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Cost-effectiveness analysis of adding omega-3 or vitamin D supplementation to standard therapy in treating painful crises of pediatric sickle cell disease patients

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Abstract. – OBJECTIVE: Painful crises represents a predominant complication of sickle cell disease (SCD). The only approved treatments for painful crises in many countries are hydroxyurea plus potent analgesics. Our earlier clinical trial concluded that omega-3 and vitamin D had a potential therapeutic impact on painful crises. However, there is limited research evaluating their therapeutic applications and cost-effectiveness. This paper aims at comparing the cost-effectiveness of omega-3 and vitamin D supplementation to the standard therapy in treating painful crises among children with SCD.

PATIENTS AND METHODS: Cost-effectiveness analyses of daily supplementation of omega-3 and vitamin D were performed. The economic evaluation was based on data derived from a prospective 10-month randomized clinical trial (n = 165 patients; 15 patients dropped). 50 patients were recruited into the omega-3 + standard therapy group (hydroxyurea and folic acid daily with ibuprofen as needed), 50 patients into the vitamin D + standard therapy group, and 50 patients receiving standard therapy alone served as a control group. Outcome 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 various outcome measures and are presented here as percent change from baseline to determine the incremental effectiveness and the incremental cost for the treatment of both interventions.

RESULTS: Adding omega-3 or vitamin D to the standard therapy was more cost-effective than standard treatment alone. Vitamin D was a cheaper but less cost-effective alternative for most outcomes between the two treatments, including LDL-C and HDL-C. It was also more cost-effective but less clinically effective in reducing vaso-occlusive crisis episodes and pain severity. Omega-3 supplementation was significantly more cost-effective than vitamin D supplementation and the standard treatment for those measures.

CONCLUSIONS: The present study showed that using vitamin D and omega-3 as add-on treatments for a painful crisis in pediatric sickle cell disease could have overall cost-saving and clinical benefits. However, further studies with a longer treatment duration are needed to establish more significant effects of the interventions for better policy and clinical decision-making.

Key Words:
Sickle cell disease, Sickle cell anemia, Cost-effectiveness, Vaso-occlusion, Children, Pediatrics, Incremental effects, Incremental costs.

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Introduction

Sickle cell disease (SCD) is associated with chronic hemolytic anemia and several clinical manifestations such as recurrent pain, substantial multi-organ failure, and stroke[1,2]. The disease is conceived to be endemic to most parts of Africa, the Middle East, India, and some locations in Mediterranean countries[3]. The disease complications, particularly acute vaso-occlusive crisis (VOC), are the hallmark of SCD. The painful episodes and other complications of SCD are associated with recurrent visits to emergency departments (E.D.), hospitalizations, lower quality of life, morbidity, and mortality[1,4]. Acute pain has been identified as the leading cause of hospitalization in patients with SCD[5]. The prevalence of SCD worldwide has been about 20 to 25 million individuals. About 50% of those patients have been in Africa, and around 100,000 individuals were affected in the United States[6]. The economic burden associated with SCD in Egypt was USD 1.3. Moreover, the societal burden associated with SCD in Egypt was USD 1.79[7]. In the USA, medical costs and healthcare resource utilization are associated with managing painful crises, which are $1.1 billion annually, and the average monthly cost per patient is $1,389[8,9].

Hydroxyurea has been one of the interventions used for a very long time as the sole pharmacotherapy for SCD. It is currently the only United States Food and Drug Administration (FDA)-approved disease-modifying therapy for SCD in children and adults. It has been reported to have significant clinical benefits[10-12]. The economic burden of SCD for patients treated with hydroxyurea plus folic acid and NSAIDs has been $20,128 in the 12 months follow-up treatment plan. Of those, $4,656 was for pharmacy costs and $2,399 for outpatients' costs[9]. Other agents targeting different vaso-occlusive mechanisms are therefore being investigated to improve pain management during a VOC, including agents targeting inflammatory processes. Thus, it has been suggested that anti-inflammatory agents can stop events leading to vaso-occlusion and subsequent VOC[4]. Omega-3 fatty acids [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] with pleiotropic effects have been demonstrated to improve SCD outcomes[4]. Previous clinical studies[13-15] on omega-3 and vitamin D supplements have shown considerable efficacy in patients with sickle cell anemia.

