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Original Research

Safety and Efficacy of Thalidomide Vs Hydroxyurea in β-Thalassemia patients: A Systematic Review of Current Evidence

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Abstract

Objective: The current systematic review was carried out to compare the safety and efficacy of thalidomide vs hydroxyurea in β-thalassemia patients. **Methods:** literature were extensively searched by using four databases: Web of Science, PubMed, Cochrane Library, and Scopus until January 22, 2024, for studies that did hit to hit comparison of thalidomide vs hydroxyurea based on safety and efficacy in β-thalassemia patients. Original research studies in English with observational and/or experimental designs, regardless of age and gender, used thalidomide for ≥3 months were included in this systematic review. Two independent reviewers extracted the data using a data extraction form. **Results:** Two studies collectively involving n=57 β-thalassemia patients fulfilled eligibility criteria. Thalidomide exhibited greater potential in improving Hb levels, HbF, and in reducing blood transfusion needs and serum ferritin levels compared to hydroxyurea in β-thalassemia patients. Mild adverse events (AEs) of non-serious nature were reported with both thalidomide and hydroxyurea. somnolence, and headache were the main AEs reported in patients treated with thalidomide, whereas abdominal pain, pruritis and gastritis were the main AEs reported in patients treated with hydroxyurea. **Conclusion:** This study demonstrates the higher potential of thalidomide in improving Hb levels and reducing transfusion requirements compared to hydroxyurea in β-thalassemia. However, these findings must be endorsed until well-designed clinical trials are conducted.

Keywords: Thalidomide; Hydroxyurea; β-Thalassemia, Systematic review; Efficacy; Safety

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INTRODUCTION

Globally thalassemia is the most prevalent inherited disease, with β-thalassemia major representing the most severe phenotype among β-thalassemia variants (Arab-Zozani et al., 2021). It arises when the production of β-globin subunit is significantly reduced or absent (Ali et al., 2021). Approximately, 5-7% of the global population, carry a mutated gene, affecting the function of haemoglobin (Hb). Each year, round 56000 new children are born with β-thalassemia syndromes (Soteriades et al., 2023). Thalassemia is predominantly prevalent in the Mediterranean region, Central Asia, the Middle East, India, and the Southern China. However, it is now not related to a specific region and is currently a global phenomenon due to frequent migrations (Ali et al., 2022). In the United States, nearly 7.5% increase in the prevalence of thalassemia has been reported

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due to frequent immigrations of affected individuals from the other countries (Sayani and Kwiatkowski, 2015).

The symptoms of β-thalassemia usually arise among children between the age of 6-24 months and are characterized by recurrent fever, pallor, feeding problems, irritability, failure to thrive and hepatosplenomegaly at the earlier stage of life (Higgs et al., 2012). Additionally, severely low Hb levels (1-7g/dL), increased hemolysis, and ineffective erythropoiesis are the other characteristics of β-thalassemia major. If left untreated, the disease may lead to stunted growth, skeletal changes, hepatosplenomegaly and eventual death at the early phase of life (Sayani and Kwiatkowski, 2015). Blood transfusions are pivotal for survival and serve as the sole treatment option for these patients (Ali et al., 2023). For normal growth and development, maintaining Hb between 9-10g/dL is crucial during the initial stage of life. However, regular transfusion poses a significant risk of iron overload resulting in subsequent damage to multiple organs. In around 71% patients with β-thalassemia, cardiac iron overload is identified as the primary cause of death (Sayani and Kwiatkowski, 2015).

Gene editing, gene therapy, and hemopoietic stem cell transplantation are other curative options, however lack of access to bone marrow transplant services, and higher costs, limits its feasibility especially in developing countries (Lu et al., 2022). Lately, fetal hemoglobin inducers (HbF) have attracted clinicians' attentions due to its promising role in reducing transfusion needs by correcting ineffective erythropoiesis such as hydroxyurea (Algiraigri et al., 2017b;a) and thalidomide (Ali et al., 2022;Lu et al., 2022). The current literature is mixed regarding the safety and efficacy of both the hydroxyurea and thalidomide in β-thalassemia, a study reported that a significant number of patients do not respond to hydroxyurea after some time (Bayanzay and Khan, 2015;Ali et al., 2023). Similarly, a handful of patients with β-thalassemia also do not show response to thalidomide therapy (Chen et al., 2021).

