Am J Blood Res 2020;10(6):447-458
www.AJBlood.us /ISSN:2160-1992/AJBR0114231

Original Article

Al-hijamah (the triple S treatment of prophetic medicine) exerts cardioprotective, tissue-protective and immune potentiating effects in thalassemic children: a pilot clinical trial

Mohamed El-Shanshory[1,2*], Nahed Mohammed Hablas[2*], Yasmin Shebel[2*], Osama Alhadramy[3*], Rehab El-Tahlawi[4,5*], Moutasem Salih Aboonq[6*], Tamer M Soliman[7*], Abdelhady Ragab Abdel-Gawad[7*], Sayed Mostafa El Sayed[8,9*], Hesham I Abdallah[8,9*], Hany Salah Mahmoud[10*], Hassan El-Allaf[11*], Samer El-Sawy[12*], Reda S Yousef[12*], Mostafa Abu-el Naga[13,14*], Reham A Mariah[15*], Manal Mohamed Helmy Nabo[16,17*], Mohamed Abdel-Haleem[18*], Ahmed Alamir Mahmoud[12*], Mohammad Ahmad Hassan[19*], Areej Hesham Al Arabi[20], Abdullah Ahmed Alnakhli[20], Salah Mohamed El Sayed[1,12,21*]

[1]Prophetic Medicine Course and Research Group, Taibah College of Medicine, Al-Madinah Al-Munawwarah, Saudi Arabia; [2]Department of Pediatrics, Tanta University Faculty of Medicine, Tanta, Gharbia, Egypt; [3]Division of Cardiology, Department of Medicine, Taibah College of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia; [4]Department of Microbiology, College of Medicine, Taibah University, Saudi Arabia; [5]Department of Microbiology, Faculty of Medicine, Zagazig University, Egypt; [6]Department of Medical Physiology, Taibah College of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia; [7]Department of Clinical Pathology, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt; [8]Department of Anatomy, Faculty of Medicine, Ain Shams University, Egypt; [9]Department of Anatomy, Taibah Faculty of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia; [10]Center of Scientific Foundation for Experimental Studies and Research, Ismailia, Egypt; [11]Department of Medical Physiology, Sohag Faculty of Medicine, Sohag University, Egypt; [12]Department of Medical Biochemistry, Sohag Faculty of Medicine, Sohag University, Egypt; [13]Department of Anatomy, College of Medicine, Al-Rayyan National Colleges, Al-Madinah, Saudi Arabia; [14]Department of Anatomy, Faculty of Medicine, New Damietta, Al-Azhar University, Egypt; [15]Department of Medical Biochemistry, Tanta Faculty of Medicine, Tanta University, Tanta, Egypt; [16]Division of Pediatric Cardiology, Pediatrics Department, Maternity and Children Hospital, Hail, Saudi Arabia; [17]Division of Pediatric Cardiology, Pediatrics Department, Sohag Teaching Hospital, Ministry of Health, Sohag, Egypt; [18]Department of Ear, Nose and Throat, Taibah Faculty of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia; [19]Department of Pediatrics, Sohag Faculty of Medicine, Sohag, Egypt; [20]Department of Cardiology, Governorate of Health, Uhud Hospital, Al-Madinah Al-Munawwarah, Saudi Arabia; [21]Department of Clinical Biochemistry and Molecular Medicine, Taibah Faculty of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia. [*]Equal contributors.

Received May 12, 2020; Accepted October 24, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Thalassemia is a major health problem in affected children due to iron overload, increased oxidative stress, atherogenic lipid profile and tissue-damage. This study aims at investigating the cardioprotective and tissue-protective benefits of Al-hijamah and their impact on cell-mediated immunity for treating thalassemic children. This study aimed also at investigating the tissue-clearance principle of Taibah mechanism: whenever pathological substances are to be cleared from the human body, Al-hijamah is indicated. Al-hijamah was done to thalassemic children (15 males and 5 females having a mean age of 9.07 ± 4.26 years) using sterile disposable sets in a complete aseptic hospital environment. Prior ethical committee agreement (in addition to written patient's consents) was obtained from Tanta Faculty of Medicine, Egypt. Twenty thalassemic children received iron chelation therapy plus Al-hijamah for one session (30-60 minutes) versus an age and sex-matched thalassemic control group treated with iron chelation therapy only. Al-hijamah is a quite safe outpatient hematological procedure that significantly decreased serum cholesterol (from 129.75 ± 3.67 to 103.5 ± 4.18 mg/dl) and decreased serum triglycerides (from 109.25 ± 8.96 to 91.95 ± 7.22 mg/dl). Interestingly, Al-hijamah exerted significant tissue-protective effects (it decreased serum GPT from 98.65 ± 12.27 to 71.65 ± 32.78 U/L and serum GOT from 96.35 ± 14.33 to 69.35 ± 34.37 U/L). Al-hijamah-induced ferritin excretion caused decreased serum ferritin (high serum ferritin negatively

correlated with cell mediated immunity). Al-hijamah exerted cardioprotective and tissue-protective and hypolipidemic effects. Al-hijamah decreased serum cholesterol and is cardioprotective for thalassemic patients as it protects against atherogenesis and atherosclerosis. Medical practice of Al-hijamah is strongly recommended in hospitals. Al-hijamah cleared blood significantly from causative pathological substances e.g. serum ferritin resulting in enhanced cell-mediated immunity (in agreement with the evidence-based Taibah mechanism).

Keywords: Thalassemia, Al-hijamah, iron chelation therapy, cholesterol, liver functions, clearance, Al-hijamah indices

Introduction

Children with β-thalassemia major exhibit increased endogenous oxidative stress-induced tissue damage evidenced by increased serum malondialdehyde (MDA), and MDA/low density lipoprotein-cholesterol (LDL-C) ratio and decreased plasma vitamin E levels [1-3]. Tissue damage in thalassemia involves many organs e.g. the liver and is characterized by raised serum hepatic transaminases (ALT and AST) in addition to elevated serum levels of cell death circulating biomarkers, M30 and M65 in patients with β-thalassemia major [4].

