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The effect of alpha lipoic acid on uterine wound healing after primary cesarean section: a triple-blind placebo-controlled parallel-group randomized clinical trial

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Abstract

Purpose To investigate the effect of alpha lipoic acid (ALA) on uterine wound healing after primary cesarean section (CS).

Methods A parallel-group, triple-blind, placebo-controlled randomized clinical trial was conducted in Ain Shams University Maternity Hospital, Cairo, Egypt, involving 102 women undergoing pre-labor primary CS. The participants were randomly assigned using a computer-generated list of random numbers to receive oral ALA or a placebo twice daily for 6 weeks after CS. Allocation to either group was in a 1:1 ratio by an independent statistician (not involved in the treatment or data collection). The primary outcome was the presence of CS defect and measuring its depth and width. Secondary outcomes were measurements of the anterior myometrial and residual myometrium thicknesses, healing ratio and the presence of intrauterine adhesions. Assessment was done using saline contrast sonohysterography.

Results Twenty (39.2%) women in the treatment group and ten (19.6%) controls had no niche (P value = 0.03, 95% CI −0.388, −0.0037). The absolute and relative risk reduction of forming a niche was 19.61% and 24.39%, respectively. The number of women needed to treat was five to avoid one niche formation. ALA use was associated with gastrointestinal upset in only three participants; however, none of the women withdrew during the study.

Conclusion In women undergoing primary CS, the administration of ALA for 6 weeks postpartum improved uterine healing and decreased the incidence of scar niche.

Keywords Cesarean-section scar · Uterine scar healing · Effect of alpha lipoic acid on uterine scar · Scar niche · Healing ratio · Saline contrast sonohysterography

Introduction

Cesarean delivery is one amongst the foremost common surgical procedures in women during their reproductive years [1], accounting for 18.6% of all births. Cesarean-section (CS) rates range from 6 to 27.2% in the least and most developed regions, respectively. Unfortunately, Egypt accounts for the highest CS rates in Africa (51.8%) [2].

The incidence of both primary and repeat cesarean delivery dramatically increased [3] leading to an increased number of scarred uteri with subsequent risky pregnancies [4]. Women with previous CS are at increased risk for uterine rupture, abnormal placental implantation, uterine scar dehiscence in subsequent pregnancies, and cesarean scar pregnancy (CSP) [5].

Previous report demonstrated that women with a large cesarean scar defect (CSD) detected by ultrasonography 6–9 months after CS presented a higher risk of uterine rupture or dehiscence in a subsequent pregnancy compared to those with a smaller defects or those without defects [6]. Furthermore, using the high-resolution ultrasound imaging in cases with very early CSP located the chorionic sac in the depth of the niche [7]. These risks can be minimized by maintaining uterine integrity through optimal cesarean wound healing [8].

Micili and colleagues [9] reported that alpha lipoic acid (ALA) enhances uterine wound healing in rat models by myofibrogenesis through different mechanisms. They reported an increased tissue expression of both alpha

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smooth muscle actin (αSMA) and vascular endothelial growth factor (VEFG) [9]. The α-SMA reflects the myofibroblast activity [10], while VEGF promotes angiogenesis and re-epithelization of the endometrium [11]. Lin et al. [12] showed that intrauterine VEGF injection promoted remodeling of the scarred uterus in rat model by regenerating the endometrium, muscular cells and vascularization, and hence improved pregnancy outcomes.

ALA supplementation has been traditionally used in pregnant women with peripheral neuropathy [13]; recently, it has been used safely in other obstetrical indications, e.g., threatened miscarriage and sub-chorionic hematoma, gestational diabetes [14], and postpartum pain [15].

The aim of this study was to investigate whether ALA supplementation decreases the incidence of CS scar defect among women undergoing pre-labor primary CS.

Methods

Study design

The current study was a parallel-group, triple-blind, placebo-controlled randomized clinical trial, performed between August 2017 and January 2018 at Ain Shams University Maternity Hospital, one of the largest tertiary referral hospitals in Cairo, Egypt, which has witnessed a steadily increase in cesarean sections from 23.47% at 2010 to 43.86% at 2014 [16].

Participants

The study population was a consecutive series of women between 18 and 35 years with singleton term pregnancy who underwent uncomplicated pre-labor primary CS through transverse lower uterine segment incision. Cases with medical diseases that can affect the healing process such as diabetes mellitus, anemia, chronic renal disease, hepatic disease, coagulopathy were excluded. Similarly, those receiving medications that can affect wound healing such as corticosteroids or anticoagulants, women using intrauterine device as a contraceptive method inserted during CS, and women with any structural uterine abnormality such as cervical stenosis or fibroid uterus or with pelvic infection at the time of saline contrast sonohysterography (SCSH) were excluded from the study.

Before study entry, potentially eligible women were informed about the study by the principal investigator and gave informed written consent.