The current literature is deficient due to lack of a precise systematic review comparing the safety and efficacy of hydroxyurea vs thalidomide in β-thalassemia. We believe that a systematic review reporting the clinical outcome of thalidomide vs hydroxyurea in improving Hb levels and reducing transfusion needs among patients with β-thalassemia will fill the partially explained gap in the existent literature. Therefore, the current review is proposed to compare the safety and efficacy of thalidomide vs hydroxyurea in β-thalassemia.

METHODS

Data Source

Literature was systematically searched using four databases (PubMed, Scopus, Cochrane Library, and Web of Science) until January 22, 2024 for studies evaluating the safety and efficacy of thalidomide vs hydroxyurea among β-thalassemia patients. Complete description of the search terms is presented in Supplementary file-1. Reference list of all primary studies were also screened and searched using hand searches in order not to miss any potential study. To find potential studies, PRISMA guidelines were followed in order to find potential studies to be included in this systematic review.

Study selection

Original research articles having experimental design, published in peer-reviewed English journals published from inception till 22nd January 2024, used comparison of thalidomide vs hydroxyurea for treatment of β-thalassemia were included. All systematic reviews, meta-analyses, review articles, case reports, advertisements, thesis, opinions, letters to the editor, conference proceedings, and qualitative studies were excluded.

Data extraction

All selected articles were extracted by using a standardized extraction form by two independent reviewers Mohammed K. Alshammari and Asma A. Alsohaibani. Disagreement between reviewers were resolved by engaging discussion until a consensus was reached. The following information was extracted from individual article: author name, publication year, type of study design, country name where the study was conducted, follow-up duration, outcomes i.e., Hb, HbF, serum ferritin, blood transfusion and most common adverse effects (AEs) observed by using either therapy.

Data analysis

Two studies that meet the inclusion criteria were not combinable for meta-analysis due to higher heterogeneity, keeping in view the nature of the data extracted the data were shortlisted for qualitative synthesis instead of quantitative synthesis.

RESULTS

Study Selection

A total of n=488 related research articles were identified, having n=42 from PubMed, n=44 from Web of Science (WOS), n=20 from Cochrane database (trials) and n= 382 from Scopus. After the removal of duplicates (n=58), a total of n=430 articles were obtained. By reviewing and screening the title and abstract of the articles, n=30 studies were obtained and upon further applying the filter (comparison of thalidomide vs hydroxyurea) a total of n=02 studies fulfilled the inclusion criteria and were included in this systematic review as shown in figure 1.

Characteristics of selected studies

Characteristics of the included studies are presented in table 1. Of the included both the studies were performed in India (Jain et al., 2021;Bhattacharjee et al., 2023), and both studies compared thalidomide vs hydroxyurea among β-thalassemia patients. One study used a prospective interventional study design (Jain et al., 2021), while other study used prospective open-label randomized controlled clinical trial (Bhattacharjee et al., 2023). The studies have different timeline for the assessment of parameters i.e. 12 months (Jain et al., 2021) and 6 months (Bhattacharjee et al., 2023). The dose of thalidomide was 50mg/day in both studies (Jain et al., 2021;Bhattacharjee

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et al., 2023), however the dose of hydroxyurea was 10–15 mg/kg/day in one study (Jain et al., 2021), and 500 mg/day in the other study (Bhattacharjee et al., 2023).

