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Cost-effectiveness analysis of Manuka honey-Omega-3 combination treatments in treating oxidative stress of pediatric β-thalassemia major

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Abstract. – OBJECTIVE: Oxidative stress represents a ruthless complication of β-thalassemia that worsens the severity of that medical condition. There is no conclusive evidence on the best antioxidant used for that issue. Our earlier clinical study concluded that Omega-3 and Manuka honey add-on to the conventional therapy had a potential therapeutic impact on reducing oxidative stress. However, there is no research evaluating their cost-effectiveness. This paper compares the cost-effectiveness of Omega-3 and Manuka honey supplementation to conventional therapy in treating oxidative stress among children with β-thalassemia major.

SUBJECTS AND METHODS: Cost-effectiveness evaluation of daily supplementation of Omega-3-Manuka honey and Manuka honey alone to the conventional therapy was performed. The economic evaluation was performed on data from a prospective 10-month randomized clinical trial. Fifty patients were recruited into the Omega-3-Manuka honey plus conventional therapy group, 50 patients were included in the Manuka honey alone plus conventional therapy group, and 50 patients receiving the conventional therapy alone served as a control group. Effectiveness measures from the randomized clinical trial were used to determine incremental effectiveness. Cost estimates were calculated from the healthcare payer's perspective. The analysis considered the improvement in oxidative stress biomarkers presented here as a percent change from baseline to determine the incremental effectiveness and cost for the treatment by both interventions.

RESULTS: Adding Omega-3 or Manuka honey to conventional therapy was a more cost-effective add-on than conventional treatment alone. Omega-3-Manuka honey was more cost-effective than Manuka honey alone in treating oxidative stress in that condition. Oxidative stress biomarkers were significantly reduced with both experimental medications compared to the conventional therapy alone.

CONCLUSIONS: The present study showed that using Manuka honey and Omega-3 as add-on treatments for oxidative stress in pediatric β-thalassemia disease could have significant cost-saving and clinical improvement.

Key Words:
Omega-3, Manuka honey, Cost-effectiveness, Oxidative stress, Children, Pediatrics, Incremental effects, Incremental costs.

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Introduction

β-thalassemia major type is a hematological recessive disorder manifested with accumulation of α-globin locus and reduced β-globin locus[1]. As a result, excessive α-globin locus continues to be produced within the erythroid precursor, forming inclusion bodies. The inclusion of bodies leads to peripheral hemolysis and ineffective erythropoiesis[2]. In addition, the excessive α-globin locus promotes the formation of reactive oxygen species (ROS), which damage the lipid constituents of cell membranes. Eventually, lipid peroxidation and oxidative stress are developed[3].

The oxidative stress in β-thalassemia major patients is a serious pathological alteration in these patients[1,4]. It leads to cell death and organ dysfunction. The oxidative stress aggravates the symptoms of β-thalassemia major patients, including hemolysis, ineffective erythropoiesis, and organ failure. In addition, hemoglobin instability is developed secondary to oxidative stress in these patients, promoting the excessive production of ROS[1,4,5]. As a result, ROS promotes the lipid oxidation of red blood cell (RBC) membranes, leading to cytotoxicity and organ failure[1].

The frequent blood transfusion leads to iron accumulation over the transferrin capacity. After that, non-transferrin-bound iron accumulates in the blood and forms liable iron pool (LIP) and iron overload (hyperferritinemia)[1,6,7]. The LIP promotes the ROS generation that leads to cytotoxicity and organ failure[1,6,7]. Moreover, the aggravated ineffective erythropoiesis secondary to ROS production decreases hepcidin expression, which is the key regulatory molecule of systemic iron homeostasis. Thus, subsequent iron overload is developed[8].

Patients with β-thalassemia major are heavily exposed to regular blood transfusion procedures as a conventional therapy for them. As a result, iron overload develops in several organs in these patients[4,9]. Free intracellular iron (Fe^{2+}) in the organs, under the effect of oxygen, activates ROS that promotes lipid peroxidation of the membrane of RBCs[1,9,10]. F2-isoprostane (8-iso-PGF2α) is significantly correlated with lipid peroxidation and oxidative stress status in these patients[11,12].