Indeed, there is a lack of health economic studies about healthcare resource utilization and costs of managing painful crises in the pediatric population. In line with that, the present study was designed to compare the cost-effectiveness of adding omega-3 or vitamin D supplementation to the standard therapy compared to the standard treatment alone (hydroxyurea, folic acid, and ibuprofen as needed) in treating painful crises in SCD among an Egyptian pediatric population.

Patients and Methods

Study Design

The present economic evaluation was performed based on a 10-months prospective, double-blinded, parallel assignment, randomized control study (1:1:1 allocation ratio)[16]. The study included child patients diagnosed with sickle cell anemia and presented with vaso-occlusive painful crises. Participants were recruited from Beni-Suef and Giza governmental hospitals. They included 165 pediatric patients (90 males, 60 females) aged 7 to 18 years with SCD who presented with an acute painful crisis. The baseline characteristics of the patients are described in Table I. Patients presented with hepatic diseases (alter the pharmacokinetics of the experimental interventions), renal disorder (induces pain masking the pain secondary to SCD), and any other chronic diseases were excluded from enrollment in the study. 15 patients from the original trial were not included in the final analysis because they either had infrequent lab test results (9 patients) or did not follow up with the treating physician regularly (6 patients). Biochemical analyses were measured using a hematology analyzer and the automated procedures of the clinical chemistry laboratory. The consent was obtained from the patients' parents before the study enrollment. Total health resources' cost and effectiveness were evaluated over 10 months. Patients were randomized to either the omega-3 supplementation group (n=50) that received 300-400 mg EPA and 200-300 mg DHA daily[17,18] or the vitamin D supplementation group (n=50) that received 1,500 IU to 3,500 IU[19,20]. The mean dose of vitamin D was 2,800 IU for 42 out of 50 patients. The treating physicians chose doses of vitamin D based on the vitamin D deficiency status of each patient. Both therapies were added to standard therapy daily for 10 months. The control group (n=50) received the standard treatment that included hydroxyurea and folic acid. All groups received standard hospital pharmacotherapy for SCD using hydroxyurea 20 mg/kg/day[21]

(maximum daily dose: 40 mg/kg) with biweekly monitoring of blood count and folic acid (0.5-1 mg/day)[22] for 3 to 4 weeks until definite hematologic response. Ibuprofen was given as needed at a maximum initial dose of 5 mg/kg[23]. Blood transfusions were administered based on hematological profiles. The primary clinical outcome of this economic evaluation was the number of painful episodes. The secondary outcomes were pain severity, hospitalization rate, low-density lipoprotein cholesterol (LDL-C) level, high-density lipoprotein cholesterol (HDL-C) level, lactate dehydrogenase (LDH) level, white blood cells (WBC) count, reticulocyte count.

The present economic evaluation is based on data from a clinical trial approved by the Beni-Suef University Institutional Review Board (IRB) (FMBSUREC/07072019/Sayed) and was registered on ClinicalTrials.gov (NCT04301336). The study was implemented following the principles of the Declaration of Helsinki.

Cost and Effectiveness

The cost estimates were calculated from the health care payer perspective, where costs were expressed in Egyptian pounds (EGP). The cost of treatment over 10 months was retrieved from the hospital financial records for each intervention. These included all costs of the resources used for standard and experimental medications. The costs were defined as the cost of all medications delivered to the patient during the 10-months period, either experimental or standard therapy, and the costs of hospitalization, blood transfusion, and physician visits.

Effectiveness was measured as a percentage of reduction (per 10-months treatment) from baseline to the following: painful episodes, pain severity, length of hospitalization, reticulocyte count, white blood cells count, and lactate dehydrogenase level. The percentage of LDL-C and HDL-C levels increased (per 10 months of treatment). All costs were estimated by identifying and quantifying all health resources used and multiplied by the cost of each unit. The utilization of health resources and unit costs (obtained from the hospital records) are described in Table II and Table III.