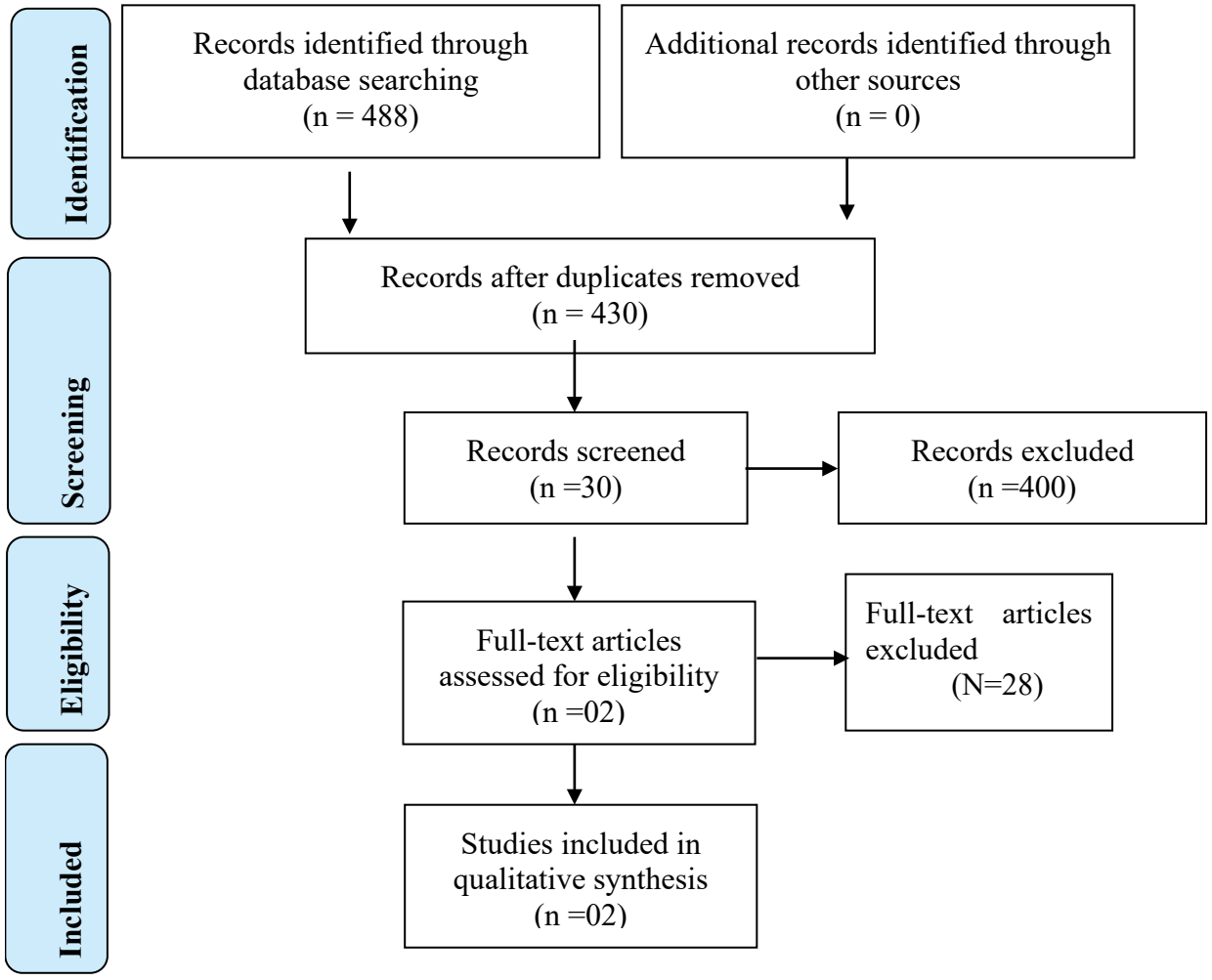

Figure 1. PRISMA flow diagram of the selected studies

Table-1: Characteristics of the selected studies

Parameters	**Study-1 (Jain et al., 2021)**	**Study-2 (Bhattacharjee et al., 2023)**
Author Name	Jain et al.,	Bhattacharjee et al.,
Publication Year	2021	2023
Patients	Hb E-β Thalassemia	β-thalassemia (TDT)
Study Design	Prospective Interventional	Open-label Randomized Controlled Trial
Country	India	India
Follow-up Duration (Months)	12	6
Blood Transfusion (End Point)	Thal: 100% Reduction in transfusion Requirements HU: 34% Reduction in transfusion requirements	Thal: 69.7 ± 25.67 HU: 76.8 ± 24.69
Mean HbF % increase (End Point)	Thal: 23.5%	Thal: NR
	HU: 23.3%	HU: NR
Mean Ferritin (ng/ml) difference (End Point)	Thal: 24.4 decrease in SF HU: 58.7 increase in SF	Thal: 1059.3 decrease in SF HU: 232.4 decrease in SF

