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Systematic Review and Meta-Analysis

The effect of Vitamin E and N-acetyl cysteine on oxidative status and hemoglobin level in transfusion-dependent thalassemia patients: A systematic review and meta-analysis

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Abstract

Background: This meta-analysis was conducted to summarize the comparative effect of Vitamin E and N-acetyl cysteine (NAC) on oxidative status, including total antioxidant capacity (TAC), total oxidative stress (TOS), oxidative stress index (OSI), and hemoglobin (Hb) in patients with TDT.

Methods: This systematic review and meta-analysis was done according to the PRISMA checklist. We searched databases including Web of Science (ISI), Scopus, Medline (via PubMed), and Embase. Meta-analysis was done using Stata statistical software version 16.0.

Results: Finally, four randomized-controlled trials (RCT) for Vitamin E and three RCTs for NAC were included. Our meta-analyses and review showed a significant increase in the weighted mean differences (WMD) of Hb and a significant decrease in the WMD of TOS and OSI in children subgroup of Vitamin E. Also, based on the results of the review in the NAC group, a significant increase in the WMD of Hb and a significant decrease in the WMD of TOS and OSI were found in children.

Conclusions: Vitamin E showed a beneficial effect on improving anemia in TDT children. Moreover, both NAC and Vitamin E seems to be effective antioxidant supplements in children with TDT. More well-designed randomized, controlled trials for the effect of NAC and Vitamin E in TDT patients are recommended with more focus on the essential influencing factors on the oxidative status in these patients.

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1. Introduction

Transfusion-dependent thalassemia (TDT) is one of the most common inherited disorders caused by a genetic mutation leading to hemolysis and impaired erythropoiesis (1, 2). Regular blood transfusion is an essential therapeutic option that has lowered the complications of severe anemia and increased the patients' survival.

However, repeated blood transfusions lead to iron deposition in various organs, including vital organs such as the heart and liver (3, 4). Although iron chelation therapy is used as an essential treatment option for iron overload, heart disease caused by cardiac hemosiderosis remains the leading cause of

death in these patients (5). The excess amount of iron in the body induces free radicals (6). These reactive molecules cause significant damage to several components including lipids, proteins, and nucleic acids resulting in mitochondrial dysfunction and apoptosis (7). Thus, iron overload is associated with increased oxidative stress, lipid peroxidation, and hepatic damage which consequently increases mortality and morbidity (8). Moreover, abnormal globin chains in thalassemia patients due to genetic mutation leads to precipitation of unstable hemoglobin (Hb) tetramers and oxidative damage (2).

The oxidative status can be assessed by distinct agents in the cells or plasma or estimated by total antioxidant capacity (TAC) which results from the combination of different measurement methods (9, 10). Various antioxidants have been used to improve the oxidative status of thalassemia patients (1, 6). N-acetyl cysteine (NAC), a mucolytic agent and paracetamol antidote, has been determined as an antioxidant supplement in recent years (11). The effects of NAC and Vitamin E as the two major groups of antioxidants have been investigated on hemolytic parameters and oxidative status of patients with TDT with controversial results (1, 6).

There has been no systematic approach or meta-analysis to evaluate the antioxidant effect of NAC and Vitamin E in patients with TDT. This meta-analysis was conducted to summarize the comparative effect of Vitamin E and NAC on oxidative status, including TAC, total oxidative stress (TOS), oxidative stress index (OSI), and Hb in patients with TDT.

2. Method

This systematic review and meta-analysis was done according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (12). We registered our study at the International Prospective Register of Systematic Reviews (PROSPERO) with the confirmed code: CRD42021250425. Also, the study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, (Ethics code: IR.SUMS.REC.1400.188).

2.1. Search strategy

2.1.1. Searched databases

The systematic search was done in February 2021. The searched databases included Web of Science (ISI), Scopus, Medline (via PubMed), and Embase. A combination of the following MeSH terms and keywords were used to conduct comprehensive literature searches. For population, we used :("Thalassemia*" OR "Beta-Thalassemia*" OR "Transfusion dependent Thalassemia" OR "TDT" "Thalassaemia" OR "β-Thalassemia major" "B-TM"). For intervention, it was ("Vitamin E" OR "Tocopherols" OR "Antioxidant*") OR ("Acetylcysteine" OR "N-acetylcysteine" OR "NAC") (**supplementary Table 1, search strategy**). Moreover, we manually checked the reference lists of the relevant articles and previously performed reviews for additional pertinent studies.

2.1.2. Inclusion and exclusion criteria

The eligible studies required meeting specific criteria including: 1- The studies were human. 2-The subjects were patients with TDT. 3-The included studies were reported. 4- The studies were randomized-controlled trials (RCT).

We excluded 1-Case reports or animal design studies, 2- Review articles or non-original articles, 3-Conference abstracts, letters, book chapters, editorials, or brief reports, and 4- Full text published in a non-English language.

2.2. Data extraction

Two researchers independently extracted the data including the name of the first author, publication year, country, the mean age of the patients, duration of treatment, the dosage of administered drug, the total number of patients, and the mean level of pre-transfusion hemoglobin, TOS, TAC and OSI from the eligible papers before and after the intervention. A third author resolved the disagreement.

2.3. Study quality assessment

Two independent authors assessed the quality of the included studies based on the Cochrane Collaboration Risk of Bias tool (13). This scale encompasses items of randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The results of the quality assessment of the included studies are presented in **Figure 1**, quality assessment.