Cost-Effectiveness Analysis

A cost-effectiveness analysis was done using the average cost-effectiveness ratio (ACER) calculations and the incremental cost-effectiveness ratio (ICER) calculations. The cost-effectiveness ratio was defined as each intervention's cost for one unit of effectiveness. CER was calculated by dividing the interventions' net costs by the total effectiveness of that intervention according to the following formula:

The ICER was defined as the add-on cost incurred to attain an extra unit of effectiveness and was calculated according to the following formula:

The present economic evaluation was done for the intervention alternatives (treatment with omega-3 or vitamin D added to hydroxyurea, folic acid, and ibuprofen (control). The Cost-effectiveness model was built by Microsoft Excel version 2016 to calculate the average cost-effectiveness ratio (ACER) and Incremental cost-effectiveness ratio (ICER).

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) version 25 (IBM Corp., Armonk, NY, USA), was used to analyze the data. The significance level was posed to $p < 0.05$. We used G-Power software (version 3.1, HHU Düsseldorf, Düsseldorf, Germany) to calculate the sample size for the data source study. The sample size was 165 patients as follows: 50 patients (control group), 50 patients (omega-3 group), and 50 patients (vitamin D group). Fifteen patients were excluded from the final statistical analysis because of irregular follow-up with the treating physician. Data analysis was presented as mean and standard deviation. Kruskal- Willis' test was performed to analyze the differences in the mean for the primary outcome. Two-way ANOVA and post-hoc LSD tests were performed to analyze the variance among the study groups for the secondary outcomes.

Results

A total of 165 patients initially participated in the study. Only 150 patients, 50 in each group, were included in the cost-effectiveness analysis (omega-3 group - mean age 8.5 ± 4, 60% males; vitamin D group - mean age 10.5 ± 3.5, 50% males; control group - mean age 11 ± 5.5, 70% males).

Costs and Resources Utilization

The results for healthcare resource utilization are presented in Table II. Statistical analysis showed that adding omega-3 or vitamin D to the standard therapy implied more healthcare utilization compared to the control group only. Despite that, both medications showed higher effective-

Table I. Effectiveness and cost effectiveness results from the analysis and differences presented as percentage change from baseline[A].

Variable	Effectiveness endpoints	Baseline values[A]	Treatment Group	Percentage differences from control	CER Value (EGP)
VOC Episodes (number of painful episodes)	Significant reduction in VOC episodes *vs.* control after 10 months treatment	3 ± 2[E]	Control[D]	–30%	29,375
		4 ± 2	Omega 3 + Standard	–45%[*,B]	37,778
		5 ± 1	Vitamin D + Standard	–31%	35,484
VOC Severity (VAS pain score)	Significant reduction in pain severity *vs.* control after 10 months treatment	6 ± 1	Control[D]	No change [F]	No change [F]
		5.5 ± 1	Omega 3 + Standard	–50%[*,C]	34,000
		5 ± 1.5	Vitamin D + Standard	–33%[*,C]	33,333
Hospital days	Significant reduction in hospitalization days *vs.* control after 10 months treatment	3 ± 1	Omega 3 + Standard	–66.7%[*,C]	25,487
		2 ± 2	Vitamin D + Standard	No change [F]	No change [F]
		2 ± 3	Control[D]	No change [F]	No change [F]
WBC, leukocytosis ($10^3/\mu L$)	Significant reduction in white blood cells count *vs.* control after 10 months treatment	15.5 ± 2.5	Omega 3 + Standard	–12.7%[*,C]	133,858
		14.8 ± 3	Control[D]	No change [F]	No change [F]
LDH (U/L)	Significant reduction in lactate dehydrogenase level *vs.* control after 10 months treatment	420 ± 25	Control[D]	–21%	41,964
		410 ± 30	Vitamin D + Standard	–26%[*,C]	42,307
LDL (mg/dL)	Significant increase in low density lipoprotein *vs.* control after 10 months treatment	51 ± 13	Control[D]	+10.5%	83,928.5
		56 ± 12	Omega 3 + Standard	+20%[*,C]	85,000
		48 ± 15	Vitamin D + Standard	+13%[*,C]	84,615
HDL (mg/dL)	Significant increase in high density lipoprotein *vs.* after 10 months treatment	34 ± 2	Control[D]	+17%	51,838
		29 ± 3	Omega 3 + Standard	+27%[*,C]	62,962
		31 ± 5	Vitamin D + Standard	+17.5%	62,857
Reticulocyte (% count)	Significant reduction in reticulocyte percent count *vs.* after 10 months treatment	6 ± 4	Control[D]	–50%	17,625
		5 ± 3	Vitamin D + Standard	–60%[*,C]	18,333