Prior literature[13-17] has previously reported that 8-iso-PGF2α was a stable and accurate biomarker for lipid peroxidation and oxidative stress. Accordingly, measuring this biomarker in response to therapeutic intervention is beneficial in managing oxidative stress in β-thalassemia major patients.

Lipid profiles, including low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C), have correlated with lipid peroxidation status in several diseases. Abnormal levels of LDL-C and HDL-C are promising biomarkers of activated lipid peroxidation in β-thalassemia major patients[18-20].

As such, measuring those biomarkers would be beneficial in response to the experimental interventions in the present study.

Lactate dehydrogenase (LDH) has been considered[21] a biomarker for intravascular hemolysis in several diseases. Oxidative stress that was developed secondary to blood transfusion-induced iron overload leads to hemolysis and ineffective erythropoiesis. Elevated serum LDH levels have been reported in β-thalassemia major patients in previous studies[21,22]. Thus, measuring this biomarker would be beneficial in response to the experimental interventions of the present study.

The complications of oxidative stress include cell injury, cell death, severe anemia, organ dysfunction, degradation of unstable hemoglobin, and iron overload[23]. In addition, frequent hospitalization is noticed with those patients for regular blood transfusion, the standard treatment of severe anemia in that case[24]. An iron chelator manages patients with β-thalassemia major to treat the elevated iron levels secondary to oxidative stress and frequent blood transfusion therapy[25].

The prevalence of β-thalassemia in Egypt is high. The carrier rate of the disease in the Egyptian population is about 9-10%[26], with about 10,000 registered cases. Conversely, there are 20,000 unregistered cases[27]. The total annual cost of β-thalassemia is 14.3 million USD (268,737,528 EGP), calculated to be 1,432 USD (EGP 26,874) per patient in one treatment year[27]. 53% of the total annual cost is incurred for the direct medical cost of the treatment, including medication and monitoring costs[28].

Previous clinical studies[28] have reported the cost-effectiveness of the conventional therapy of β-thalassemia conditions. The mean annual direct medical cost in Dubai has been reported to correspond to 131,156 United Arab Emirates dirham (AED) (USD 35,713). In the United Kingdom, the life cost of treating β-thalassemia major has been reported to correspond to £219,068[28]. In the USA, the cost of treatment of

β thalassemia has been calculated to correspond to $127,553 as mean annual costs per patient[29]. The lifetime treatment cost of β-thalassemia with chelation therapy has been calculated at USD 3.7 millions[30].

Management of oxidative stress in β-thalassemia patients could be clinically impactful[12]. Our previous clinical study[31] has implied a significant effectiveness of adding Omega-3 – Manuka honey combination to the conventional therapy (blood transfusion and iron chelator) of β-thalassemia. Adding that combination to conventional therapy has significantly reduced the oxidative stress biomarkers (serum LDH and CRP). In addition, it has significantly increased the lipid stability of the RBC membrane (Increasing LDL-C and HDL-C)[31].

To date, no cost-effectiveness study denotes conclusive clinical evidence on managing β-thalassemia disorder with its associated complications. The present study was conducted to compare the cost-effectiveness of adding Omega-3-Manuka honey combination or Manuka honey alone to the conventional therapy compared to the conventional treatment alone (blood transfusion + iron chelator) in treating β-thalassemia and its oxidative stress among the Egyptian pediatric population.

Subjects and Methods

Study Design and Interventions

The present economic study was performed based on our previous clinical study[31] and investigated the effectiveness of our experimental interventions. The present economic study investigated child patients diagnosed with β-thalassemia major and who presented oxidative stress (elevated 8-iso-PGF2α level) and oxidative stress-induced iron overload (hyperferritinemia). Participants were recruited from Beni-Suef Health Insurance Hospital and other Giza governmental hospitals. They included 165 pediatric patients (86 males, 64 females) aged 7-18 years with SCD who presented with elevated 8-iso-PGF2α and serum ferritin levels. The baseline characteristics of the patients are described in Table I. The time horizon of the present economic study is 10 months, from 2019-11-05 to 2020-11-05. Patients received conventional therapies during the first two months of the study. After that, they received the experimental medications combined with the conventional therapy for ten months. Thus, the cost of treatment for the first two months was measured for the conventional therapies only and the combination of experimental and conventional therapies in the subsequent ten months.