2.4. Statistical analysis

All statistical analyses were performed using STATA version 16.0 (Stata Corp., College Station, TX). The effect of NAC and Vitamin E on Hb, TAC, TOS, and OSI was reported

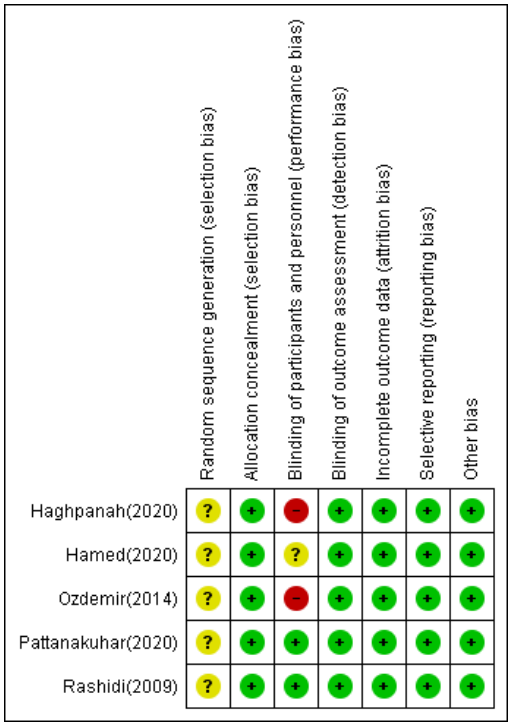

Figure 1. Quality assessment of the included studies.

as mean (SD) change in the intervention and the control groups. When RCTs did not report the mean and SD change, we calculated the mean changes and their corresponding SDs using the following formula: [meanpost – meanpre] and $\sqrt{(SD^2_{pre}+SD^2_{post}-(2*r*SD_{pre}*SD_{post}))}$, respectively (14). The correlation coefficient (r) was calculated based on the study conducted by Haghpanah et al. (1), using an appropriate formula suggested by Cochrane guidelines for systematic reviews and meta-analysis (15). Statistical heterogeneity was determined using Cochrane's Q test and the I^2 statistic with I^2> 50% and Cochrane's Q test as $p < 0.1$. We used the random-effects model [with DerSimonian–Laird method] to pool the weighted mean differences (WMDs) and 95% confidence intervals (CIs). In a set of subgroup analyses, we assessed the effect of age on Hb, TAC, TOS, and OSI, for either NAC or Vitamin E. We assessed the presence of potential evidence of publication bias using the Egger regression and Begg's funnel plots, with $p < 0.05$ suggesting publication bias.

3. Result

3.1. Literature search and study characteristics

Our primary search included 3102 papers that were reduced to 1069 documents when duplicated papers were removed. By screening the titles and abstracts, 1009 papers were excluded, so 60 full texts were criteria in our analysis [1, 6, 7, 16, 17] (**Figure 2**, PRISMA). The general characteristics of the included studies are summarized in **Tables 1** and **2**.

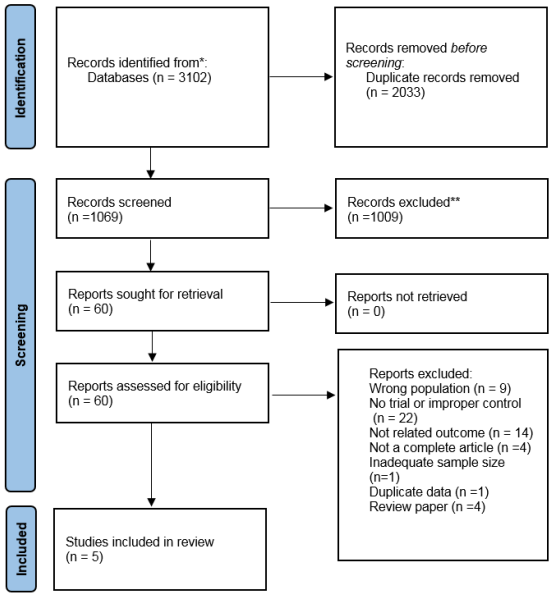

Figure 2. PRISMA Flowchart of the identification studies and selection process.

screened. Finally, five articles met the inclusion criteria in our analysis (1, 6, 7, 16, 17) (**Figure 2, PRISMA**). The general characteristics of the included studies are summarized in **Tables 1** and **2.**

3.2. General effects

3.2.1 Vitamin E

The effects of vitamin E on Hb, TAC, TOS, and OSI are shown in **Figure 3** and **4**. By using the random-effect model, our meta-analyses showed no significant changes in the WMD of Hb (three included studies), TAC (three included studies), TOS (two included studies), or OSI (two included studies).

3.2.2 NAC

The effects of NAC on Hb, TAC, TOS, and OSI are shown in **Figure 5** and **6**. Using random-effect model, our meta-analysis was not significant for Hb (three included studies), TAC (two included studies), TOS (two included studies), and OSI (two included studies). Egger regression and Begg's funnel plots were used for evaluating the evidence of potential publication bias (**Supplementary Figures 1 and 2**).

3.3 Subgroup analysis

Based on the mean age of the patients, we divided our included studies into two categories: adults (>18 years) and children (≤ 18 years).