[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 Willis test, [C]Post-hoc comparison with the control group, [D]Control group received the standard therapy, [E]Mean ± SD (all such values), [F]No change from baseline, [*]Significantly different from control group value at $p < 0.05$. SD, standard deviation; EGP, Egyptian pounds; ACER, Average cost effectiveness ratio; VOC, vaso-occlusive; LDL, Low-density lipoprotein; HDL, High density lipoprotein; LDH, lactate dehydrogenase.

ness which was significantly higher (p=0.033 for omega-3, p=0.042 for vitamin D) than the control group (Table I). The utilization of healthcare resources for blood transfusion and physician visits was not statistically significant between all groups. Thus, all groups in the comparison analysis showed a consistent utilization of values. The mean values of hospitalization days for omega-3 and vitamin D were (1 ± 0.75, p=0.027; 2 ± 0.80, p=0.038; respectively) compared to the control group (3 ± 0.45). For the medication utilization, the mean values of resources utilization for omega-3 and vitamin D were (12.5 ± 2, p= 0.029; 9.2 ± 2.5, p= 0.042; respectively) compared to the control group (7 ± 3). Table II shows the detailed analysis findings.

Costs were obtained from the hospital records and reported for each patient monthly. All costs were expressed with the national currency unit (EGP, Egyptian pound). Costs were estimated based on the healthcare payer perspective, including all direct costs (Table III). The results showed that adding omega-3 or vitamin D to the standard therapy resulted in more than the standard therapy alone. The mean values of total monthly healthcare costs for omega-3 and vitamin D (Table III) were significantly higher (1,700, p= 0.048; 1,100, p= 0.044) than in the control group (881.25).

Cost-Effectiveness Analysis

The cost-effectiveness analyses for omega-3 and vitamin D showed a consistent improvement in the effectiveness variables compared to the control group (Table I). The average cost-effectiveness ratio (ACER) for reducing the number of painful crises was 37,778 Egyptian pounds

Table II. Mean of healthcare resource utilization during 10-months treatment.

Resource	Control	Omega-3 + standard treatment group	Vitamin D + standard treatment group
Hospitalization (days)	3 ± 0.45	1 ± 0.75[*,A]	2 ± 0.80
Blood transfusion (number of session)	2 ± 2.3	2 ± 1	2 ± 1.5
Physician visits (number of visits)	1 ± 0.25	1 ± 0.60	1 ± 0.36
Medications (Packs)[a]	7 ± 3	12.5 ± 2[*,A]	9.2 ± 25[*,B]

[a]: Pack of medication, omega-3 supplements (each pack of 30 capsules), vitamin D (each pack of 30 ml), Ibuprofen (150 ml, 5 mg/100 ml), folic acid (each pack of 10 tablets). [*]: Significantly different from control group value at $p < 0.05$; [A]: Post-hoc comparison between Omega-3 and control; [B]: Post-hoc comparison between Vitamin D and control.