The study's patients were randomly divided into three groups: 1) the Omega-3 + Manuka honey supplementation group (n=50), which received 350 mg (12 mg/kg/day) of eicosapentaenoic acid (EPA), 250 mg (6 mg/kg/day) of docosahexaenoic acid (DHA)[32,33], Manuka honey lozenge MGO-400 (Methylglyoxal-400)=344 (12 mg/kg/day), and Unique Manuka Factor-13 (UMF-13)[34-36]; the Manuka honey alone supplementation group (n=50), which received MGO-400=344 mg (12 mg/kg/day), and UMF-13[34-36]; the control group (n=50), which received the conventional treatment alone (deferasirox 21 mg/kg/day)[37] for ten months (maximum dose of 28 mg/kg/days) plus regular sessions of blood transfusion adjusted to the patient profile. All study groups received the conventional therapy of β-thalassemia.

The experimental interventions used in the study were obtained from well-known, recognized producers as follows: the Omega-3 supplements were sourced from 'SEDICO' pharmaceutical company (6-October City, Egypt), while the Manuka honey supplements were sourced from 'Manuka Health' (Auckland, New Zealand).

The primary clinical outcome of this economic evaluation was the level of 8-iso-PGF2α (oxidative stress biomarker). The secondary outcomes were blood transfusion frequency, hospitalization rate, LDL-C level, HDL-C level, LDH serum level, and serum ferritin level.

The clinical effectiveness of the experimental intervention was investigated in our previous clinical trial[31] as follows: blood specimen was collected and transported to the hospital's hematology laboratory of Beni-Suef University, Egypt, or occasionally to Alfa-Lab Diagnostics, Egypt. The hematological parameters (serum LDH and ferritin) were measured using a hematology analyzer (LH-series and AU-series Beckman coulter commercial kits, Beckman Coulter Inc., Fullerton, California, USA). The lipid profile (serum LDL-C and HDL-C) was measured through the clinical chemistry laboratory using automated procedures on the biochemical auto-analyzer (Hitachi 912 auto-analyzer, Roche Boehringer Mannheim Diagnostics, Indianapolis, IN, USA).

The F2-isoprostane (Plasma of 8-iso-PGF2α) was measured following adaptive protocol from the previous literature[38]. The plasma of 8-iso-PGF2α was measured quantitatively using Hewlett

Table I. Average cost-effectiveness ratio for ten months of treatment and differences presented as percentage change from the control group.

Clinical variable	Effectiveness definition	Baseline values[A] mean ± SD	Treatment group	Effectiveness percentage differences	ACER value (USD)
8-iso-PGF2α (pg/mL)	Significant reduction of 8-iso-PGF2α in plasma level compared to the control group at month ten treatment	541 ± 19	Control	-11%	10,409.00
		538 ± 16.2	Omega 3-Manuka honey + Standard	- 67%*[,C]	2,561.00
		544 ± 15.6	Manuka honey alone + Standard	- 60%*[,C]	2,805.00
Blood transfusion frequency (Number of sessions of transfused blood)	Significant reduction of blood transfusion frequency compared to the control group at month ten treatment	8.5 (8.1, 9.1)[E]	Control	- 14%	8,179.00
		7.4 (6.9, 8.1)[E]	Omega 3-Manuka honey + Standard	- 45%*[,B]	3,813.00
		8.9 (8.2, 9.4)[E]	Manuka honey alone + Standard	- 35%*[,B]	4,809.00
Hospitalization rate (Residency days at the hospital)	Significant reduction of hospitalization rate compared to the control group at month ten treatment	4 ± 1	Control	Zero%*[,D]	Zero%*[,D]
		2 ± 2	Omega 3-Manuka honey+ Standard	- 50%*[,B]	3,432.00
		3 ± 2	Manuka honey alone + Standard	- 40%*[,B]	4,207.00
Serum ferritin, (ng/mL)	Significant reduction of serum ferritin level compared to the control group at month ten treatment	1,690.00 ± 202	Control	- 22%	5,205.00
		1,700.00 ± 230	Omega 3-Manuka honey+ Standard	- 38%*[,C]	4,516.00
		1,623.00 ± 189	Manuka honey alone + Standard	- 37%*[,C]	4,549.00
Serum LDH (U/L)	Significant reduction of LDH level compared to the control group at month ten treatment	519 ± 139	Control	- 4%	28,625.00
		513 ± 122	Omega 3-Manuka honey+ Standard	- 37%*[,C]	4,637.00
		522 ± 145	Manuka honey alone + Standard	- 3%*[,C]	84,150.00
Serum LDL-C (mg/dL)	Significant reduction of LDL-C level compared to the control group at month ten treatment	50 ± 15.4	Control	+13%	8,807.00
		52 ± 11.5	Omega 3-Manuka honey + Standard	+29%*[,C]	5,917.00
		54 ± 10.5	Manuka honey alone + Standard	+16%*[,C]	10,519.00
Serum HDL-C (mg/dL)	Significant reduction of HDL-C level compared to the control group at month ten treatment	37 ± 7.3	Control	+5%	22,900.00
		32 ± 6.7	Omega 3-Manuka honey+ Standard	+22%*[,C]	7,800.00
		35 ± 5.8	Manuka honey alone + Standard	+7.5%*[,C]	22,440.00