Table 1. General characteristics of the included studies (Vitamin E)

Author	Country/Population	Age group mean(control/ intervention)	Study design	Intervention	Treatment duration	Sample size (control/intervention)	Presented data
Haghpanah/2020	Iran/patients with transfusion-dependent β-thalassemia	(28.3±4.4), (27.8±4.9)	Open-label randomized controlled trial	vitamin E 10 U per kg per day (maximum dose of 400 IU)	3 months	51(25/26)	Hb(g/dl), TAC(mmol/l), TOS(umol/l), OSI
Hamed /2020	Egypt/transfusion dependent beta thalassemia children	(11.6±3.98), (11.73±3.03)	Stratified randomized controlled study	vitamin E (400 mg) once daily	6 months	80(40/40)	Hb(g/dl)
Ozdemir /2014	Turkey/Children with b-TM	(8.56±4.1), (10.3±4.09)	Open-label randomized controlled trial	vitamin E 10 U/kg maximum dose 400 IU) once daily	3 months	50(25/25)	Hb(g/dl), TAC(mmol/l), TOS(umol/l), OSI
Rashidi /2009	Iran/Beta thalassemia major Patients	(21.1±9.7), (21.1±9.7)	Double blind randomized clinical trial	400 mg vitamin E supplement daily	3 months	60(30/30)	TAC(mmol/l)

Table 2. General characteristics of the included studies (NAC)

Author	Country/Population	Age group mean(control/ intervention)	Study design	Intervention	Treatment duration	Sample size (control/intervention)	Presented data
Haghpanah/2020	Iran/patients with transfusion-dependent β-thalassemia	(28.3±4.4), (29.4±6)	Open-label randomized controlled trial	NAC 10 mg per kg per day (maximum dose of 600 mg)	3 months	50(25/25)	Hb(g/dl), TAC(mmol/l), TOS(umol/l), OSI
Ozdemir/2014	Turkey/Children with b-TM	(8.56±4.1), (9.65±4.15)	Open-label randomized controlled trial	NAC 10 mg per kg per day (maximum dose of 600 mg)	3 months	50925/25)	Hb(g/dl), TAC(mmol/l), TOS(umol/l), OSI
Pattanakuhar/2020	Thailand/Transfusion-dependent Thalassemia Patients	(27±8), (28±8)	Double-blind Single Center Randomized Controlled Trial	600 mg NAC daily	6 months	59(29/30)	Hb(g/dl)

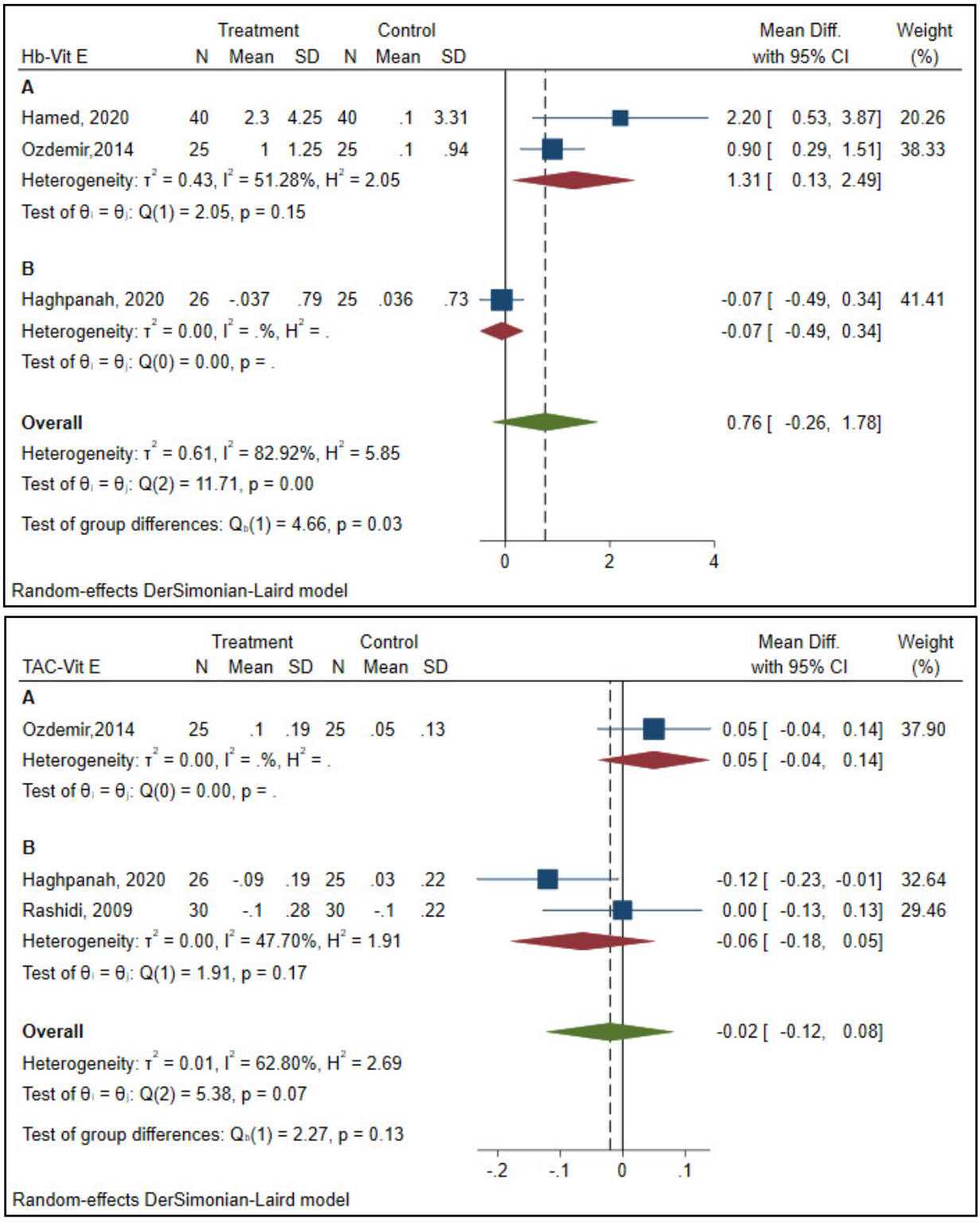

Figure 3. The Effect of Vitamin E on hemoglobin and TAC in patients with transfusion-dependent thalassemia (TAC: total antioxidant capacity, Hb: hemoglobin)