Thalassemia causes an atherogenic lipid profile (high serum cholesterol and LDL-C) where subclinical atherosclerosis started prematurely in children with beta-thalassemia than can be radiologically diagnosed through estimating the carotid artery intima to media thickness [5]. Currently, there is no single available treatment modality for thalassemia that exerts tissue-protective effects and improves patients' immunity.

Cupping therapy is a medical term that describes applying sucking cups to the skin for therapeutic purposes and includes both dry cupping therapy (DCT) and wet cupping therapy (WCT). Traditional WCT is currently practiced in Chinese hospitals (less frequently than DCT) and many other parts of the world for treating different medical conditions e.g. shoulder and neck pain [6]. Suction applied to cups is an external factor that can be controlled according to the therapeutic indications [7-12]. DCT is a one-suction step technique (single S technique) while wet cupping includes traditional Chinese WCT and prophetic medicine WCT (Al-hijamah). Al-hijamah is not practiced in Chinese medicine but is highly recommended in so many prophetic ahadith (sayings). Traditional Chinese WCT is a two-step technique (skin scarification and suction, double S technique). Al-hijamah is Arabic WCT of prophetic medicine and is a three-step technique (skin suction, scarification and suction, triple S technique) practiced in Arabic countries. Al-hijamah is a promising excretory treatment to clear blood of causative pathological substances (CPS) according to the evidence-based Taibah mechanism (Taibah theory). Taibah mechanism states that Al-hijamah uses a physiological excretory mechanism (pressure-dependent filtration and excretion) through the fenestrated capillaries of the skin dermis (acting as a filter) that resemble the fenestrated capillaries of the renal glomeruli. In Taibah mechanism, Al-hijamah also acts as a super kidney that can excrete all causative pathological substances (CPS) collectively and simultaneously outside the human body. This clears the tissues, serum and intercellular fluids from CPS and enhances the immunity.

In a previous report, Al-hijamah was reported to reduce serum ferritin (circulating iron stores) in healthy people (in one session) significantly by about 22.25% [13]. Excessive traditional Chinese WCT decreased serum iron significantly causing iron deficiency (in multiple sessions) [14]. Al-hijamah is an alternative treatment to phlebotomy for treating thalassemia with the advantage of minimal blood loss. We previously suggested Al-hijamah as a possible treatment for thalassemia [9, 10]. In this study, we aimed at investigating the two principles of Taibah mechanism: "whenever pathological substances are to be cleared from the human body, Al-hijamah is indicated. Al-hijamah enhances immunity". Moreover, in this study, we investigated Al-hijamah as a promising treatment for thalassemic children.

Materials and methods

Goals of the study

Primary goals of our study are to confirm safety, simplicity and effectiveness of Al-hijamah as an outpatient clinic therapeutic procedure that carries a lot of therapeutic benefits for treating thalassemic children. Secondary goals

of our study are to confirm safety of Al-hijamah in pediatric practice and to highlight its hypolipidemic effects. Investigating Al-hijamah-induced tissue protective effects is important to confirm safety of Al-hijamah in childhood medical practice.

Study design and participants

In a previous report, we proved that Al-hijamah is a powerful iron reduction therapy through direct excretion of iron and ferritin in the cupped bloody excretion expelled out during Al-hijamah [15]. In this study, we aimed at investigating the tissue-protective and possible hypolipidemic effects of Al-hijamah. Our study was conducted in 20 thalassemic children diagnosed with β-thalassemia major.

Ethics approval and consent to participate

Ethical committee approval from Tanta Faculty of Medicine, Tanta University, Gharbeya governorate, Egypt in 24-10-2014 and written patient's agreement consents were done to start this clinical trial. Committee's reference number is NCT 02761395. Trial registration was done in (www.ClinicalTrials.gov): under the name "*Study of The Therapeutic Benefits of Al-hijamah in Children with Beta-thalassemia major*" NCT 02761395. This clinical trial was registered in 30th January 2016.

Patients

All patients and their mothers were informed in detail about the steps of Al-hijamah. All patients and their guardians gave a written consent for joining the study. All participants were children having beta thalassemia major receiving regular treatment at the hematology unit, Tanta University Hospital, Tanta University, Egypt. All participants' families and patients themselves were educated well about the study and signed written agreement consent to perform the study. Inclusion criteria for our study included diagnosis of β-thalassemia major, desire to join the study and regular intake of iron chelation therapy. Exclusion criteria included hypersplenism, presence of associated medical conditions (thalassemia complicated with stroke) and severe anemia.

Study place and preparations

Al-hijamah was done at the pediatric hematology department, pediatric hospital, Tanta University, Egypt. Al-hijamah was done in a complete aseptic atmosphere by three physicians including pediatric hematologists and the corresponding author. All the procedure steps were approved by the ethical committee of Tanta faculty of medicine (Tanta University, Egypt) and according to Helsinki declaration. Duration of study was six months.

Careful donor selection and screening using voluntary regular non-remunerated blood donation was done. Before each transfusion, full blood cross-matching, screening for new antibodies and red cell antigen typing of patients (at least for C, E and Kell) were routinely done. Keeping a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient is a routine.

Procedures and variables assessment

Methods of our study included estimation of serum liver enzymes, cholesterol and triglycerides in all the investigated thalassemic children: control subjects (thalassemia children receiving iron chelation therapy) and also in the treatment group (receiving both Al-hijamah and iron chelation therapy) before and after Al-hijamah.

Precautions before the intervention

Blood samples were collected from the control group and intervention group (before Al-hijamah). Al-hijamah was done after receiving blood transfusion (variable duration ranged from 2 days to 2 weeks after transfusion). We did Al-hijamah for all patients having hemoglobin ≥9 g/dl at the time of the procedure. If patient's hemoglobin was less than 9 g/dl, blood transfusion was given first to raise hemoglobin to 9 g/dl then Al-hijamah was done.

Iron chelation therapy was matched in all groups of studied thalassemic children. All patients were treated with deferasirox in a dose of 20-30 mg/kg/day (once daily before meals). For patients having persistently high serum ferritin levels above 3000 ng/ml, deferasirox was combined with desferoxamine (20-40 mg/kg for 8-12-hour) via subcutaneous infusion using infusion pump or continuous intravenous infusion for 8-10 hours/day for 10 days per month. Patients' compliance was good in general.