[A]Baseline value was the data of variables over 10 months prior to the start of the study and was retrieved from the hospital records during the first two months of this present study, [B]Kruskal-Wallis test, [C]Post-hoc comparison with the control group, [D]No change from baseline, [E]Median (Quartile 1, Quartile 3), *Significantly different from control group value at $p < 0.05$. SD, standard deviation; USD, United States Dollar; ACER, Average cost-effectiveness ratio; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; LDH, lactate dehydrogenase.

Packard 1100 high-performance liquid chromatography system series with 1100 photodiode array detectors (HP 1100 HPLC, Agilent Technologies, Wilmington, DE) linked to Gas chromatography-mass spectrometry (GC-MS system). The GC-MS system was composed by Hewlett Packard 5890 Series II Gas chromatography and Trio 1000 mass spectrometry (HP 5890 series II GC - Trio 1000 MS, Fisons instruments, Manchester, United Kingdom).

The present economic study is conducted based on data from a clinical trial approved by the Be-

Table II. Health resources utilization over ten months of treatment.

Health resource units[C]	Control	Omega-3 – Manuka + conventional treatment group	Manuka honey alone + conventional treatment group
Hospitalization (number of days)	7 ± 1.5	4 ± 1.5*,A	5 ± 0.85*,B
Blood transfusion (number of session)	8.5 ± 2.5	7.4 ± 1*,A	8.9 ± 1.8
Follow-up and monitoring visits (number of visits)	8 ± 2	5 ± 1.7*,A	6 ± 0.42*,B
Omega-3 supplements (1,000 mg/30 capsules)	0	40 ± 2	0
Manuka honey (400 mg unit/15 Loz)	0	18 ± 0.5	18 ± 1
Deferasirox (360 mg/30 tab)	10 ± 1.0	10 ± 1.50	10 ± .2.5

*Significantly different from control group value at $p < 0.05$; [A]: Post-hoc comparison between Omega-3-Manuka honey and control; [B]: Post-hoc comparison between Manuka honey alone and control; [C]: Unit of medication, omega-3 supplements (each unit of 30 capsules), Manuka honey lozenge (each unit of 15 lozenge), Deferasirox (each unit of 30 tables of 360 mg).

ni-Suef University Institutional Review Board (FMBSUREC/07072019/Gamaleldin) and was registered on ClinicalTrials.gov (NCT04292314). The study was implemented according to the principles of the Declaration of Helsinki.

Cost and Effectiveness

The healthcare payer perspective was applied in estimating the cost calculation of the study, where costs were expressed in American dollars (USD) at the exchange rate of the 2020 year. The cost of healthcare resources was obtained from the hospital records for all interventions and monitoring procedures on the last ten months of the treatment duration.

The effectiveness endpoint was calculated as a percentage reduction for the following variables: 8-iso-PGF2α, hospitalization rate, blood transfusion frequency, serum ferritin, and LDH. Conversely, endpoints for LDL-C and HDL-C variables were calculated as a percentage increase. The time horizon for the effectiveness was ten months of treatment (Table I).

