Implications of the KIWE trial for low-income and lower-middle-income countries

We read with interest the Article reporting findings of the KIWE trial,[1] which compared the ketogenic diet with antiseizure medications in infants with drug-resistant epilepsy. The trial did not show a significant difference between diet and medication in terms of efficacy and tolerability; however, we wish to highlight several concerns.

Given that 50% of the study cohort had infantile epileptic spasms syndrome (IESS), we trust that the findings are relevant to management practices of patients with IESS in low-income and lower-middle-income countries.[2] The trial found a low clinical response in infants on the ketogenic diet in terms of achieving seizure freedom at 8 weeks.[1] However, in this era of precision medicine, characterisation of the electroclinical syndrome and the underlying cause or genetic diagnosis in the children who became seizure-free in both groups would be crucial for a better understanding of these findings.[3] Electroclinical remission is a key aim in treating IESS, while a clinical response to either the ketogenic diet or antiseizure medications might be an over-representation of efficacy.

See Online for appendix

The dose and choice of antiseizure medications in the comparison group were not specified, but they could have influenced outcomes. Antiseizure medications can have variable response rates (eg, 42% electroclinical response with nitrazepam) in patients with IESS, as shown in prospective studies.[4,5] Although indirect comparison is not appropriate, these studies suggest that a trial comparing the ketogenic diet with other antiseizure medications might be enticing.

A long treatment lag after diagnosis and a structural cause of the epilepsy, particularly in patients with IESS in low-income and lower-middle-income countries, can preclude a therapeutic response.[2] In the KIWE trial, the patients with IESS presumably had a short treatment lag akin to previous studies from the UK.[5]

The deaths of three children exclusively in the ketogenic diet group are of concern, as the study might not have been adequately powered for safety analyses. The authors did not perform a cost-effectiveness analysis for either group. The ketogenic diet often requires careful monitoring, consultations with dieticians, and laboratory testing to achieve optimum therapeutic response. Low-income and lower-middle-income countries are not only short of ketogenic diet centres but also paediatric neurologists. Therefore, a trial of other antiseizure medications might be a cost-effective alternative.

Overall, we congratulate the KIWE trialists for their study, which provides crucial data on treatment options for infants with drug-resistant epilepsy. More data from future studies evaluating cause-specific IESS with a head-to-head comparison between various antiseizure medications and the ketogenic diet are needed.

We declare no competing interests. Members of the South Asia allied IESS Research Group are listed in the appendix.

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Authors' reply

We thank Jitendra Kumar Sahu and colleagues for their Correspondence on the KIWE trial, which evaluated the safety and efficacy of the ketogenic diet compared with standard antiseizure medication in the treatment of infants with drug-resistant epilepsy.[1]

We note their comments pertain to children presenting with infantile epileptic spasms syndrome (IESS), who comprised 50% of our study cohort. Sahu and colleagues mention that this group would be expected to have had a shorter treatment lag akin to other UK studies. This group might have had a shorter treatment lag in terms of the time elapsed before commencing first line treatment, but one of the requirements for KIWE participants was not responding to a minimum of two antiseizure medications; most children in the study had trialled more than this minimum. The antiseizure medications used were chosen by the caring physician according to the consensus flow chart provided in the appendix of the Article.

Although an optimal response to treatment for patients with IESS is electroclinical remission, the likelihood of achieving this remission after not responding to vigabatrin or corticosteroids is known to be low.[2] Furthermore, this study did not consider only IESS, but children with all types of epilepsy presenting in the first 2 years of life. We agree that, when

choosing antiseizure medication, the physician might not have considered emerging precision treatments relevant to the cause of epilepsy, but the number of children for whom this consideration would be relevant was very small. Analysis by electroclinical syndrome or causal diagnosis, or both, would also be desirable, but the small numbers of each in this study preclude any meaningful statistical analyses.

Sahu and colleagues highlight the three deaths, all of which occurred in the ketogenic diet group. These deaths were reviewed in detail by the local medical teams and data monitoring committee, and determined to be unrelated to the intervention. The children within the study were all vulnerable, as highlighted by the high prevalence of developmental delay and other neurological diagnoses.

We acknowledge that the external validity of clinical trials can be problematic, particularly in differing geographical settings, and accept that there are different causes of infantile epilepsies in low-income and middle-income countries. Furthermore, these countries might not have the services to provide a ketogenic diet, although recommendations are available for safe provision of the ketogenic diet in such settings through the International League Against Epilepsy, and standard antiseizure medication might be difficult to access in some settings.[3] We acknowledge that a cost-effectiveness evaluation might be useful, and this evaluation will be the focus of a future study.

The KIWE trial achieved its aims of showing that the ketogenic diet is tolerable and safe for use in infants with epilepsy and could therefore be considered a treatment option in infants who continue to have seizures despite having tried two antiseizure medications.

JHC reports having a patent nutritional product (WO2013186570) and a patent anticonvulsant compound (WO2016038379A1) issued and receiving honoraria from Nutricia and grants from Vitaflo (International), GW Pharmaceuticals, Zogenix, Marinius, and Ovid. NES was supported for a research post by Vitaflo (International) and received grants from Nutricia Advanced Medical Nutrition, Vitaflo (International), and Matthew's Friends charity, and honoraria from Nutricia Advanced Medical Nutrition, Vitaflo (International), and Dr Schaer. NF reports receiving grants from the National Institute for Health and Care Research, the Medical Research Council, Cure Parkinson's Trust, and the European Union, consultancy fees from ALK, Sanofi Aventis, Gedeon Richter, Abbott, Galderma, AstraZeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune, and Ipsen, and honorarium from Abbott Singapore. LM declares no competing interests. The KIWE investigators and study group members are listed in the appendix.

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Pragmatic solutions for the global burden of stroke

We commend Valery L Feigin, Mayowa O Owolabi, and colleagues on their insightful Commission.[1] The integration of evidence-based methods with pragmatic strategies provides a progressive pathway that will resonate with clinicians and researchers aiming for improved stroke care. It is particularly noteworthy to see a global, inclusive perspective, which is a fresh addition to the prevailing stroke research paradigm. However, in a paper that tries to consider stroke from the lens of various under-represented populations, we feel one important population has not been given suitable consideration—older adults living with frailty.[2]

People with stroke often have frailty syndrome, a condition characterised by increased vulnerability due to reduced physiological reserve.[3] Recent estimates from a meta-analysis of international studies suggest that two-thirds of people with acute stroke already have a frailty syndrome and those that survive are more likely to transition from robust old age to frailty.[4]

See **Online** for appendix

We, as an international collective dedicated to understanding this intersection, emphasise that overlooking frailty provides a restricted and potentially skewed perspective on the multifaceted landscape of stroke. It is imperative to recognise that a generalised approach might not suffice for this population with frailty, given the distinct health-care requirements of those with both stroke and frailty.

The interplay between frailty and stroke is intricate, and neglecting to account for this interplay could possibly lead to skewed conclusions, potentially sidelining the most vulnerable stroke survivors. Addressing this complex nexus might be challenging, but it is indispensable for creating comprehensive, nuanced strategies that cater to diverse stroke-affected populations. We ardently appeal to the research community to incorporate frailty into any discussions of evidence from studies on patients with stroke, to ensure that future policies align with the intricate realities faced by these patients.

We declare no competing interests.

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