Intervention

The therapeutic intervention given to the treatment group was Al-hijamah (suction, scarifica-

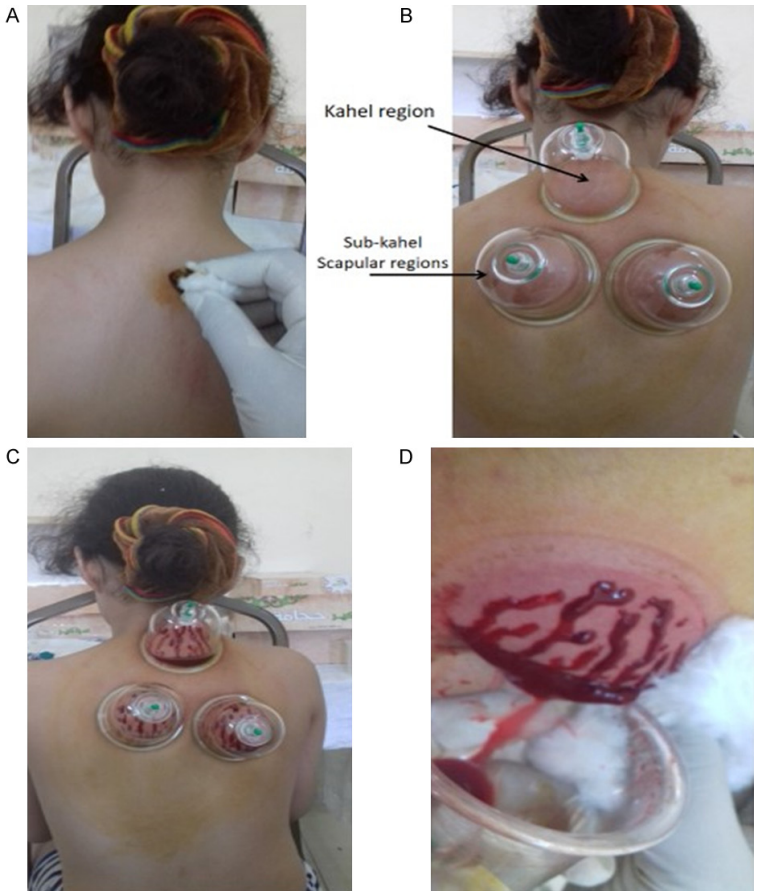

Figure 1. First step of Al-hijamah is skin suction (preceded by prior sterilization). A. Skin sterilization. B. Skin suction using sterile disposable sucking cups. Inside sucking cups, viscoelastic nature of the skin allows skin to be stretched forming hemidomes (skin upliftings) that are created beneath which exist collected filtered fluids and tissue fluids that cannot be excreted due to the presence of an intact skin barrier. The collected fluids contain causative pathological substances (CPS) e.g. high serum cholesterol and triglycerides. C. Shartat mihjam (skin scarifications during Al-hijamah): Skin scarifications should be multiple, longitudinal (about 1-2 mm in length i.e. not pinpoint pricks), in parallel rows, equally distributed, and productive. Proper superficial scratching (skin scarifications) during shartat mihjam is characterized by lack of profuse bleeding after scarification. Faulty deep scarifications may produce more bleeding. Sucking cups are applied immediately to encourage the excretion of collected fluids beneath the skin upliftings. D. Streaks of bloody excretion are coming out through the skin scarifications (shartat mihjam) until clotting terminates the excretion.

tion and suction = triple S therapeutic technique). Steps of Al-hijamah were done as previously reported [7-11]. Briefly, children and their families were informed in advance regarding the detailed steps of Al-hijamah procedure. Sterilization using sterile cotton soaked with povidone iodine was applied to the upper back and upper sternum (**Figure 1A**). First suction was done through applying sucking cups to indicated skin sites (**Figure 1B**) for 5 minutes using moderate suction induced via a hand-held pump. Skin upliftings were created (beneath which collected and filtered fluids containing CPS are gathered) after lifting the sucking cups. Sucking cups were also put at the upper sternum few centimeters below the neck. Skin upliftings were created. Skin scarifications were done as usual and sucking cups were applied to do the second suction step. Sterilization was done at the scarification sites. Sucking cups usually leave a well-demarcated skin upliftings that should be scarified immediately (**Figure 1B** and **1C**). Skin scarification was done in all Al-hijamah-induced skin upliftings (**Figure 1C**, **1D**). Skin scarification was superficial, vertical (1-3 mm in length), productive and in parallel rows confined to the skin upliftings (**Figure 1C**, **1D**). Second suction step was done immediately following skin scarification to allow for getting rid of the bloody excretion containing the CPS according to the evidence-based Taibah mechanism [7-11, 15].

Data monitoring and adverse events

Al-hijamah was terminated after putting the cups twice or three times. All patients in the intervention group were happy and comfortable. No adverse events were recorded. The bloody excretion got during Al-hijamah in pediatric practice was minimal. Finally, strict sterilization is applied.

Endpoints assessment

We assessed Al-hijamah-induced therapeutic effects regarding tissue protection, serum cholesterol and triglycerides. That was done within days to less than one month after Al-hijamah.

Evaluation of therapeutic indices of Al-hijamah [9, 11, 15]

All the measurements were done within one month duration after the single session of Al-hijamah. Indices of Al-hijamah were estimated as previously described [9, 11].

1. Excretion index (excretion value, EV) was estimated. EV is the quantity of noxious substances excreted after the end of the session of Al-hijamah in quantity units/volume units. EV can be calculated by determining the difference in levels of noxious substances before versus after Al-hijamah (in quantity units/volume units).

EV = [(Initial concentration of any substance in serum before Al-hijamah in concentration unit/blood volume unit) - (concentration of the same substance in serum after Al-hijamah in concentration unit)/blood volume unit)].

2. Purification index (PI): PI is the percentage purification of plasma from any CPS component estimated at different time points after Al-hijamah. Plasma clearance index, or purification index (PI), is the percentage purification of plasma from any noxious substance or component. PI can be calculated by estimating the difference between the concentrations of a noxious substance before versus after Al-hijamah divided by its initial plasma concentration level. PI can be calculated from the formula: PI = 100 × [(Initial concentration of any substance in serum before Al-hijamah - concentration of the same substance in serum after Al-hijamah)]/initial concentration of same substance in serum before Al-hijamah].