Thal: Thalidomide; HU: Hydroxyurea; TDT: Transfusion-dependent β-thalassemia; NR: Not Recorded; SF: Serum Ferritin

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The mean age of the patients in the thalidomide group (mean ± SD) was 20.3 ± 9.3 years, and 14.1 ± 12.5 in the hydroxyurea group (Jain et al., 2021); while in the second study, the mean age was 26.14 ± 4.27 and 26.15 ± 5.25 in the thalidomide group and hydroxyurea group, respectively (Bhattacharjee et al., 2023). In one study, the number of patients in both of the groups were n=15 (Jain et al., 2021), whereas in the second study, included n=14 patients in the thalidomide group, and n=13 patients in the hydroxyurea group (Bhattacharjee et al., 2023).

OUTCOME ASSESSMENT

Hb Level (g/dl)

In the one study, a significant increase in Hb levels was observed in both of the groups after 12 months of treatment. Patients in the thalidomide group exhibited a noteworthy increase in Hb from a baseline mean of 7.02 ± 0.77 to 9.15 ± 0.64 g/dl. Whereas patients in hydroxyurea group experience am increase in Hb levels from a baseline mean of 6.89 ± 1.12 to 7.76 ± 0.59 g/dl, constituting a 26.3% increase in the thalidomide group vs 11.9% in the hydroxyurea group after 12 months of treatment (Jain et al., 2021). Furthermore, in the thalidomide treated patients, a significant increase in Hb level was observed after 15 days of treatment compared to hydroxyurea treated patients where significant rise in Hb levels was seen after 2 months of treatment. Similarly, the Hb levels were significantly higher in the thalidomide group vs hydroxyurea group after 1 month of initiation of therapy.

In the second study, the Hb level increased from a baseline mean of 8.7 ± 0.99 to 9.2 ± 1.56 in the thalidomide group, and 8.9 ± 0.71 to 9.0 ± 1.77 in the hydroxyurea group after 6 months of treatment (Bhattacharjee et al., 2023), reflecting a 5.6% increase in the thalidomide group compared to 1.1% in the hydroxyurea group.

HbF Level (%)

There was a significant progressive HbF increment with both thalidomide group from a baseline mean HbF of 23.4 ± 3.94% to 29.63 ± 4.35% at 12-months and hydroxyurea group from a baseline mean HbF of 28.93 ± 12.68% to 36.57 ± 11.86% after 12-months, reflecting a 23.5% increments in the thalidomide group vs 23.3% increase in the hydroxyurea group (Jain et al., 2021). However, the second study did not perform the assessment of HbF at baseline and at 6 months (Bhattacharjee et al., 2023).

Serum Ferritin (ng/ml)

In thalidomide group, there was a decrease in ferritin (mean ± SD) from a baseline mean of 307.33 ± 131.99 to 282.93 ± 117.23 ng/ml at 12-months; while there was an increase in ferritin level in hydroxyurea group from baseline 587 ± 151.1 to 645.67 ± 113.36 ng/ml at 12-months (Jain et al., 2021). This reflects to 8.3% decrease in the serum ferritin level in the thalidomide vs 9.5% increase in the serum ferritin levels in the hydroxyurea group. For another study, the mean serum ferritin levels for the thalidomide group improved from 3309.4 ± 3342.39 at baseline to 2587.4 ± 2204.39 reflecting to 24.5% decrease after 6 months of thalidomide treatment, while in hydroxyurea group it decreased from a baseline mean of 2671.6 ± 2084.59 to 2635.4 ± 1869.75 reflecting 1.4% decrease after 6 months of treatment with hydroxyurea (Bhattacharjee et al., 2023).

Transfusion Requirements

The transfusion requirements vary among both the studies. In the thalidomide group, the transfusion requirement at baseline was 2.2 ± 1.22 units/year and reduced to no single transfusion was required for the patients after 12 months; while for the hydroxyurea group, the transfusion requirement reduced by 34% from baseline 3.4 ± 1.23 units/year to 2.2 ± 1.21 units/year after 12 months (Jain et al., 2021). This reflects to 100% transfusion independence in the thalidomide group compared to 34% in the hydroxyurea group.