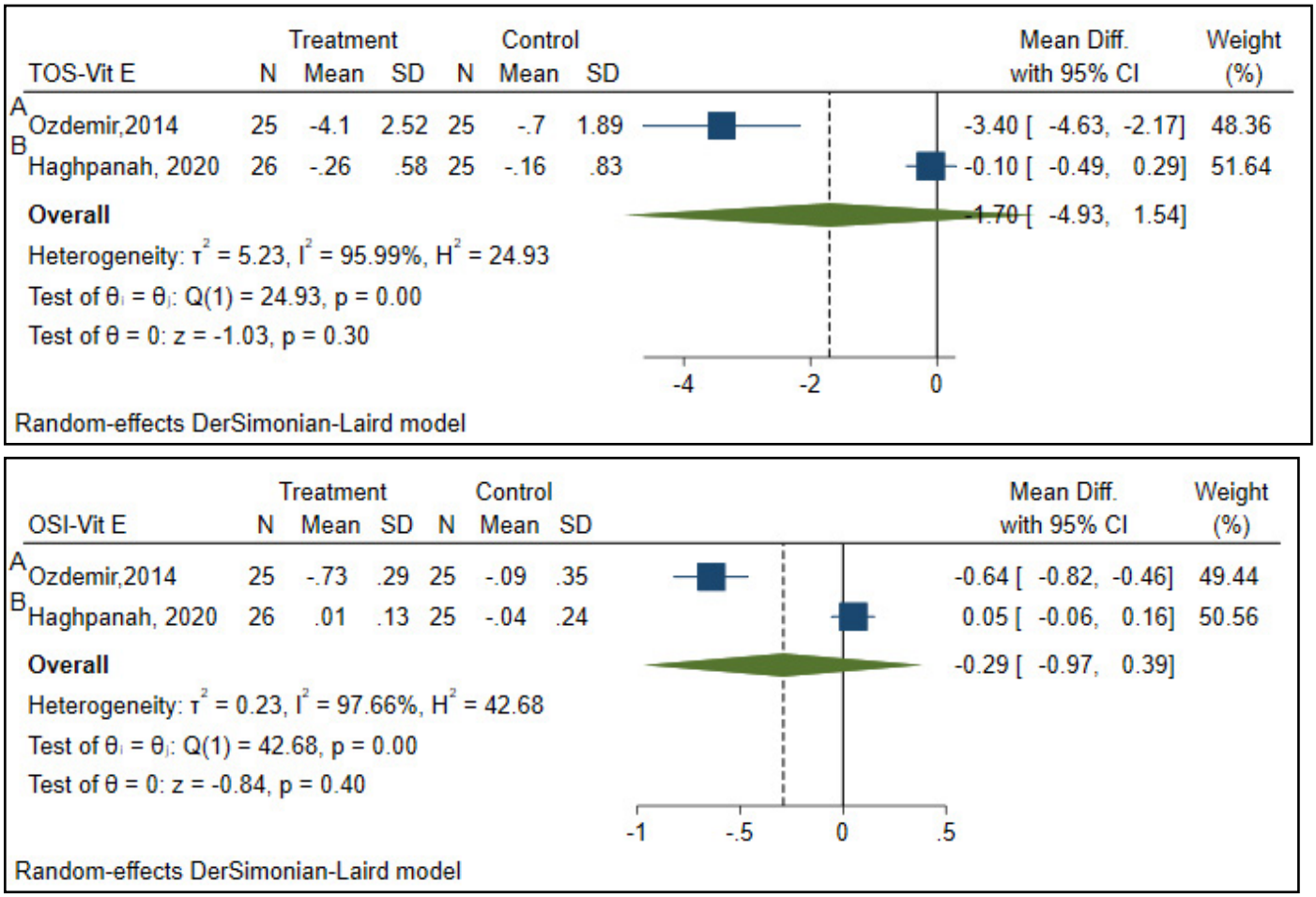

Figure 4. Effect of Vitamin E on TOS, and OSI in patients with transfusion-dependent thalassemia (TOS: total oxidative stress, OSI: oxidative stress index).

Figure 3 to 6 demonstrates the effects of NAC and Vitamin E supplementation therapy on Hb, TAC, TOS, and OSI through subgroup analyses based on age (A: children, and B= adult) in patients with TDT.

3.3.1. Hb

- Vitamin E

We found a significant increase in Hb at the end of the study compared to the baseline value only in children with TDT [WMD 1.31; 95% CI, 0.13-2.49, I^2 =51.28% (two included studies)]

- NAC

We found a significant increase in Hb at the end of the study compared to the baseline value only in children with TDT [WMD 1.10; 95% CI, 0.47-1.73, I^2 =0.0% (one study)]

3.3.2 TAC

- Vitamin E

No significant changes in the WMD of TAC were observed in children or adults with TDT.

- NAC

No significant changes in the WMD of TAC were observed in children or adults with TDT.

3.3.3. TOS

- Vitamin E

TOS significantly decreased at the end of the study only in children [WMD -3.40%; 95% CI, -4.63- - 2.17] (one included study).

- NAC

TOS significantly decreased only in children at the end of the study [WMD -7.80; 95% CI, −9.30 - – -6.3, I^2 =97.35% (one included study)]

3.3.4. OSI

- Vitamin E

OSI significantly decreased in children at the end of the study compared to the baseline value [WMD -0.64; 95% CI, −0.82 - −0.46] (one included study).