3. Pharmacological potentiation index (PPI) measures the degree of pharmacological potentiation gained when conventional pharmacological treatments are administered concomitantly with practicing Al-hijamah. It also compares the therapeutic benefits added by combining pharmacological treatments with Al-hijamah versus using conventional pharmacological treatment as a sole treatment.

4. Clinical therapeutic index (CTI): CTI is the percentage improvement of an investigated clinical parameter (e.g. liver function tests, diastolic blood pressure value, systolic blood pressure value, pain intensity value, disease activity value, and others) after Al-hijamah (as a sole treatment or as a combined treatment). It may be measured at different time points versus the same value before Al-hijamah.

CTI = [100 × (clinical parameter before Al-hijamah - clinical parameter after Al-hijamah)]/clinical parameter before Al-hijamah].

Biochemical evaluation

Serum liver enzymes e.g. serum glutamate pyruvate transaminase (SGPT = ALT, alanine transaminase), serum glutamate oxaloacetate transaminase (SGOT = AST, Aspartate transaminase), serum total cholesterol and triglycerides were measured in patients' serum in the central laboratory of the hematology and clinical pathology department at Tanta university hospital, Tanta, Egypt.

Statistical analysis

Data was collected, analyzed using SPSS software and presented as mean ± standard error of mean. Paired samples t test was used to compare results before and after Al-hijamah in the treatment group (paired data) i.e. within the same group (intervention group). Pearson correlation was studied between serum ferritin and CD4 and CD8 counts before Al-hijamah. Pearson correlation was also studied between previously reported serum ferritin [15] and CD4 and CD8 counts after Al-hijamah. * indicated $p < 0.05$, ** indicated $p < 0.01$ and *** indicated $p < 0.001$. Independent samples t test was used to compare results between different groups (intervention group versus controls). # indicated $p < 0.05$, ## indicated $p < 0.01$ and ### indicated $p < 0.001$.

Results

In this study, both Al-hijamah and iron chelation therapy were conducted on twenty patients previously diagnosed as β-thalassmia major. They were 15 males and 5 females. Mean age was 9.07 ± 4.26 years. Another twenty children having thalassemia major with matching age, sex and duration of illness served as controls that were maintained on iron chelation therapy (**Table 1**).

Table 1. Demographic data of patients (treatment and control groups) who participated in the study. All patients were age- and sex-matched and were allocated randomly in either a treatment or control group

Parameters	Number of patients in control group (n = 20)	Number of patients in the treatment group (n = 20)
Clinical features		
-Pallor	20	20
-Jaundice	20	19
-Splenomegaly	19	19
-Hepatomegaly	5	6
Frequency of blood transfusion		
-Every 2 weeks	18	17
-Monthly	3	2
Positive Consanguinity	15	15
Age at diagnosis (in months)	6-7.3	6-7.3

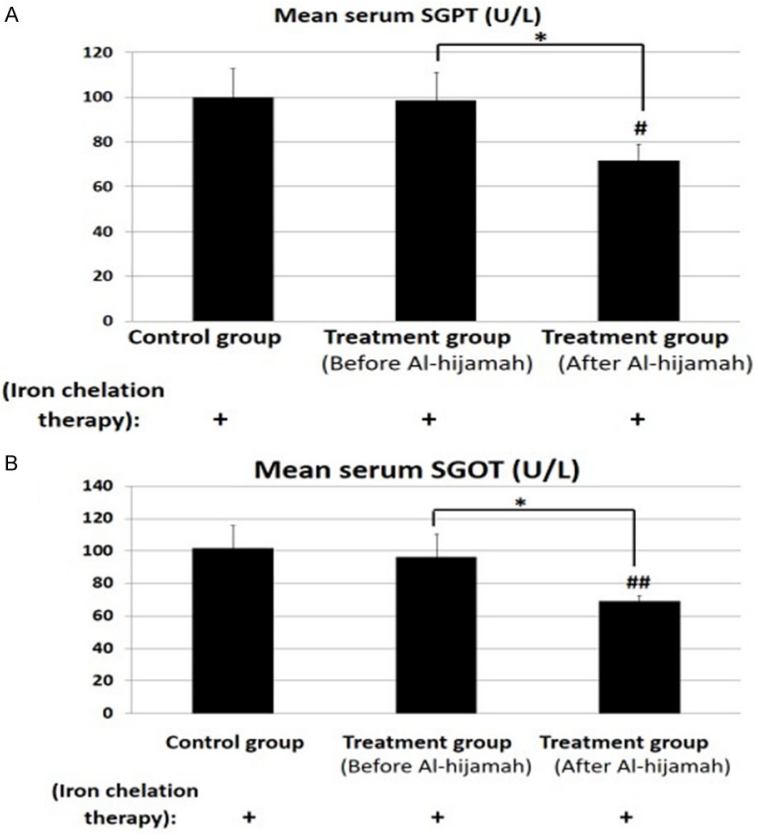

Figure 2. Combining Al-hijamah with iron chelation therapy exerted tissue-protective effects. A. Combining Al-hijamah with iron chelation therapy significantly decreased thalassemia-induced liver damage as evidenced by the decreased serum SGPT (ALT) ($p < 0.05$). B. Combining Al-hijamah with iron chelation therapy significantly decreased thalassemia-induced tissue damage as evidenced by the decreased serum SGOT (AST). * indicated $p < 0.05$ within the same group (intervention group). # indicated $p < 0.05$ and ## indicated $p < 0.01$ to compare results between different groups (intervention group versus controls).

*Al-hijamah exerted significant tissue-protective effects (**Figure 2A, 2B**)*

Al-hijamah proved to be hepatoprotective. Serum liver enzymes showed a significant decrease ($p < 0.05$) after the procedure where SGPT and SGOT were 98.65 ± 12.27 U/L and 96.35 ± 14.33 U/L, respectively before Al-hijamah and then dropped (after Al-hijamah) to 71.65 ± 32.78 U/L ($p = 0.03$) (**Figure 2A**) and 69.35 ± 34.37 U/L ($p = 0.02$) (**Figure 2B**), respectively (**Table 2**). There was no significant difference ($p > 0.05$) between the patients' serum liver enzymes in the control group (receiving iron chelation therapy only) versus the intervention group before Al-hijamah. SGPT was (99.70 ± 9.6 U/L (in control group) versus 98.65 ± 12.28) in intervention group before Al-hijamah (**Figure 2A**). SGOT was (101.65 ± 11.18 U/L (in control group) versus 96.35 ± 14.35) in intervention group before Al-hijamah (**Figure 2A**, **2B**). Using independent samples t test, serum SGPT (after Al-hijamah) was significantly different from the control group ($p < 0.05$) and so was serum SGOT ($p < 0.01$).