The costs included in the present study were the direct medical (medications costs) and non-medical costs (monitoring costs). The medication costs include the experimental and conventional therapy (blood transfusion and the iron chelator) costs. The monitoring costs include clinician visits, hospitalization, and biochemical lab investigations. The costs for all resources were calculated for each resource unit and then were multiplied by the number of utilized resources (Tables II and III).

Cost-Effectiveness Analysis

The average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) calculations were used in the present cost-effectiveness economic analysis. The following formula calculated the cost-effectiveness ratio (CER) for a unit of effectiveness:

$$\mathrm{ACER}_{\mathrm{Intervention}} = \frac{\text{Total costs}_{\text{ Intervention}}}{\text{Total effectiveness}_{\text{ Intervention}}}$$

Table III. Total costs per patient over ten months of treatment.

Health resource	Conventional therapy group (control) USD	Omega-3-Manuka + conventional treatment group USD	Manuka honey alone + conventional treatment group USD
Hospitalization (days)	57 ± 1.45	33 ± 0.67	40 ± 1
Blood transfusion (number of session)	174 ± 2.6	151 ± 1.4	181 ± 2.1
Follow-up and monitoring visits (number of visits)	98 ± 2	62 ± 1	74 ± 2
Omega-3 supplements (1,000 mg/30 cap)	Zero	163 ± 1.9	Zero
Manuka honey (400 mg/15 Loz)	Zero	735 ± 2.2	735 ± 2.9
Total costs	1,145.00 ± 2.3	1,716.00 ± 1.3*,A	1,683.00 ± 2.1*,B

USD, United States Dollar. *: Significantly different from the control group value at $p < 0.05$. [A]: Post-hoc comparison between Omega-3-Manuka honey and control, [B]: Post-hoc comparison between Manuka honey alone and control.

The ICER was defined as the additional costs calculated to attain an extra unit of effectiveness and was calculated according to the following formula:

$$ICER_{\text{Intervention-1 vs. Intervention-2}} \frac{Cost_{\text{Intervention-1}} - Cost_{\text{Intervention-2}}}{Effectiveness_{\text{Intervention-1}} - Effectiveness_{\text{Intervention-2}}}$$

The intervention alternatives of the study were the Omega-3 combined with Manuka honey supplements or Manuka honey supplements alone, in addition to the Deferasirox (iron chelator) and blood transfusion (control). Microsoft Excel version 2016 (Microsoft Corporation, Redmond, Washington, USA) was used to implement the decision tree of the pharmacoeconomic analysis and calculate ACER and ICER values.

Statistical Analysis

The data was analyzed using the SPSS (Statistical Package for the Social Sciences) version 25 (IBM Corp., Armonk, NY, USA). The *p*-value <0.05 was considered significant. The investigators used G-Power software (version 3.1, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany) to calculate the sample size for the data retrieved from our previous clinical trial. The sample size was made by 165 patients, divided as follows: 50 patients (control group), 50 patients (Omega-3 combined with Manuka group), and 50 patients (Manuka honey alone group). Fifteen patients were dropped from the final statistical analysis because of adherence to the treatment. Descriptive data were presented as mean and standard deviation. Kruskal-Wallis' H test was performed to analyze the differences in the mean for blood transfusion frequency and hospitalization rate variables. Two-way analysis of variance (ANOVA) and post-hoc LSD tests were performed to analyze the variance among the study groups for the rest of the variables.

Results

One hundred fifty (150) patients were allocated in the final analysis as follows: 53 in the control group (mean age 11 ± 3.5), 49 in the Omega-Manuka group (mean age 12.5 ± 5.5), 48 in the Manuka alone group (mean age 9 ± 4).