- NAC

A significant decrease in OSI was shown at the end of the study compared to the baseline value in children. [WMD -1.26; 95% CI, −1.58 - −0.94] in only one study.

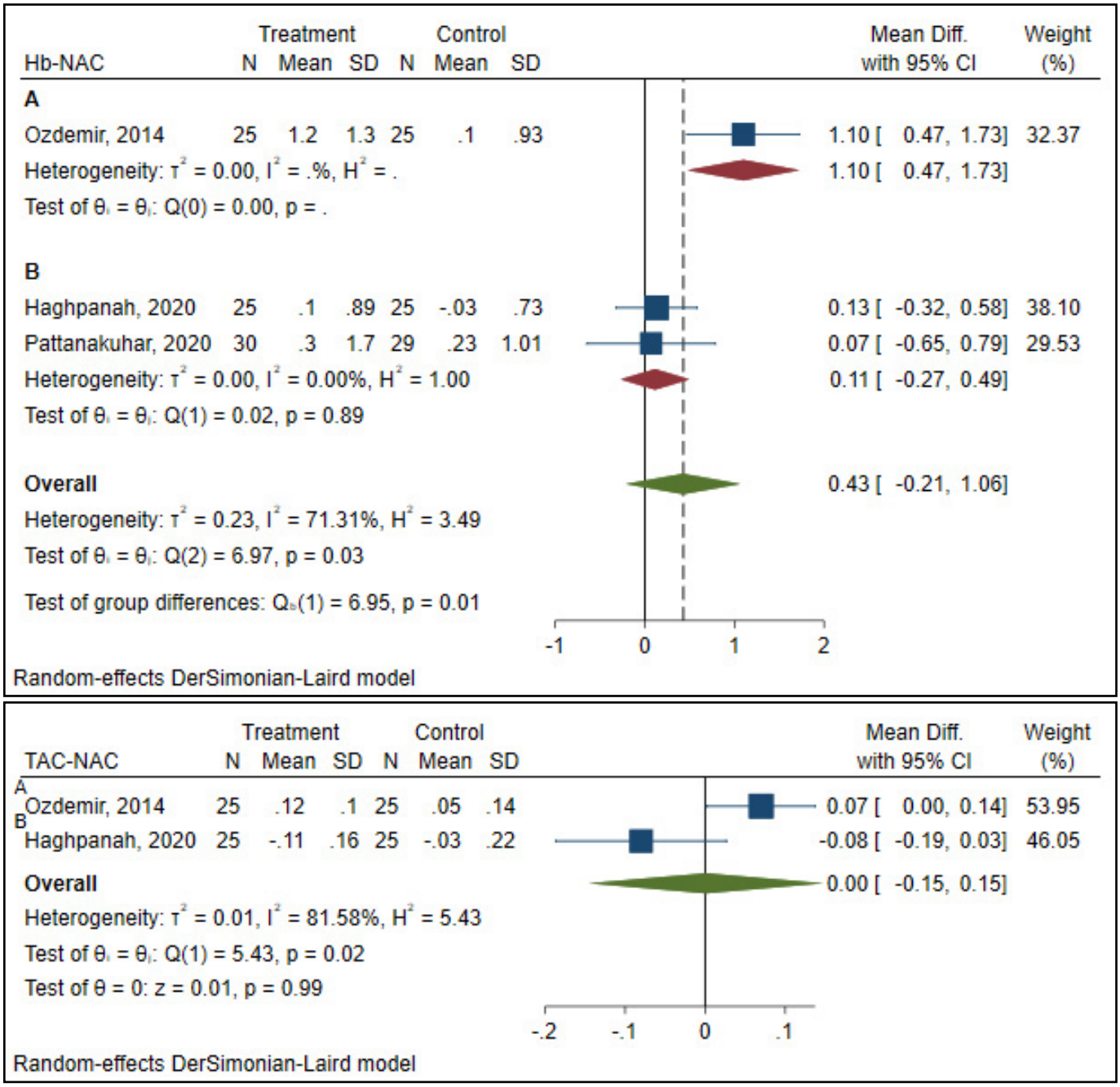

Figure 5. Effect of NAC on hemoglobin and TAC in patients with transfusion-dependent thalassemia (TAC: total antioxidant capacity, Hb: hemoglobin)

4. Discussion

To the best of our knowledge, this is the first meta-analysis which investigated the effect of NAC and Vitamin E on oxidative status and hemoglobin in adults and children with TDT. Finally, four articles with 121 patients for Vitamin E (10 IU per kg per day (maximum dose of 400 IU) and duration of 3 to 6 months), and three articles including 80 patients for NAC (10 mg per kg per day (maximum dose of 600 mg) and duration of 3 to 6 months) were investigated. Our meta-analysis and review in TDT patients showed a significant increase in the WMD of Hb and a significant decrease in the WMD of TOS and OSI in children subgroup of the Vitamin E group. Similarly, based on the results of the review in the NAC group, a significant increase in the WMD of Hb and a significant