Al-hijamah induced significant cardioprotective effects (decreasing serum lipids)

No significant difference ($p > 0.05$) was found regarding serum cholesterol before Al-hijamah versus the control group. Al-hijamah significantly decreased serum cholesterol ($p < 0.001$) (**Figure 3A**) where serum cholesterol before Al-hijamah was 129.75 ± 3.67 mg/dl and decreased to 103.5 ± 4.18 mg/dl after Al-hijamah (**Table 3**). Using independent

Table 2. Tissue-protective effects exerted by Al-hijmah

	Serum GPT (ALT) (U/L)			Serum GOT (AST) (U/L)		
	Control	Before Al-hijamah	After Al-hijamah	Control	Before Al-hijamah	After Al-hijamah
	55	42	40	65	45	52
	80	71	115	99	55	71
	180	193	43	107	127	49
	78	68	64	57	52	58
	46	36	40	57	42	45
	148	168	114	192	212	142
	72	52	64	53	68	58
	78	98	90	140	125	122
	86	76	55	70	60	42
	135	145	140	95	85	83
	170	145	60	206	256	58
	82	71	115	145	125	122
	180	193	43	99	60	42
	57	68	60	71	81	68
	50	13	24	49	39	36
	76	55	42	95	62	45
	125	145	60	117	127	49
	108	98	90	62	52	58
	78	68	60	62	42	45
	108	168	114	197	212	142
Mean	99.7	98.65	71.65	101.65	96.35	69.35
SD	42.94976	54.90688	32.78523	49.95461	64.16531	34.27639
SEM	9.60	12.28	7.33	11.18	14.35	7.67

samples t test, serum cholesterol (after Al-hijamah) was significantly different from the control ($p < 0.001$). No significant difference ($p > 0.05$) was found regarding serum triglycerides before Al-hijamah (109.25 ± 8.96 mg/dl) versus the control group (110.9 ± 7.21 mg/dl) (**Table 3**) and **Figure 3B**. Al-hijamah significantly decreased serum triglycerides ($p < 0.01$) (**Figure 3B**). Before Al-hijamah, serum triglycerides were 109.25 ± 8.96 mg/dl and decreased to 91.95 ± 7.21 mg/dl (**Table 3**). Using independent samples t test, serum triglycerides (after Al-hijamah) was significantly different from the control ($p < 0.001$).

Efficacy of Al-hijamah as a general clearance treatment (therapeutic indices of Al-hijamah)

Therapeutic indices of Al-hijamah were calculated as previously reported [9, 11].

1. Excretion value (EV) for serum cholesterol = 129.75 - 103.5 = 26.25 mg/dl (**Figure 3A**) (**Table 2**). i.e. upon treating thalassemic children with Al-hijamah, about 26.25 mg/dl cholesterol was excreted from patients' blood (in cupped blood). Excretion value for serum triglycerides = 109.25 - 91.95 = 17.3 mg/dl i.e upon treating thalassemic children with Al-hijamah, about 17.3 mg/dl triglycerides was excreted from patients' blood (in cupped blood) (**Figure 3B**) (**Table 2**).

2. Purification index (PI, clearance index) for cholesterol = (129.75 - 103.5)/129.75 = 20.23%, i.e. a single session of Al-hijamah purified plasma from cholesterol (decreased serum cholesterol) by about 20.23%.

Excretion value for serum triglycerides = (109.25 - 91.95)/109.25 = 15.8%, i.e. a single session of Al-hijamah purified plasma from triglycerides (decreased serum triglycerides) by about 15.8%.

3. Pharmacological potentiation index (PPI) = [100 × therapeutic effects of (Al-hijamah + conventional pharmacological treatments)/(Therapeutic effects of conventional pharmacological treatments only)].

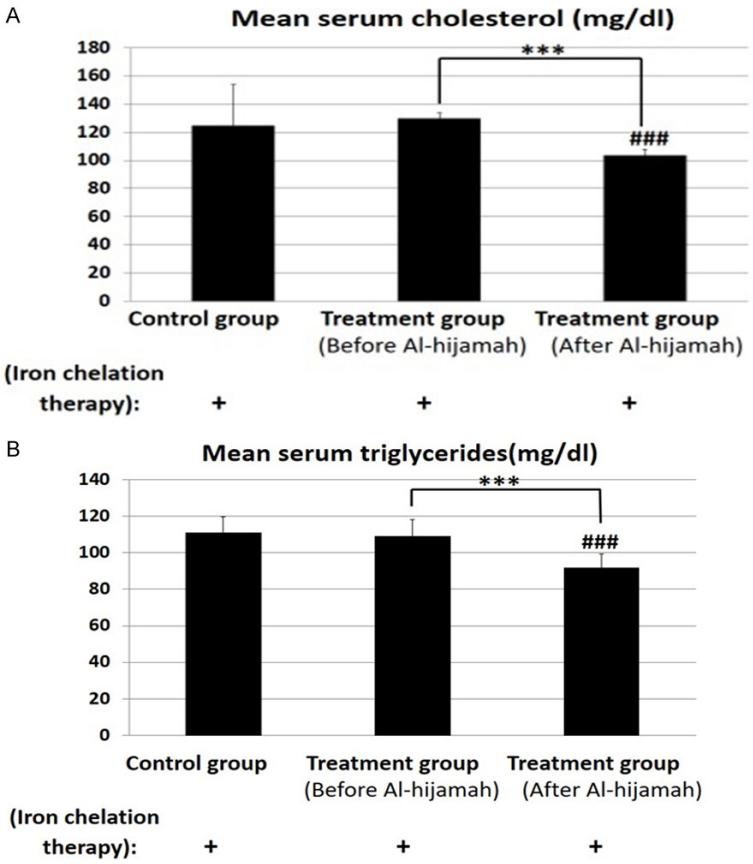

Figure 3. Al-hijamah exerted significant hypolipidemic effects. A. Combining Al-hijamah with iron chelation therapy significantly decreased serum cholesterol. B. Combining Al-hijamah with iron chelation therapy significantly decreased serum serum triglycerides. *** indicated $p < 0.001$ within the same group (intervention group). ### indicated $p < 0.001$ to compare results between different groups (intervention group versus controls).

