitant–induced hepatic encephalopathy treatment: Look at new and old precipitants!

To the editor,

We read with interest the article by Jain et al., in which the researchers conclude that the combination of L-ornithine L-aspartate (LOLA) with lactulose and rifaximin was more effective than lactulose and rifaximin in improving HE and mortality.[1]

The researchers enrolled 134 patients with episodic HE, a condition characterized by the presence of a precipitant. In fact, both in the treatment arm (62 of 67) and control group (64 of 67), at least one precipitant was found and treated with the appropriate medical therapy. Therefore, amelioration on the mental state is certainly a result of two parallel approaches: early identification and resolution of the precipitant and effect of the combined treatment proposed. The analysis of the data should not overlook the important role of treating precipitants, both for HE resolution and mortality. In fact, mortality is certainly influenced by the copresence of potentially fatal determinants, which are also known precipitants of HE. Moreover, a competitive risk analysis for mortality, considering liver transplantation, could be useful for better clarifying the role of some risk factors or given treatments on mortality. Furthermore, several other conditions are now well known as potential risk factors for HE: shunts and muscular alterations that require a different and non-"classical" management.

The design and performing of randomized controlled trials (RCTs) on episodic HE is extremely challenging, given that they are still based on a "therapeutic approach," the only known management of the precipitant(s) sufficient to resolve HE; therefore, effect of the active treatment and the role of stopping the precipitant can be difficult to determine To avoid these confounding factors, maintaining a standard and well-defined *a priori* treatment in both groups and adding the treatment under investigation in the study group only and a placebo in the control group could be useful. On the contrary, in the case of a positive result, the outcome could be considered as the effect of a combined treatment's approach, and there is no need to suggest the use of the new treatment alone instead of the existing treatment.[2] RCTs should also have an adequate sample-size calculation. In this case, this was performed in a not readily translatable work. Moreover, the same group showed a 76% resolution of HE in an RCT comparing lactulose and rifaximin (the control group of this article) with lactulose alone.[3] This rate could be considered as the expected effect of treatment in the control group, and this hypothesis on an additive effect of LOLA should be used for sample-size calculation in future RCTs.

CONFLICT OF INTEREST

Nothing to report.

AUTHOR CONTRIBUTIONS

Conceptualization and manuscript draft, critical revision for important intellectual content, final approval: Lorenzo Ridola. Critical revision for important intellectual content: Stefania Gioia, Silvia Nardelli, Jessica Faccioli and Oliviero Riggio.

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