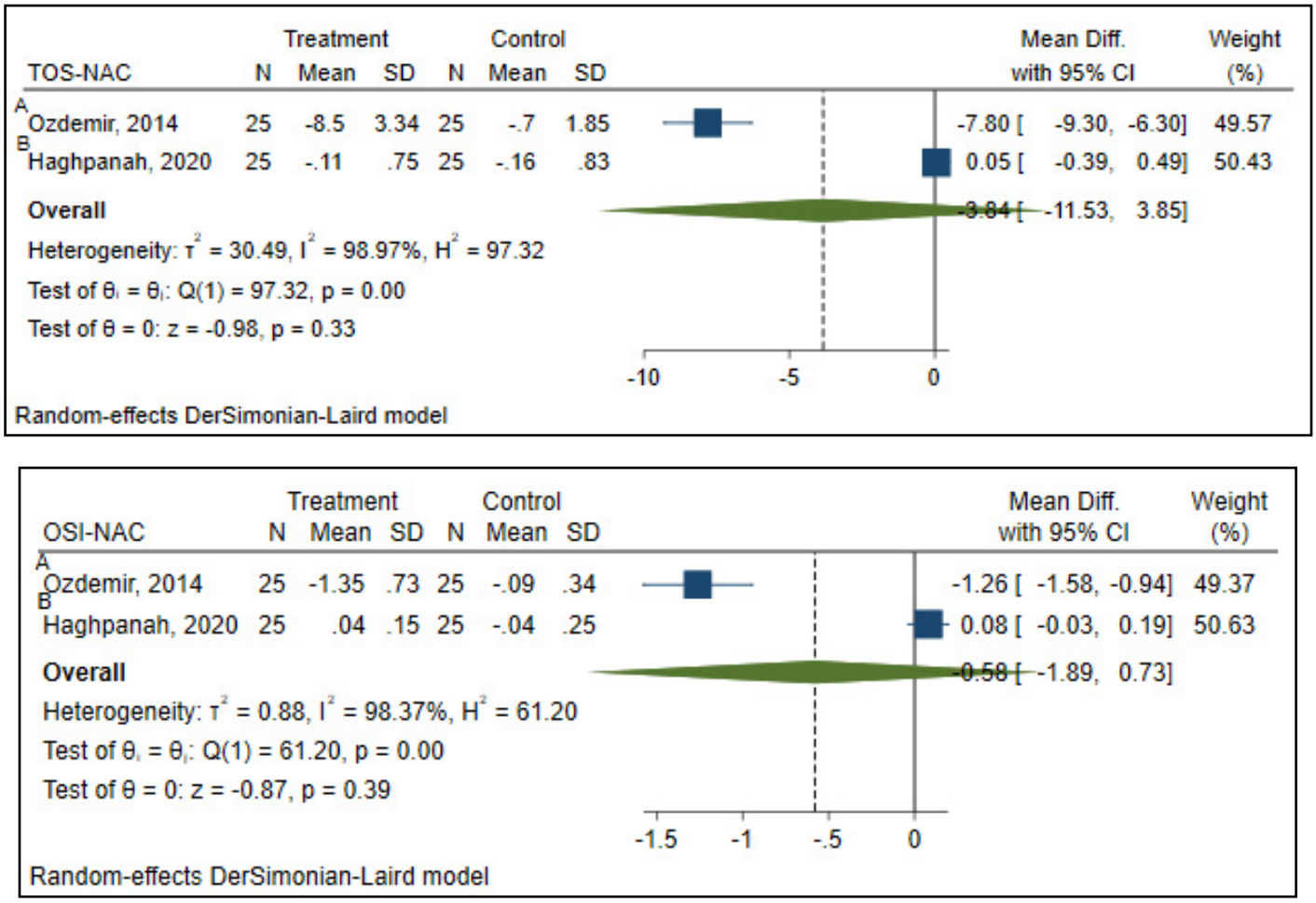

Figure 6. Effect of NAC on TOS, and OSI in patients with transfusion-dependent thalassemia (TOS: total oxidative stress, OSI: oxidative stress index).

decrease in the WMD of TOS and OSI were detected in children.

Oxidative stress is considered a major contributing pathogenic factor for disease progression in patients with TDT. Different contributing mechanisms include globin chain imbalance resulting in excess α-chain precipitation, hemolysis, and iron overload, which altogether enhance the production of reactive oxygen species (ROS), leading to lipid peroxidation (LPO) and oxidation of polypeptide chains and DNA damage (6, 18). Consequently, cell death, organ impairment, hypoxia, and inflammation occur in these patients (19).

The presence of an adequate antioxidant supply can modulate the severity of oxidative stress and its destructive consequences. Lesser antioxidant capacity in patients with thalassemia compared to healthy controls has been reported in several related studies due to enhanced oxidative stress and confrontation of this condition. Based on the findings of a systematic review and meta-analysis of case-control studies, TAC was significantly lower in thalassemia patients compared to healthy individuals in the total studied population of adults and children without subgroup analysis and regardless of disease severity (beta-thalassemia trait, beta-thalassemia major, and hemoglobin E)(20).

Moreover, reduced antioxidant capacity, reduction in Vitamin E, and decreased superoxide dismutase and glutathione peroxidase activity or level were reported in children with thalassemia major(21) and a group of patients with β thalassemia major with unknown age range(22). Furthermore, the antioxidant deficiency was reported in patients affected by thalassemia syndrome (thalassemia major, intermedia, HbE, and sickle thalassemia) with a median age of 26.0 years (IQR 15.3–38.80) (19).

Meanwhile, in a small proportion of studies, higher

TAC has been reported in children with thalassemia (23, 24) and thalassemia trait adults compared with healthy controls (25). The compensating antioxidant response as a result of excessive oxidative stress, a higher proportion of younger red blood cells in TDT patients, and chelation therapy by deferoxamine were mentioned as the possible suggested mechanisms for increased TAC in patients with β-thalassemia major (24).

As described above, most of the studies are in accordance with decreased antioxidant capacity in thalassemia patients, which supports the possible beneficial effects of antioxidant therapy in these patients. NAC and Vitamin E have been used as antioxidant agents in thalassemia patients for this purpose with controversial results.

Vitamin E is one of the most potent natural lipid-soluble antioxidants in the body. It acts as a potent scavenger of lipid radicals in the membranes of red blood cells and inhibits the propagation of free radical reactions (26, 27).