4. Clinical therapeutic index (CTI) for SGPT (ALT, liver functions) = [100 × (90.9 - 69.55)/90.9] = 23.48% (**Figure 2A**). i.e. combination of Al-hijamah with iron chelation therapy improved liver functions by about 24% and exerted tissue protection.

CTI for SGOT (AST) = [100 × (96.35 - 69.35)/96.9] = 28% (**Table 2**). i.e. combination of Al-hijamah with iron chelation therapy did improve the serum level of the marker of tissue function tests (SGOT, AST) by about 28% and exerted tissue protection (**Figure 2B**).

Serum ferritin negatively correlated with cell-mediated immunity

In investigated thalassemic children before Al-hijamah, high serum ferritin (3778.35 ± 551.89 ng/ml) significantly (P = 0.004) and negatively correlated with CD4 count (124.1 ± 30.27 cells/mm^3) (Pearson correlation = -0.612) and significantly (P = 0.036) and negatively correlated with CD4 count (124.1 ± 30.27 cells/mm^3) (Pearson correlation is negative = -0.470).

After Al-hijamah, serum ferritin was significantly decreased (P < 0.001) due to percutaneous excretion during Al-hijamah. Al-hijamah-induced decrease in serum ferritin negatively correlated with CD4 counts (Pearson correlation = 0.-173) and also negatively correlated with CD8 counts (Pearson correlation is negative = -0.191) (**Table 4**).

Discussion

So many reported therapeutic benefits were attributed to both traditional WCT and WCT of prophetic medicine (Al-hijamah) that are promising to counteract many characteristic features of thalassemia [11]. In this study, we aimed at investigating the tissue-protective effects, immune potentiating effects, hypolipidemic effects and hypocholesterolemic effects of Al-hijamah. Immuno-modulatory effects of Al-hijamah were previously confirmed in rheumatoid arthritis patients [16]. Moreover, drug cupping therapy enhanced immunity in asthmatic subjects [17].

Moreover, young thalassemic patients exhibit an atherogenic lipid profile with high serum total cholesterol, triglycerides and oxidized LDL antibodies [18] while serum HDL is decreased. Carotid intima-media thickness (CIMT) may be elevated in thalassemic subjects and is usually correlated with serum ferritin, and cholesterol levels [19]. Recently, we introduced Al-hijamah as a novel iron reducing therapy that decreased serum iron overload and related oxidative stress [15]. Our current study confirmed that Al-hijamah treated many pathogenesis criteria of beta-thalassemia as we will discuss below.

Table 3. Hypolipidemic effects exerted by Al-hijamah

	Serum cholesterol (mg/dl)			Serum triglycerides (mg/dl)		
	Control	Before Al-hijamah	After Al-hijamah	Control	Before Al-hijamah	After Al-hijamah
	99	110	92	172	180	162
	136	146	95	83	79	40
	130	120	80	99	89	92
	119	137	110	128	114	98
	151	142	97	163	180	162
	124	132	130	87	79	40
	120	110	92	95	89	92
	136	146	95	93	87	72
	130	120	80	67	77	76
	127	137	110	99	112	99
	152	142	97	149	178	114
	142	132	130	136	98	102
	156	155	105	90	98	102
	93	101	125	97	92	79
	116	126	130	61	45	50
	150	140	114	127	134	98
	122	92	60	99	87	72
	139	128	121	89	77	76
	149	137	110	121	112	99
	122	142	97	163	178	114
MEAN	130.65	129.75	103.5	110.9	109.25	91.95
SD	17.1227	16.42807	18.70407	32.25866	40.07477	32.27428
SEM	3.830582	3.675184	4.184355	7.216702	8.965272	7.220196

Moreover, Al-hijamah clears blood significantly of CPS using the pressure-dependent and size-dependent filtration and excretion at the fenestrated dermal capillaries in a manner similar to the physiological renal excretion (according to the evidence-based Taibah mechanism). Al-hijamah adds a further advantage over phlebotomy where tissue clearance from CPS occurs through Al-hijamah but not through phlebotomy [12-16, 19].

Interestingly, our previous report [15] and current data proved that Al-hijamah exerted hepatoprotective and tissue-protective effects through reducing oxidative stress [15] and the liver function tests to near normal values (**Figure 2A**, **2B**). That can be explained on the bases that Al-hijamah decreases iron over load (through excreting iron, ferritin and tissue damaging oxidants in the cupped bloody excretion) and consequently decreases iron-induced free radical generation [15]. That greatly protects the liver and other tissues and helps to decrease serum transaminases (ALT and AST). Al-hijamah-induced decrease in serum cholesterol and triglycerides (**Table 3**) was evident and appears to be promising to bring serum lipids to near normal values. That can be explained on excretory bases (**Figure 3A**, **3B**) where we can get rid of a significant portion of serum cholesterol in the cupped bloody excretion during Al-hijamah. Al-hijamah-induced cardioprotection is multifactorial. Al-hijamah induced a significant decrease in iron overload and oxidative stress markers resulting in a subsequent significant increase in total antioxidant capacity [15] that is cardioprotective. It can be explained on the basis that when iron overload decreases in patients' serum, iron deposited in the tissues (e.g. heart, liver, skin, endocrine glands and others) will be mobilized from the tissues to blood. With subsequent sessions of Al-hijamah, more blood clearance of iron and iron-induced free radicals will occur. Consequently, more mobilization of the iron deposited in the tissues to the blood stream will take

Table 4. Correlation between Al-hijamah-induced ferritin excretion and Al-hijamah-induced enhanced cell mediated immunity