(EGP) for omega-3 (p=0.033), and 35,484 EGP for vitamin D (p=0.042) compared to the control group (29,375 EGP). Thus, both interventions were significantly costly compared to the control group. For the painful crisis severity, omega-3 was significantly costly (34,000 EGP, p=0.030) compared to the control group. Omega-3 was inevitably the most cost-effective among other interventions in the hospitalization variable (25,487 EGP, p=0.022). ACER for lactate dehydrogenase variable showed no significant difference between vitamin D and the control group. For low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), omega-3 and vitamin D were significantly costly compared to the control groups (Table I). Both omega-3 and vitamin D showed higher costs than the control group among all variables; nevertheless, both interventions showed higher effectiveness compared to the control group. Thus, an incremental cost-effectiveness ratio was calculated to investigate the additional costs incurred to the extra effectiveness induced by both interventions.

Incremental cost-effectiveness ratio **(**ICER) comparing the alternative treatments was also determined for the number of painful episodes, pain severity, LDL, HDL, LDH, and Reticulocyte (Table IV) except for hospitalization and white blood cells count (no change from baseline was reported). For the number of painful crises, the incremental cost-effectiveness ratio of omega-3 was 5,458 EGP, posed to additional 15% effectiveness compared to the control group. Conversely, no significant change was reported between vitamin D and the control group (Table I, Table IV).

The incremental cost for reducing pain severity showed that omega-3 and Vit-D treatments were cost-effective compared to standard treatment (control) with hydroxyurea and folic acid alone. The incremental cost-effectiveness ratio for reducing the pain severity was 3,529 EGP posed to additional 17% effectiveness between omega-3 and vitamin D interventions. The vitamin D group showed an ICER value of 4,375 EGP for additional 5% effectiveness compared to the control group. Results showed that the ICER value for LDL was 8,618 EGP for additional 9.5% effectiveness (omega-3) and 8,750 EGP for additional 2.5% effectiveness (vitamin D) compared to the control group. Similarly, The ICER value for HDL was 8,187.5 EGP for additional 10% effectiveness (omega-3) compared to the control group. For the Reticulocyte, the ICER value was 2,187.5 EGP for additional 10% effectiveness (vitamin D) compared to the control group. No significant change in the effectiveness was reported

Table III. Mean of total monthly costs during ten months treatment.

Resource	Control costs (EGP)	Omega-3 + standard treatment group costs (EGP)	Vitamin D + standard treatment group costs (EGP)
Hospitalization (days)	200 ± 1.45	200 ± 0.67	200 ± 1
Blood transfusion (number of session)	500 ± 2.5	500 ± 1.7	500 ± 2
Physician visits (number of visits)	10 ± 2	10 ±1	10 ±2
Study medications	171.25 ± 4.3	990 ± 2.2	390 ± 3.1
Total costs	881.25 ± 2.9	1700 ± 1.8[*,A]	1100 ± 2[*,B]

EGP, Egyptian pounds. [*]: Significantly different from control group value at $p < 0.05$. [A]: Post-hoc comparison between omega-3 and control, [B]: Post-hoc comparison between vitamin D and control.

Table IV. The incremental cost-effectiveness ratio (ICER) values for all groups.

Variable	Treatment Group A	Treatment Group B	ICER Value (EGP)
VOC Episodes	Omega-3 + Standard	Control	5,458
VOC severity	Omega-3 + Standard	Vitamin D + Standard	3,529
LDH	Vitamin D + Standard	Control	4,375
LDL	Omega-3 + Standard	Control	8,618
	Vitamin D + Standard	Control	8,750
HDL	Omega-3 + Standard	Control	8,187.5
Reticulocyte %	Vitamin D + Standard	Control	2,187.5

EGP, Egyptian pounds; VOC, vaso-occlusive; LDL, Low-density lipoprotein; HDL, High density lipoprotein.

for the HDL level between vitamin D and the control group.

Discussion

The cost-effectiveness evaluation showed that omega-3 and vitamin D were significantly effective compared to the control group. Incremental costs for both interventions were offset by their significant efficacy compared to the control group (Table IV).