Costs and Resource Utilization

Healthcare resource utilizations are presented in Table II. Results showed that adding Omega-3-Manuka honey combination or Manuka honey alone to the conventional therapy increased the healthcare utilization compared to the control group only. Nevertheless, both medications denoted higher effectiveness, which was significantly higher (p=0.041 for Omega-3-Manuka, p=0.039 for Manuka alone) than the control group (Table I). The utilization of healthcare resources for hospitalization and follow-up/monitoring visits was statistically significant for the experimental groups only compared to the control group. In addition, the utilization of blood transfusion was statistically significant for the Omega-Manuka group only compared to the control group. The hospitalization residency for Omega-3-Manuka and Manuka alone were (mean of 4 ± 1.5, p=0.031; mean of 5.00 ± 0.85, p=0.042; respectively) compared to the control group (7 ± 1.5). For the follow-up/monitoring visits utilization, the mean values of resource utilization for Omega-3-Manuka and Manuka alone were (5 ± 1.7, p=0.021; 6 ± 0.42, p=0.036, respectively) compared to the control group (8.00 ± 2.00). Table II shows the detailed analysis findings.

Costs were retrieved from the hospital records and reported for each patient monthly. All costs were expressed in the United States dollar (USD) year of 2022. The healthcare payer perspective is applied in cost calculations. The results showed that adding Omega-3-Manuka or Manuka alone to the conventional therapy resulted in more extra costs than the conventional therapy alone.

Cost-Effectiveness Analyses

Cost-effectiveness analyses for Omega-3-Manuka and Manuka honey alone showed remarkable effectiveness variables compared to the control group (Table I). The utilization costs of health resources over ten months of treatments were 1,716 USD for the Omega-Manuka group, 1,683 USD for the Manuka alone group, and 1,145 for the control group. Thus, experimental interventions were cost-increasing with higher effectiveness compared to the control group (Table I). The ACER calculations for reducing the level of 8-iso-PGF2α (oxidative stress biomarker) was 2,561 USD for the Omega-3-Manuka honey group (p=0.023) and 2,805 USD for the Manuka honey alone group (p=0.039) compared to the control group (10,409 USD). Similarly, Omega-3-Manuka honey combination (3,813 USD, p=0.035) and Manuka honey alone (4,809 USD, p=0.045) groups showed cost-effective

interventions in blood transfusion frequency variables, compared to the control group (8,179 USD).

Omega-3-Manuka honey combination (3,432 USD, p=0.049) and Manuka honey alone (4,207 USD, p=0.028) were cost-effective interventions with remarkable effectiveness compared to the control group without effectiveness for the hospitalization rate variable. For the serum LDH variable, the Omega-3-Manuka honey combination (4,637 USD, p=0.025) was more cost-effective than the control group (28,625 USD). Omega-3-Manuka honey combination and Manuka honey alone groups were more cost-effective than the control group for the lipid peroxidation-induced- oxidative stress biomarkers (LDL-C and HDL-C) (Table I).

Eventually, both experimental interventions were cost-increasing and more effective than the control group. Therefore, an incremental cost-effectiveness ratio was calculated to figure out the additional costs incurred to the extra effectiveness.

The incremental cost-effectiveness ratio (ICER) was calculated for the oxidative stress biomarkers to determine the additional costs per extra effectiveness (Table IV). For the level of 8-iso-PGF2α, the ICER value of the Omega-3-Manuka group was 1,020 USD, implying 56% additional effectiveness compared to the control group. For the Manuka alone group, the ICER was 1,098, implying 49% additional effectiveness.

The ICER calculations showed that Omega-Manuka and Manuka-alone interventions were cost-effective in reducing the frequency of blood transfusion in β-thalassemia patients. The ICER for reducing the blood transfusion frequency was 1,841 USD, implying 31% (Omega-Manuka group) and 21% (Manuka alone group) of additional effectiveness compared to the control group.

The control group showed no significant change from the baseline for the hospitalization rate. Conversely, the ICER value of the Omega-Manuka group was 330 USD, implying 10% additional effectiveness compared to the Manuka alone group (Table IV).

The ICER value for the hemolysis biomarkers (serum LDH) denoted that the Omega-Manuka group was cost-effective compared to the Manuka alone and control groups. The ICER for reducing serum LDH of the omega-Manuka group was 1,730 USD (33% additional effectiveness) compared to the control group and 97 USD (34% additional effectiveness) compared to the Manuka alone group.