Patient's number	Before Al-hijamah			After Al-hijamah		
	Serum ferritin (ng/ml)	CD4 count (cells/mm^3)	CD8 count (cells/mm^3)	Serum ferritin (ng/ml)	CD4 count (cells/mm^3)	CD8 count (cells/mm^3)
1	2210	150	108	1148	183	118
2	7251	31	28	6120	343	258
3	4200	35	70	2712	185	125
4	3400	42	88	2398	168	105
5	3316	44	71	2241	965	729
6	2864	60	32	1990	150	76
7	2210	200	184	1148	709	293
8	3215	53	43	1990	116	550
9	2325	108	73	1426	724	235
10	2799	77	35	1870	532	79
11	1000	450	552	400	124	322
12	9210	15	33	8530	186	113
13	1407	425	200	977	350	258
14	2105	283	73	1065	183	125
15	7527	31	58	6692	343	105
16	3316	50	61	2182	185	729
17	2799	60	32	1900	67	150
18	1988	300	200	1005	709	293
19	3215	53	43	1990	116	550
20	9210	15	22	8530	186	235
Mean	3778.35	124.1	100.3	2825.3	326.2	272.4
SD	2466.986853	135.32	120.04	2499.65789	259.11	207.41
SEM	551.8986249	30.27	26.85	559.207582	57.97	46.34

place and so on. Purification of patients' tissues from deposited iron is quite tissue-protective.

Another mechanism to explain the cardioprotective effects of Al-hijamah in thalassemic patients is that Al-hijamah may be protective against atherogenesis and atherosclerosis. Al-hijamah-induced decrease in serum cholesterol (**Figure 3A**) may be promising in treating thalassemia-associated atherosclerosis. Moreover, Al-hijamah-induced decrease in serum triglycerides (**Figure 3B**) may be promising in treating conditions of hypertriglyceridemia. Al-hijamah also induced a significant decrease in serum triglycerides that was also significantly different from the control thalassemic group. Actually, a single session of Al-hijamah may be enough before repeating it after 2-3 months. Each patient should be individualized to decide the suitable time for the next session based on follow-up investigations e.g. serum ferritin, cholesterol, MDA and others. Al-hijamah-induced tissue-protective effects are due to excretion of harmful pathological substances (CPS) in cupped blood.

Al-hijamah-induced increase in cell-mediated immunity (CD4 and CD8 counts) can be explained by Al-hijamah-induced clearance of disease-causing substances e.g. high serum ferritin. A negative correlation was evident where decreasing serum ferritin (through Al-hijamah-induced percutaneous excretion) was associated with an increase in CD4 and CD8 counts. That partly explains Al-hijamah-induced immune potentiation (**Table 4**).

Our data are in agreement with the report by Bashiri et al. who reported that WCT improved patients having non-alcoholic fatty liver disease via inducing a significant decrease in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and serum ALT and AST

[20]. Our data also agreed with Tagil et al. who reported removal of oxidants (tissue-damaging mediators) via WCT (Al-hijamah) with a subsequent decrease in oxidative stress [21]. A similar report confirmed the blood clearance effects of WCT through decreasing serum levels of heavy metals (Aluminium, zinc, and cadmium) after cupping therapy (Al-hijamah) compared to their serum levels before [22]. Husain et al. reported that serum uric acid and systolic blood pressure showed a significant reduction at one and four months after Al-hijamah compared with baseline [23]. All those are in agreement with Taibah mechanism.

Conclusion

Al-hijamah did better than iron chelation therapy (in exerting tissue protection and immunological potentiation) and potentiated its therapeutic effects. Al-hijamah functions as an excretory treatment that excreted noxious substances in the cupped bloody excretion e.g. cholesterol. Al-hijamah did not aggravate the anemic status in thalassemic children owing to the minimal blood loss occurring during Al-hijamah. Practicing Al-hijamah as an outpatient therapeutic procedure is so beneficial for patients suffering from many different diseases for the large magnitude of its therapeutic benefits. Al-hijamah-induced clearance of tissue and blood CPS e.g. high blood cholesterol confirmed Al-hijamah-induced tissue protection. Primary goals of our study confirm safety, simplicity and effectiveness of Al-hijamah as an outpatient clinic and therapeutic procedure that carries a lot of therapeutic benefits for treating thalassemic children and related tissue protection effects induced by Al-hijamah to its antioxidant effects (mediated through free radical excretion). Al-hijamah cleared blood significantly from CPS e.g. serum ferritin resulting in enhanced cell-mediated immunity. Our data confirmed the two principles of Taibah mechanism: whenever pathological substances are to be cleared from the human body, Al-hijamah is indicated.

Limitations

Our study was limited by the small sample number that needs a bigger number of patients. This study was limited also by the small number of control thalassemic patients. This is a preliminary pilot study having a small sample size that is a limitation also. This study was a pilot clinical trial as indicated in the flow chart. Randomization was done while blindness was not possible as Al-hijamah is a skin procedure known to the patients and treating physicians not a blind drug treatment.

Future perspectives

We plan to do more detailed future large scale studies to investigate more detailed research items e.g. ratio of Th1/Th2. In our expanded future study, we plan to investigate total iron binding capacity (TIBC) also.

Acknowledgements

We are so grateful to Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia for kindly providing research materials and to Tanta University, Egypt for the efforts to perform this clinical trial. We are very grateful to Mr. Adel Joraibei Al-Obaidi, Mr. Raed Ali Al-Raddadi, Mr. Sultan Al-Hussini, Mr. Mohamed Abdelsamad and Mr. Wael Barakat from the administrative department, College of Medicine, Taibah University for their technical help and support to this work. This manuscript contains individual person's data images regarding performing Al-hijamah on the corresponding author's healthy child (an 8-years old daughter) for demonstration to show methodology of pediatric WCT of prophetic medicine (Al-hijamah). This is for age-matching with the thalassemic children that participated in the study. Both the guardian (corresponding author) and daughter agreed at the consent to publish. This consent is available from now on and can be submitted to the journal upon request at any time.

Disclosure of conflict of interest

None.

Abbreviations

CPS, Causative pathological substances; EDTA, Ethylenediaminetetraacetic acid; HDL, High density lipoprotein; LDL-c, Low density lipoprotein cholesterol; ROS, Reactive oxygen species; SGOT, Serum glutamate oxaloacetate transaminase; SGPT, Serum glutamate pyruvate transaminase; WCT, Wet cupping therapy.

