Letter to the Editor Regarding "Low Back Pain Management with a Combination of Uridine Triphosphate, Cytidine Monophosphate, and Hydroxocobalamin: A Systematic Review and Meta-Analysis"

Carta ao Editor sobre "Tratamento da dor lombar com uma combinação de trifosfatodeuridina, monofosfato de citidina e hidroxicobalamina: Uma revisão sistemática e metanálise"

Enilton de Santana Ribeiro de Mattos[1,2,3] Alex Guedes[1,3] Eduardo Silva Reis Barreto[3] César Romero Antunes Júnior[3]

[1] Department of Experimental Surgery and Surgical Specialties, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, BA, Brazil
[2] Department of Orthopedics and Traumatology, Hospital Santo Antonio, Organizações Sociais Irmã Dulce, Salvador, BA, Brazil
[3] Orthopedics and Traumatology Research Group, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, BA, Brazil

Address for correspondence Enilton de Santana Ribeiro de Mattos, Av. Araújo Pinho 421, Canela, CEP 40110-150, Salvador, BA, Brazil (e-mail: eniltonmattos@hotmail.com).

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Dear Editor,

It is with great interest that we write, after reading the article by Mibielli et al.,[1] "Low back pain management with a combination of Uridine Triphosphate, Cytidine Monophosphate, and Hydroxocobalamin: A Systematic Review and Meta-Analysis." We congratulate the authors for investigating a subject of such clinical importance.

We feel the need to communicate our concerns about the methodology used, which, in our view, compromises the validity of the evidence provided by this meta-analysis.

The quality of the evidence, as assessed by the authors using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria,[2] is classified as low to very low. Therefore, the article's conclusion, which adds "efficacy and safety" to the combination of uridine triphosphate, cytidine monophosphate, and hydroxocobalamin for the treatment of low back pain associated with nerve root compression, constitutes an extrapolation unsupported by the evidence presented.

The meta-analysis of randomized clinical trials showed a nonsignificant result ($p = 0.15$) for pain improvement, with a 95% confidence interval that included zero (−3.22 to 20.76); this, per se, indicates that the measured effect cannot be distinguished from chance. In addition, the statistical heterogeneity is substantially high: $I^2 = 100\%$, a warning sign that, in our view, has not been properly addressed by the authors. The most likely explanation for this variance is that the studies inappropriately combined clinically distinct patient populations: two studies measuring chronic neuropathic pain (radiculopathy) were pooled with another study of acute and nonspecific low back pain. These are different conditions, with different pathophysiology and prognosis, and the combined effect estimate is not clinically adequate.

Additionally, the design of the primary studies limits interpretation. The use of vitamin B12 as an active control, rather than an inert placebo, does not allow evaluation of the combination's absolute efficacy, but only of the marginal benefit of nucleotides. The issue becomes even more critical

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given that the meta-analysis grouped randomized clinical trials with different comparators, since one study used a B vitamin complex (B1, B6, B12) as a control rather than B12 monotherapy.

In addition, the apparent lack of prior registration on platforms such as the Prospective Register of Systematic Reviews at York University raises concerns, as this step is an important aspect for promoting transparency and open science, reducing reporting bias, and preventing unintentional duplication of research.[3]

The non-formal assessment of the risk of bias in the included data is an additional concern, as it is a fundamental step recommended by consolidated guidelines that recommend using tools such as Risk of Bias 2.[4] In the absence of this analysis, the primary data are of uncertain reliability.

We believe that the results of the study in question should be interpreted with extreme caution. We believe that these observations may contribute to improving academic dialogue and future publications.

Data Availability

Data will be available upon request to the corresponding author.

Authors' Contributions

ESRM and AG: conceptualization, critical review of the project, writing – original draft. ESRB and CRAJ: data curation and application of instruments.

Conflict of Interests

The authors have no conflict of interests to declare.

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