The ICER value for reducing the lipid peroxidation biomarkers (LDL-C and HDL-C) denoted a cost-effectiveness result compared to the control group. The ICER for increasing LDL-C was 3,569 USD (16% extra effectiveness) compared to the control group and 254 USD (13% extra effectiveness) compared to Manuka alone group. The ICER value for increasing HDL-C was 3,359 USD (5% extra effectiveness) compared to the control group and 228 USD (14.5% extra effectiveness) compared to the Manuka alone group.

Table IV. The incremental cost-effectiveness ratio (ICER) calculations for all groups per ten treatment months.

Variable	Treatment group A	Treatment group B	ICER Value (USD)
Plasma 8-iso-PGF2α	Omega-3-manuka	Control	1,020.00
	Omega-3-manuka	Manuka alone	471
	Manuka alone	Control	1,098.00
Blood transfusion frequency	Omega-3-manuka	Control	1,841.00
	Omega-3-manuka	Manuka alone	330
	Manuka alone	Control	2,562.00
Hospitalization rate	Omega-3-manuka	Manuka alone	330
Serum LDL-C	Omega-3-manuka	Control	3,569.00
	Omega-3-manuka	Manuka alone	254
	Manuka alone	Control	17,933.00
Serum HDL-C	Omega-3-manuka	Control	3,359.00
	Omega-3-manuka	Manuka alone	228
	Manuka alone	Control	21,520.00
Serum LDH	Omega-3-manuka	Control	1,730.00
	Omega-3-manuka	Manuka alone	97

USD, United States Dollar; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; LDH, lactate dehydrogenase.

Discussion

The present pharmacoeconomic study concluded that the Omega-Manuka combination and Manuka alone were cost-effective treatments for the oxidative stress of β-thalassemia major children. The incremental costs of both interventions were relevant to their effectiveness in reducing oxidative stress biomarkers compared to the conventional therapy alone (Table I, Table IV).

Previous health economic studies concluded that managing β-thalassemia disease (including the disease complications) resulted in a higher health burden from the payer economic perspective[39]. In line with that, developing countries faced significant difficulty in containing the costs of that disease because of the higher costs associated with the conventional therapy of β-thalassemia[40]. Therefore, the management of β-thalassemia represents an arduous challenge for most health systems in developing countries[41].

A previous economic study[42] reported rigorous costs in managing the oxidative stress of several diseases. In line with that, iron overload-induced oxidative stress increases the costs of managing the oxidative stress conditions, i.e., using an iron chelator and a potent antioxidant in managing oxidative stress[5,43].

Our study denoted conclusive evidence on managing oxidative stress secondary to iron overload with cost-effective treatment options. Adding Omega-3 and Manuka honey supplements to conventional therapy implied a 56% extra effectiveness compared to the 11% effectiveness implied by conventional therapy alone (Table I).

The cost of ten months of treatments with the conventional therapy in reducing the level of 8-iso-PGF2α (oxidative stress biomarker) by 11% from the baseline value was 11,450 USD compared to 17,160 USD with 67% from the baseline value by adding the Omega-3-Manuka honey to the conventional therapy (Table I-III).

As evident, incremental costs in reducing the level of 8-iso-PGF2α (oxidative stress biomarker) over ten months of treatment with the Omega-3-Manuka honey compared to the conventional therapy alone to attain extra effectiveness (56%) were 1,020 USD, which are cost-effective strategy compared to the conventional therapy (Table IV).

Blood transfusion therapy in β-thalassemia has shared about 30%, $1.6 million of the total cost of the disease in the USA. Although, it has resulted in iron overload and oxidative stress in those patients[30,44]. Our results showed significant evidence of reducing the costs and the frequency of transfusion sessions by adding Omega-3 and Manuka honey supplements to conventional therapy. The incremental cost of an additional 31% effectiveness in reducing the blood transfusion frequency was 1,841 USD over ten months of treatment with Omega-3-Manuka honey compared to the conventional therapy alone (14% effectiveness).

Previous studies[2,5,16,18,20,45] have reported that oxidative stress damages thalassemic patients' RBCs' lipid composition (lipid peroxidation). Thereby, peripheral hemolysis is developed, which leads to increasing the blood transfusion frequency in those patients. Excessive blood transfusion leads to iron overload and elevated oxidative stress biomarkers (8-iso-PGF2α). Besides, it increases the cost of treating thalassemia patients using iron chelator and frequent blood transfusion[2,5,16,18,20,45].