Address correspondence to: Dr. Salah Mohamed El Sayed, Department of Clinical Biochemistry and Molecular Medicine, Taibah Faculty of Medicine,

Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia. Tel: +966-50-355-1588; +966-54-2927-804; +2-0934-602-963; Fax: +2-0934-602-963; E-mail: salahfazara@yahoo.com

References

[1] Rund D and Rachmilewitz E. β-thalassemia. N Engl J Med 2005; 353: 1135-1146.

[2] Yanpanitch OU, Hatairaktham S, Charoensakdi R, Panichkul N, Fucharoen S, Srichairatanakool S, Siritanaratkul N and Kalpravidh RW. Treatment of β-thalassemia/hemoglobin E with antioxidant cocktails results in decreased oxidative stress, increased hemoglobin concentration, and improvement of the hypercoagulable state. Oxid Med Cell Longev 2015; 2015: 537954.

[3] Nasr MR, Abdelmaksoud AM, Abd El-Aal KS, Mabrouk NA and Ismael WM. Plasma lipid profile and lipid peroxidation in beta-thalassemic children. J Clin Lipidol 2008; 2: 405-409.

[4] Esmaeil N, Moayedi B, Gharagozloo M and Maracy MR. Elevated serum levels of cell death circulating biomarkers, M30 and M65, in patients with β-thalassemia major. Hemoglobin 2013; 37: 404-410.

[5] Sherief LM, Dawood O, Ali A, Sherbiny HS, Kamal NM, Elshanshory M, Alazez OA, Alhady MA, Nour M and Mokhtar WA. Premature atherosclerosis in children with beta-thalassemia major: new diagnostic marker. BMC Pediatr 2017; 17: 69-77.

[6] Arslan M, Gökgöz N and Dane Ş. The effect of traditional wet cupping on shoulder pain and neck pain: a pilot study. Complement Ther Clin Pract 2016; 23: 30-33.

[7] El Sayed SM, Mahmoud H and Nabo M. Medical and scientific bases of Wet Cupping Therapy (Al-Hijamah): in light of modern medicine and prophetic medicine. Altern Integr Med 2013; 5: 1-16.

[8] El Sayed SM, Mahmoud H and Nabo M. Methods of wet cupping therapy (Al-Hijamah): in light of modern medicine and prophetic medicine. Altern Integr Med 2013; 1-16.

[9] El Sayed SM, Baghdadi H, Abou-Taleb A, Mahmoud HS, Maria RA, Ahmed NS and Helmy Nabo MM. Al-hijamah and oral honey for treating thalassemia, conditions of iron overload, and hyperferremia: toward improving the therapeutic outcomes. J Blood Med 2014; 5: 219-37.

[10] El Sayed SM, Abou-Taleb A, Mahmoud HS, Baghdadi H, Maria RA, Ahmed NS and Nabo MM. Percutaneous excretion of iron and ferritin (through Al-hijamah) as a novel treatment for iron overload in beta-thalassemia major, hemochromatosis and sideroblastic anemia. Med Hypotheses 2014; 83: 238-246.

[11] El Sayed SM, Al-quliti AS, Mahmoud HS, Baghdadi H, Maria RA, Nabo MM and Hefny A. Therapeutic benefits of Al-hijamah: in light of modern medicine and prophetic medicine. AJMBR 2014; 2: 46-71.

[12] Ahmadi A, Schwebel DC and Rezaei M. The efficacy of wet-cupping in the treatment of tension and migraine headache. Am J Chin Med 2008; 36: 37-44.

[13] ALSHOWAFI FK. Effect of blood cupping on some biochemical parameter. MJCU 2010; 78.

[14] Sohn IS, Jin ES, Cho JM, Kim CJ, Bae JH, Moon JY, Lee SH and Kim MJ. Bloodletting-induced cardiomyopathy: reversible cardiac hypertrophy in severe chronic anaemia from long-term bloodletting with cupping. Eur J Echocardiogr 2008; 9: 585-586.

[15] El-Shanshory M, Hablas NM, Shebl Y, Fakhreldin AR, Attia M, Almaramhy HH, Baghdadi H, Ayat M, Albeihany A and El-Dardear A. Al-hijamah (wet cupping therapy of prophetic medicine) significantly and safely reduces iron overload and oxidative stress in thalassemic children: a novel pilot study. J Blood Med 2018; 9: 241-251.

[16] Ahmed SM, Madbouly NH, Maklad SS and Abu-Shady EA. Immunomodulatory effects of blood letting cupping therapy in patients with rheumatoid arthritis. Egypt J Immunol 2005; 12: 39-51.

[17] Zhang C, Liang T and Zhang W. Effects of drug cupping therapy on immune function in chronic asthmatic bronchitis patients during protracted period. Zhongguo Zhong Xi Yi Jie He Za Zhi 2006; 26: 984-987.

[18] Brizzi P, Isaja T, D'Agata A, Malaguarnera L, Malaguarnera M and Musumeci S. Oxidized LDL antibodies (OLAB) in patients with β-thalassemia major. J Atheroscler Thromb 2002; 9: 139-144.

[19] Tantawy AA, Adly AA, El Maaty MG and Amin SA. Subclinical atherosclerosis in young β-thalassemia major patients. Hemoglobin 2009; 33: 463-474.

[20] Bashiri H, Bozorgomid A and Shojaeimotlagh V. Efficacy of hijamat (wet cupping therapy) in Iranian patients with nonalcoholic fatty liver disease: a controlled clinical trial. Turk J Med Sci 2020; 50: 354-359.

[21] Tagil SM, Celik HT, Ciftci S, Kazanci FH, Arslan M, Erdamar N, Kesik Y, Erdamar H and Dane S. Wet-cupping removes oxidants and decreases oxidative stress. Complement Ther Med 2014; 22: 1032-1036.

[22] Umar NK, Tursunbadalov S, Surgun S, Welcome MO and Dane S. The effects of wet cupping therapy on the blood levels of some heavy metals: a pilot study. J Acupunct Meridian Stud 2018; 11: 375-379.

[23] Husain NN, Hairon SM, Zain RM, Bakar M, Bee TG and Ismail MS. The effects of wet cupping therapy on fasting blood sugar, renal function parameters, and endothelial function: a single-arm intervention study. Oman Med J 2020; 35: e108.