Previous health economic studies[7,9] have found that managing sickle cell anemia (including the painful crises) incurred a considerable cost. In line with that, many countries around the globe showed a consistent increase in the cost of the management of sickle cell anemia which inevitably represents a big challenge for most health systems to manage the condition effectively with the least possible cost. The cost-effectiveness analyses of hydroxyurea medication in managing sickle cell anemia have shown a dramatically high cost. As such, it was reported that hydroxyurea cost $16,810 annually[24].

The results showed that adding omega-3 and vitamin D to the standard therapy included additional costs compared to the standard therapy alone. Although, significant effectiveness was reported for both interventions compared to the control group. As evident, healthcare decision-makers could easily prefer adding omega-3 or vitamin D to the standard therapy denoting the additional effectiveness (Table IV).

The ICER value of omega-3 supplements was 5,458 EGP for additional effectiveness. Results showed that omega-3 attained an extra 15% over the control group. In line with that, the addition of vitamin D to the standard therapy was not significantly different from the control group. The ACER analyses showed that hydroxyurea medication (standard therapy) cost 29,375 EGP per 10-months treatment in favor of a 30% reduction in the number of painful crises. For the pain severity, the standard therapy showed no significant difference from the baseline level.

Conversely, omega-3 and vitamin D significantly changed compared to the control group. Omega-3 posed a 50% reduction in pain severity (ACER=34,000), while vitamin D showed a 33% reduction in pain severity (ACER=33,333). Accordingly, the ICER value between both interventions was 3,529 EGP per extra 17% effectiveness in favor of omega-3 supplements (Table IV). This finding highlights the importance of adding both medications to the standard therapy. In addition, omega-3 addition was more cost-effective in reducing the pain severity than vitamin D.

Previous studies[17,25,26] have concluded that other biomarkers may help manage the number and severity of painful episodes, including LDL-C, HDL-C, LDH, and reticulocyte count. Our results concluded that omega-3 and vitamin D were cost-effective in addition to the standard therapy posed to those biomarkers (Table I, Table IV).

For LDH level, the standard therapy (hydroxyurea) costs 41,964 EGP to attain 21% effectiveness from baseline level over ten months of treatment. However, vitamin D cost 42,307 EGP to attain 27% effectiveness with an ICER value of 4,375 EGP for a 6% difference. Accordingly, vitamin D was a cost-effective addition to the standard therapy.

As for LDL-C and HDL-C levels, our results noticed that omega-3 was the best cost-effective addition to the standard therapy. Moreover, omega-3 was more cost-effective compared to vitamin D. Similarly, vitamin D was a cost-effective addition to the standard therapy in reducing the reticulocyte percentage count (Table I, Table IV).

Conclusions

The present CEA demonstrated that implementing a more cost-effective intervention could result in economic savings in the healthcare setting com-

pared to current standard therapy. Similar to literature, the present study found that managing painful crises in SCD was associated with high costs. Nevertheless, the results suggested that adding vitamin D or omega-3 to standard therapy increases overall effectiveness with slight cost increases compared to the standard treatment alone. Omega-3 was more cost-effective than vitamin D but costs slightly higher. These findings highlight the value of using omega-3 and vitamin D as a cost-effective add-on intervention that improves clinical outcomes compared to standard therapy for managing vaso-occlusive painful crises. Whether omega-3 and vitamin D used with standard therapy would result in even better outcomes than either agent used alone with standard therapy is unknown. A study comparing those treatments might be helpful. The knowledge gained in this study could have significant implications on policy, clinical decision-making, and the cost of treatment for VOC painful crises in pediatric patients with SCD. Policymakers and clinicians should adopt the interventions to improve outcomes for this patient population.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Contributions

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Ethics Statement

The present study was approved by the Beni-Suef University Institutional Review Board (IRB) (FMBSU-REC/07072019/Sayed) and was registered on ClinicalTrials.gov (NCT04301336). The study was implemented following the principles of the Declaration of Helsinki.

Informed Consent

All participants were recruited with a signed informed consent of their parents.

Data Availability

The original data supporting this study's findings are available on request from the corresponding author, [S.M. Abdelhalim]. The data are secured and not publicly available due to their containing information that could compromise the privacy of research participants.

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