Based on the findings of our meta-analysis, the effect of Vitamin E therapy, as an antioxidant agent, was mainly related to the subgroup of children, as hemoglobin significantly increased, and TOS and OSI both significantly decreased in children which raise the hypothesis of possible beneficial antioxidant effect of Vitamin E in the children subgroup affected by TDT. Noteworthy, both of these findings were only limited to one study in children.

On the other hand, regarding our recent RCT on adult TDT patients, a significant decrease in TOS after three months of Vitamin E therapy was detected (1). Given the change score in this meta-analysis, the findings should be interpreted cautiously, indicating that further well-designed controlled clinical trials with larger sample sizes; considering other important influencing factors are needed to more precisely evaluate the antioxidant effect of Vitamin E both in adults and children with TDT.

Researchers reported favorable antioxidant effects of 90 days of supplementation therapy with the combination of Vitamin E and C in patients with type-2 diabetes mellitus (28), as well as combination daily supplement therapy with magnesium (250 mg and Vitamin E 400 mg for 12 weeks) in women with polycystic ovary syndrome. However, the level of thiobarbituric acid-reactive substances (TBARS), as a maker of serum lipid peroxidation, was not significantly decreased (29). Also, the immunomodulatory effects of supplemental Vitamin E have been clarified in alleviating several viral, bacteria, and allergic diseases such as asthma (30).

Some studies investigated the effect of Vitamin E on oxidative stress status in TDT patients by measuring different biomarkers of oxidative stress and antioxidant capacity, not TOS and TAC as a whole. Thus, we could not include their results in our meta-analysis but discuss their findings here.

Trangsuwanet al. (26) reported the successful effect of 6-month Vitamin E therapy (200-400 mg per day) in children with β-thalassemia major and Hb E/β-thalassemia patients. They illustrated the possible effect of Vitamin E with 10 mg per kg daily on partially reduced oxidative stress by correcting Vitamin E level and improving the glutathione peroxidase level. However, transfusion requirement or hemolytic parameters were not improved. The authors concluded that this finding might be related to the persistent high iron overload in these patients, which causes the failure of using Vitamin E alone to improve other oxidative biomarkers and clinical endpoints. However, adding vitamin C in another study as 3-month combination therapy of Vitamin E and vitamin C in children with TDT who had low levels of vitamins E and C again showed similar findings. At the end of the study, Vitamin E and vitamin C levels, and glutathione, were significantly increased. However, MDA, TAC, and hemoglobin showed no significant changes (31).

On the other hand, the addition of another antioxidant to Vitamin E supplement [cocktails consisting of a combination of hydrophobic (Vitamin E or curcuminoids) and hydrophilic antioxidants (NAC) and an iron chelator (Deferiprone)] showed more beneficial effects on oxidative stress, hemoglobin concentration, and hypercoagulable state in adult patients with non-transfusion dependent β-thalassemia/Hb E patients (32). It seems that combination therapy compared to monotherapy and persistently high iron overload can partly explain the difference in clinical response among previous studies (26, 31, 32).

Mahjoub et al. (33) reported a marked reduction in malondialdehyde (MDA) concentration as an index of lipid peroxidation in erythrocytes membranes in patients with beta-thalassemia major with a mean age of around 18 following four weeks of vitamin E therapy (550/kg). In contrast, children with

β-thalassemia major who were treated with vitamin E supplement with the dosage of 200-600 mg/kg/day for four weeks showed no significant change in the MDA level or endogenous antioxidants, but a substantial effect on RBCs membrane was observed by indirectly increasing the level of haptoglobin levels and decreasing hemolysis (27).

Conventionally recommended antioxidant mechanisms for NAC include direct oxidant scavenging, disulfide reduction in the lung mucins, and GSH biosynthesis. However, A new conceptual framework for NAC mechanism, namely as a Cys pro-drug, is evolving, leading to the modest elevations of H2S and sulfane sulfur species inside cells (11).

The beneficial antioxidant effect of NAC, as an adjunct therapy, has been described in some diseases, including patients with sepsis (34), hospitalized patients with HIV associated tuberculosis (35), and in combination with glycine in older adults for improvement of the insults of human aging such as mitochondrial dysfunction and inflammation (36). However, high dose infusion of NAC for 24 hours revealed no significant improvement in the total antioxidant potential in critically ill patients (37), which can be related to the short duration of treatment with NAC. Moreover, various performances following NAC consumption have been reported in the literature, possibly due to differences among individuals regarding the level of NAC absorbed by the body as well as the amount of developing endogenous antioxidants (38).

Based on our review, the effectiveness of NAC in thalassemia patients was limited to children. As in subgroup analysis, NAC significantly increased Hb and decreased TOS and OSI in children, suggesting that NAC can be an effective antioxidant agent in children affected by TDT. Although various factors might affect TAC in thalassemia patients, age can be a crucial influencing factor considering our results. However, due to the lack of required data, we could not evaluate other possible influencing factors concurrently in this meta-analysis.

In summary, most of the studies mentioned above showed various degrees of antioxidant effects of Vitamin E and NAC therapy, even with a similar protocol. Several factors such as age, details of the treatment protocol, disease severity, and iron overload could affect clinical response with NAC or Vitamin E.