Randomization and masking

At time of randomization, the first 102 eligible women were randomly allocated to receive either alpha lipoic acid (thiotacid® film-coated tablet 600 mg—EVA PHARMA) for 6 weeks after cesarean section at the dose of 600 mg twice/day orally (intervention group), while the control group received a placebo film-coated tablet twice/day for the same duration as the study group (control). Allocation to either one of the two groups was in a 1:1 ratio. Randomization numbers were completed using the computer-generated list of random numbers. An independent statistician not involved in the treatment or data collection was responsible for random allocation of participants to the two groups. The final group assignment was sealed in sequentially numbered opaque envelopes. The principal investigator, participants, and the sonographer were all blinded in this trial.

During designing the study, we intended to mask the participants and the primary investigator only, but before trial commencement, the decision to blind the sonographer was made to minimize possible bias.

Procedures

All participants were subjected to a detailed clinical assessment including: a detailed history, general, abdominal, pelvic examinations, routine obstetric ultrasonography, preoperative and post-operative complete blood count, Rhesus factor, and blood grouping. All data were documented in their medical records.

All cesarean uterine incisions were closed using a unified double-layer uterine closure technique (the first layer includes the deep myometrial edge with minimal decidua and the second layer completes the myometrial approximation, effectively buries the first layer and ensures hemostasis) (Fig. 1) with continuous unlocked absorbable polyglactin (910) 1 suture (Vicryl® Ethicon). At 6 weeks post-operatively, the participants received either alpha lipoic (thiotacid® film-coated tablet 600 mg—EVA PHARMA, Egypt, twice daily (intervention group), or a placebo film-coated tablet twice daily (control group). The participants were monitored for possible side effects or drug discontinuation during the follow-up.

Outcome measures

6 weeks after the cesarean section, all participants (from both groups) were assessed for any contraindications to perform saline contrast sonohysterography (SCSH). Transvaginal sonography (TVUS) examination was performed

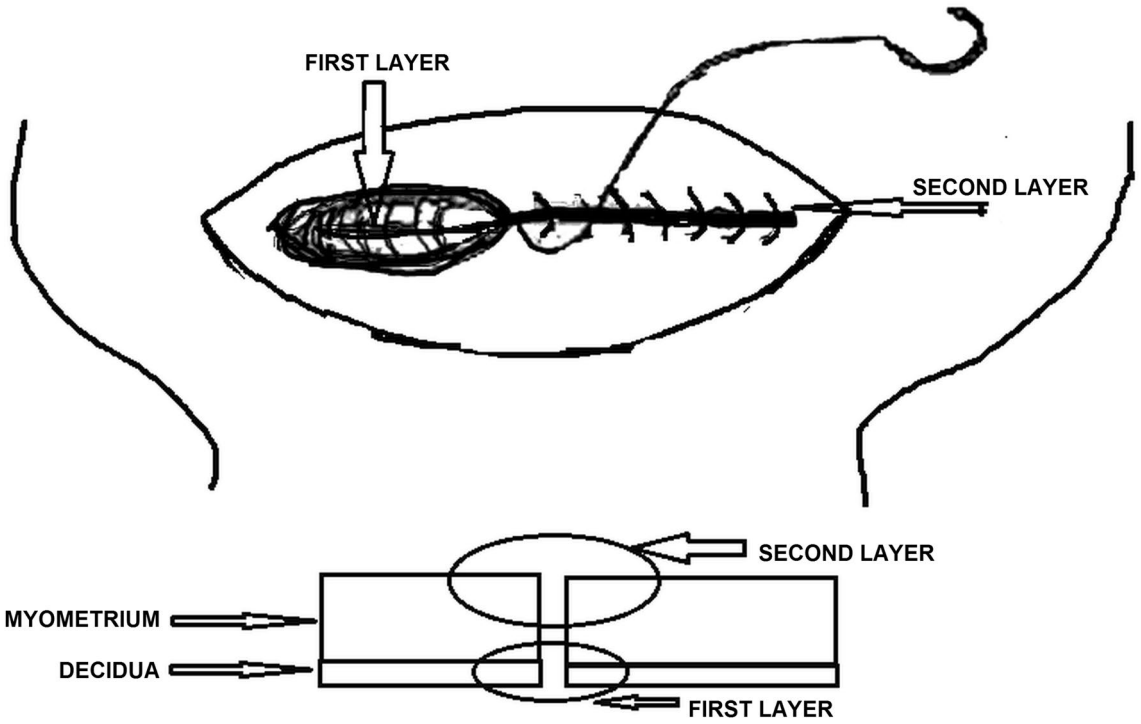

Fig. 1 Illustration of double layer uterine closure technique

prior to SCSH to exclude any abnormality. Both TVUS and SCSH were performed by a single sonographer.

Although uterine niches can be identified by TVUS, the SCSH provided better detection with more distinct delineation of scar defects [17]. El-Mazny and colleagues [18] found that SCSH was well tolerated, cost effective, not time consuming, and could be performed in office-based gynecological practice; it was comparable to diagnostic hysteroscopy with an overall accuracy of 96% in the diagnosis of scar defect.