In other study, the mean volume per unit weight of blood transfused (ml/kg) at baseline 90.4 ± 29.89 reduced to 69.7 ± 25.67 after 6 months in the thalidomide group which corresponds to 25.9% reduction in blood transfusion volume, while for hydroxyurea group it reduced from 84.9 ± 22.93 at baseline to 76.8 ± 24.69 and after 6 months, reflecting 10% reduction in the blood transfusion volume (Bhattacharjee et al., 2023).

AEs of Thalidomide and Hydroxyurea

List of AEs reported in the included studies are presented in table-2. In the first study, all the patients tolerated the agents well with most common side-effects as mild gastrointestinal related symptoms like somnolence in 67% and headache in 33% of patients who received thalidomide, while diarrhea, abdominal pain and gastritis in 46% of patients who received hydroxyurea (Jain et al., 2021). In both of the groups, none of the patient required interruption or medical intervention due to AEs.

Similarly, second study by Bhattacharjee et al., reported that all of the observed AEs were non-serious in nature in both the thalidomide and hydroxyurea group. Abdominal pain (Grade 1-2, 23.1%) and pruritus (Grade 1, 15.4%) were the main AEs in hydroxyurea arm, while somnolence was the main AEs in the thalidomide group observed among 78.3% of patients (Grade-1: 42.8%, and Grade-2, 35.7%). Other AEs include grade-2 presyncope in 7.1%, grade-3 syncope in 7.1%, grade-2 headache in 14.3%, grade-2 hyperbilirubinemia in 7.1%, grade-2 transaminitis in 7.1% and grade-1 constipation in 7.1% in the thalidomide group; whereas, grade-2 mucositis in 7.7%, and grade-2 transaminitis in 7.7% were the other AEs reported in the hydroxyurea group (Bhattacharjee et al., 2023). One patient on hydroxyurea required 50% dose reduction due to abdominal pain; whereas, in the thalidomide group eight patients' dose was 50% reduced due to somnolence.

DISCUSSION

This systematic review aimed to assess the clinical effectiveness of thalidomide in comparison to hydroxyurea

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Table-2: Adverse Events reported in the included studies

Adverse Events	Jain et al., (Jain et al., 2021)		Bhattacharjee et al., (Bhattacharjee et al., 2023)	
	Thalidomide	Hydroxyurea	Thalidomide	Hydroxyurea
Diarrhoea	-	46%	-	-
Abdominal Pain	-	46%	-	23.10%
Gastritis	-	46%	-	-
Somnolence	-	67%	78.50%	-
Headache	-	33%	14.30%	-
Mucositis	-	-	-	-
Pruritus	-	-	-	15.40%
Transaminitis	-	-	7.10%	7.70%
Constipation	-	-	7.10%	-
Hyperbilirubinemia	-	-	7.10%	-
Presyncope	-	-	7.10%	-
Syncope	-	-	14.30%	-

among β-thalassemia patients. Numerous studies have documented the HbF-inducing properties of thalidomide (Begum et al., 2020;Yang et al., 2020;Ali et al., 2021;Chandra et al., 2021;Ali et al., 2023) and hydroxyurea (Akram et al., 2022;Lu et al., 2022;Yasara et al., 2022) as a single-agent therapy for β-thalassemia patients. Additionally, a limited number of studies have explored the concurrent use of thalidomide and hydroxyurea in β-thalassemia patients (Shah et al., 2020;Bhurani et al., 2021;Ansari et al., 2022). Our review incorporated two studies that met the predetermined inclusion criteria, focusing on the direct comparison of safety and efficacy between thalidomide and hydroxyurea within the same study involving β-thalassemia patients (Jain et al., 2021;Bhattacharjee et al., 2023).