Age is an important factor in oxidative stress status and antioxidant capacity and consequently on the response to antioxidant therapy in thalassemia patients. As children affected by thalassemia showed increased TAC compared to healthy individuals (23, 24) as well as good clinical response to antioxidant agents in our pooled meta-analysis and in some other studies (6). In addition, iron is the main initiator of oxidative stress in patients with β-thalassemia by increasing ROS production. Iron excess in thalassemia patients is mainly due to transfusion iron overload and suppressing hepcidin synthesis, a regulatory hormone produced by the liver. The suggested mechanism of suppressing hepcidin is enhanced erythropoiesis, leading to increased gastrointestinal iron absorption in these patients (39). It is hypothesized that patients with thalassemia may poorly respond to vitamin E with inadequate improvement in oxidative biomarkers due to persistent iron overload (26). Iron status is affected by several factors such as the disease severity, volume and interval of blood transfusions, hepcidin synthesis, type of iron chelation therapy, and patients´ compliance. All of these factors can consequently ameliorate oxidative stress status. Therefore, accurate assessment of iron status with T2*MRI of heart and liver or liver iron concentration (LIC) should be considered in proper evaluation of oxidative stress biomarkers and response to antioxidant therapy. Unfortunately, our meta-analysis faced many missing data, so we could not consider serum ferritin level as a marker of iron overload and an influencing factor in evaluating the exact response to antioxidant therapy. Moreover, other components such as uric acid, ascorbate or plasma proteins, and bilirubin as endogenous antioxidants have been reported as influencing agents on the TAC level either by interfering with the measurement of TAC or by expressing as the main component of TAC (9). Higher uric acid and bilirubin in thalassemia patients were determined as the potential causes of higher TAC in these patients compared to healthy individuals. However, after adjusting these two components, TAC remained higher, indicating the likelihood of other unidentified factors affecting the oxidative pathway (24). Uric acid was determined to increase TAC in leukemia/solid gynecological tumors compared to healthy individuals (40). Accordingly, Manafikhi et al. (20) suggested that the interference of hyperuricemia and hyperbilirubinemia should be considered for evaluating the antioxidant status of thalassemia patients. Corrected TAC based on these

two factors and especially uric acid-independent TAC can be a more accurate index.

Another concern is the controversial findings regarding the effect of splenectomy on oxidative biomarkers in thalassemia patients. Splenectomized patients experience more severe oxidative stress and damage compared to non-splenectomized patients (19). The suggested mechanism is that the circulating abnormal red cells enhance the potential for free radical production and deplete antioxidants, which result in considerable oxidative damage compared to the patients with an intact spleen. Increased % MetHb was determined as another cause of worsening oxidative stress status in splenectomized patients (41). In contrast, TOS was significantly lower in TDT patients who were splenectomized than non-splenectomized ones (1). Also, lower MDA level was reported after splenectomy in patients with thalassemia intermedia, probably due to less transfusion requirement (42). These discrepancies suggest the possibility of uncontrolled concurrent confounding factors affecting oxidative and antioxidant pathways in patients.

Disease severity is another challenging issue that seems to be influential on oxidative biomarkers of thalassemia patients. This hypothesis is supported by substantial variability in biomarkers of oxidative damage which are observed both within and between different types of thalassemia syndromes (19). However, Manafikhiet al. (20) reported no significant association between disease severity and oxidative status of thalassemia patients.

Moreover, some disease-related complications in TDT patients such as chronic liver disease might impact the endogenous antioxidants synthesis, making impairment in oxidative status and antioxidant capacity (43). Another influential issue on oxidative status of thalassemia patients can decrease the dietary intake of Vitamin E and C which vary both between individuals and within various syndromes (19).

Another question raised here is whether iron chelation therapy has beneficial effects on oxidative biomarkers in thalassemia patients. Possibly, it depends on the effect of ICT on the patients' iron status, whether it is helpful to improve oxidative stress status of the patients (24), or no impressive results probably due to the persistent iron overload despite chelation therapy (19, 21).

As to drug safety, both NAC (10 mg per kg per day for3-6 months) and Vitamin E (10 IU per kg per day for 3-6 months) were well tolerated by thalassemia patients without any severe adverse event. Only mild transient gastrointestinal symptom, skin rash, and flushing were reported (1, 32, 44-46). However, high-dose Vitamin E supplementation (≥ 400 IU/d for at least one year) increased all-cause mortality in adults (47). Also, side effects of NAC occur more frequently while using a higher dosage of NAC (>5 g per day) compared to a smaller dosage (<2 g per day)(38) or using incorrect dosing (48).

Our study had some limitations. The population was heterogeneous due to different age groups. The number of relevant published papers was limited, and we evaluated only English-language papers. Moreover, we were not able to do subgroup analysis due to some potentially confounding factors. However, our study was the first meta-analysis on this topic and, with subgroup analysis based on age, provided some insights into the beneficial effects of antioxidant therapy in TDT patients.

5. Conclusions

Based on this meta-analysis, Vitamin E (10 IU per kg per day for 3-6 months) improved anemia in TDT children. Similarly, NAC (10 mg per kg per day for 3-6 months) increased Hb in TDT children based on the review. Moreover, both Vitamin E and NAC showed a beneficial antioxidant effect in TDT children based on our review. More well-designed randomized, controlled trials on the effect of NAC and vitamin E in adults and children are recommended besides paying attention to the essential influencing factors, especially uric acid level and iron status in TDT patients.

Abbreviations

Transfusion-dependent thalassemia (TDT)
N-acetyl cysteine (NAC)
Total antioxidant capacity (TAC)
Total oxidative stress (TOS)
Oxidative stress index (OSI)
Randomized-controlled trials (RCT)
Weighted mean differences (WMD)
Hemoglobin (Hb)
International Prospective Register of Systematic Reviews (PROSPERO)

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Conflict of Interest

No conflict of interest

Ethics approval

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethics code: IR.SUMS.REC.1400.188).

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