The present study concluded that Omega-3 and Manuka honey supplements significantly reduced lipid peroxidation status measured by lipid biomarkers (LDL-C and HDL-C). The incremental costs for increasing the level of LDL-C over ten months of treatment with the Omega-3-Manuka honey compared to the conventional therapy alone to attain extra effectiveness (16%) were 3,569 USD, which were cost-effective strategy compared to the conventional therapy (Table I, IV).

Similarly, incremental costs for increasing the level of HDL-C over ten months of treatment with the Omega-3-Manuka honey compared to the conventional therapy alone to attain extra effectiveness (17%) were 3,359 USD, which were cost-effective strategy compared to the conventional therapy (Table IV).

The present economic evaluation shows the difference in cost and effectiveness between adding Omega-3-Manuka honey combination and Manuka honey alone to the conventional therapy of β-thalassemia. However, the findings concluded that adding Omega-3-Manuka honey combination to the conventional therapy was more cost-effective than Manuka honey alone (Table I).

Incremental costs in reducing the level of 8-iso-PGF2α (oxidative stress biomarker) over ten months of treatment with the Omega-3-Manuka honey to attain extra effectiveness (7%) were 471 USD, which were cost-effective strategy compared to Manuka honey alone (Table IV).

Similarly, incremental costs in reducing the blood transfusion, serum LDH level (hemolysis biomarker), and lipid peroxidation biomarker (LDL-C and HDL-C) over ten months of treatment with the Omega-3-Manuka honey compared to Manuka honey alone to attain extra effectiveness were cost-effective (Table IV).

Limitations

The current study denoted some limitations, including the medium sample size, and further future investigation should be performed with a larger sample size. In addition, there were few prior research articles on the cost-effectiveness of the conventional therapy for β-thalassemia. Thus, the cost-effectiveness of conventional therapy is still inconclusive. Moreover, the duration of the current study was too short to include all clinical outcomes in the cost-effectiveness analysis model.

Conclusions

The present economic evaluation study demonstrated that implementing a more cost-effective intervention could result in cost-effective treatment of the oxidative stress secondary to β-thalassemia. In agreement with previous studies in the literature, the present study found that treating oxidative stress in β-thalassemia was associated with high costs. However, the results suggested that adding Omega-3 or Manuka honey supplements to conventional therapy increases overall effectiveness with the relevant cost incurred to that effectiveness. Omega-3-Manuka honey combination and Manuka alone were a cost-effective add-on to the conventional therapy in treating oxidative stress of β-thalassemia. Besides, the Omega-3-Manuka honey combination was a more cost-effective add-on than Manuka honey alone.

These findings shed light on the importance of those interventions in treating oxidative stress and improving the clinical outcomes of thalassemic patients. The knowledge gained in this study could have significant implications on policy and clinical decision-making in treating and managing pediatric β-thalassemia major.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contribution

The corresponding author, on behalf of all authors, hereby states that all authors have made substantial contributions to the design of the work. Conceptualization, Material preparation, data collection, and analysis were performed by M. Gamaleldin. The first draft of the manuscript was written by M. Gamaleldin, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Study design, supervision, review, and editing, I. Abraham, M. Meabed; Review and supervision, A. Elberry; Data interpretation, supervision, and review, R. Hussein; Data collection, patient site recruitment, A. Hussein; Data interpretation and statistical analysis, S. Abdelhalim, and D. Waggas. Dr. R. Hussein and Prof. I. Abraham, respectively, were the chair and co-chair of the Ph.D. dissertation that generated the present article.

Ethics Approval

The present study was performed based on a previous clinical trial approved by the Beni-Suef University Institutional Review Board (FMBSUREC/07072019/Gamaleldin) and was registered on ClinicalTrials.gov (NCT04292314). The study was implemented following the principles of the Declaration of Helsinki.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. The data are secured and not publicly available due to their containing information that could compromise the privacy of the research's patients.

Informed Consent

A signed consent form was obtained from the legal guardians of all participants who were enrolled in this study. All participants were recruited voluntarily with the signed informed consent of their legal guardians (parents).

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