Findings of the current study revealed that thalidomide resulted in 31.9% cumulative increase in Hb levels compared to 13% increase by hydroxyurea, reflecting an overall increase of 2.2 g/dl in Hb level by thalidomide, and 0.9% by hydroxyurea. Similarly, none of the patient in the thalidomide group required blood transfusion after treatment, 100% of the patients achieved transfusion independence compared to hydroxyurea where 34% achieved transfusion independence (Jain et al., 2021). Furthermore, in the study by Bhattacharjee et al., thalidomide resulted in 25.5% reduction in blood transfusion requirement compared to only 10% reduction in blood transfusion volume by hydroxyurea (Bhattacharjee et al., 2023). Thereby, indicating that thalidomide is more efficacious than hydroxyurea among β-thalassemia patients.

Thalidomide and hydroxyurea have both shown promise in alleviating transfusion needs among β-thalassemia patients as a single agent as evident from the current literature. A meta-analysis conducted by Algiraigri et al. among β-thalassemia patients indicated that hydroxyurea exhibited good clinical efficacy in elevating Hb levels (Algiraigri et al., 2017b). Whereas, a meta-analysis measuring the safety and efficacy of thalidomide reported that thalidomide is a well-tolerated and effective drug in transfusion dependent β-thalassemia (Ali et al., 2022). Another meta-analysis by Lu et al., reported that thalidomide is relatively safe and effective drug among β-thalassemia patients (Lu et al., 2022). Similarly, a study by Ali et al., reported the long-term safety and efficacy of thalidomide among hydroxyurea refractory transfusion-dependent β-thalassemia patients (Ali et al., 2023).

Regarding HbF percentage in the included studies, a notable and progressive increase in HbF level amounting to 23.5% in the thalidomide group was observed vs 23.3% increase in the hydroxyurea group (Jain et al., 2021). These results are consistent with other studies reporting the HbF inducing properties of thalidomide among β-thalassemia patients (Yang et al., 2020;Ali et al., 2021;Chandra et al., 2021). Similarly, findings of a meta-analysis revealed higher HbF levels in patients receiving hydroxyurea (Hatamleh et al., 2023). In both the studies, there was a notable reduction in serum ferritin level in the thalidomide treated patients, amounting to 32.8% decrease; whereas, hydroxyurea treated patients exhibited a cumulative increase of 8.1% in serum ferritin levels. This significant reduction in the serum ferritin among the thalidomide treated patients is attributed to its role in reducing blood transfusions need as evident from our findings as well as results of other similar studies conducted in β-thalassemia patients (Ramanan and Kelkar, 2017;Jiskani and Memon, 2018;Yassin, 2020;Ali et al., 2023). Whereas, the insignificant decrease (1.4%) in a study by Bhattacharjee et al., (Bhattacharjee et al., 2023) and a 9.5% increase in the serum ferritin levels among the hydroxyurea treated patients is attributed to its insignificant impact on blood transfusions needs as evident from this study (Jain et al., 2021).

AS far as tolerability of thalidomide and hydroxyurea is concerned, both the agents were well-tolerated, and all of the AEs were of non-serious and mild in nature. Somnolence, and headache were the main AEs reported in the thalidomide treated patients; whereas, abdominal pain, pruritis and

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gastritis were the main AEs reported among the hydroxyurea treated patients.

Taken together, this study demonstrates the promising role of thalidomide in terms of efficacy and tolerability among patients with β-thalassemia compared to hydroxyurea based on the current evidence and hit to hit comparison of both the agents. Thalidomide has shown greater potential in improving Hb levels, and in attaining transfusion independence in considerable number of patients compared to hydroxyurea. This promising role of thalidomide is attributed to its greater potential in inducing HbF vs hydroxyurea as evident from this systematic review.

One of the major strengths of this systematic review is its uniqueness, the first of its kind study reporting hit-to hit comparison of thalidomide and hydroxyurea in β-thalassemia. While, limitations of this review incudes; a) a smaller number of studies reporting comparison of thalidomide and hydroxyurea, b) short follow-up duration, and c) small sample size.

CONCLUSION

Based on the findings of this study thalidomide is the most efficacious drug among β-thalassemia patients because of its higher HbF inducing properties compared to hydroxyurea. However, these findings must be interpreted with caution given the smaller number of comparison studies, in future larger clinical studies with stringent designs are highly recommended until these results can be endorsed.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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