Sonohysterographic examination was performed using Samsung H60 EV ~ 4–9 MH vaginal probe. It was performed as described by Goldstein [19]. The participant was in the lithotomy position with an empty bladder, a sterile vaginal speculum was inserted and the cervix was cleaned with an antiseptic solution. A thin Foley's catheter (size CH 8) was placed into the cervical os and the balloon was inflated with 2–5 ml of sterile saline for stabilization and occlusion of the internal cervical os. The speculum was carefully removed and 20-ml plastic syringe containing sterile saline was attached to the catheter. The ultrasound probe was gently introduced into the posterior fornix of the vagina; the incision site was viewed longitudinally.

Our primary outcome was the presence of CS scar defect. While the secondary outcomes included the measurements of the following parameters:

1. The width, depth, and shape of the niche.
2. Anterior myometrial thickness (the myometrium bordering the scar).
3. The thickness of residual myometrium related to scar.
4. Intrauterine adhesions.
5. The healing ratio (the thickness of residual myometrium covering the defect divided by the sum of the thickness of residual myometrium covers the defect and the height of wedge-shaped defect).

Ethical consideration

The study purpose and procedures were explained to all enrolled women and a written informed consent was obtained from each participant. The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Ain Shams University, in August 2017. The study methodology was registered on clinical trials: NCT03257514. https://clinicaltrials.gov/ct2/show/NCT03257514.

Statistical analysis

The required sample size has been calculated using the IBM© Sample Power© software version 3.0.1 (IBM© Corp.,

Armonk, NY). Considering the target outcome measures were the incidence of niche and the healing ratio.

The previous studies reported that the incidence of niche following cesarean delivery as diagnosed by SCSH was 56% [20], and the mean of healing ratio ± SD healing ratio was 0.83 ± 0.1 [21].

To date, the information regarding the effect of lipoic acid on the healing of cesarean scar in human is lacking. Hence, we assumed the effect size that would be of clinical value in this study would be a reduction in the incidence of niche by 50% (i.e., from 56 to 28%) and an increased healing ratio by 10% (i.e., from 0.81 to 0.91). Consequently, it was estimated that a sample size of 48 patients in either study group (total 96 patients) achieves a power of 80% (type 2 error 0. 20) to detect a statistically significant difference of 28% between the two groups as regards the incidence of niche using a two-sided chi-squared test with a confidence level of 95% (type 1 error 0.05). The incidence of niche was assumed to equal 56% in both groups under the null hypothesis and to equal 28% and 56% in the lipoic acid group and in control group, respectively, under the alternative hypothesis.

On the other hand, this sample size of 48 patients per group would achieve a power of 97% (type 2 error 0.03) to detect a statistically significant difference of 0.8 between the two groups as regards the healing ratio using a two-sided unpaired t test with a confidence level of 95% (type 1 error 0.05). The mean ± SD healing ratio was assumed to equal 0.83 ± 0.1 in both groups under the null hypothesis and to equal 0.91 ± 0.1 in the lipoic acid group or control group, respectively, under the alternative hypothesis. Assuming a dropout rate of about 5%, 51 patients were included in either arm (total 102 patients).

Statistical methods

On the basis of the normality of the data, continuous variables were compared using Student *t* tests. Categorical data were compared using χ^2 test. Two-sided *P* value < 0.05 was considered statistically significant. Data were analyzed using SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA).

Results

Between August 2017 and January 2018, 255 women were assessed for eligibility. 116 were ineligible and 37 declined to participate in the study. 102 women were randomized to the intervention ($n = 51$) and the placebo ($n = 51$) groups (Fig. 2).

The baseline characteristics of women, i.e., age, parity, weight, height, body mass index (BMI) in both groups were similar (Table 1).

Table 2 shows the measured outcomes registered after 6 weeks of follow-up. Twenty women in the treatment group and ten controls had no niche on SCHG assessment (*P* value = 0.03, relative risk 0.756 (95% CI 0.584, 0.979). The incidence of scar niche was 60.7% in intervention group and 80.39% in control group. The absolute and relative risk reduction of forming a niche was 19.61% and 24.39%, respectively. The number of women needed to treat was five to avoid one niche formation (Table 3).

The anterior myometrial thickness, thickness of residual myometrium, and the healing ratio were significantly lower in the placebo group compared to ALA group with mean difference of 0.81 (95% CI 0.0276, 1.5924), 2.94 (95% CI 2.0362, 3.8438), and 18.4 (95% CI 13.0707, 23.7293), respectively. The depth and width of scar niche were significantly smaller in the intervention group. However, there were no large scar defects detected in both groups.

ALA was generally well tolerated with only three participants in the ALA group and two controls experienced gastrointestinal side effects during the treatment period not severe enough to quit the trial (Table 4).

Discussion

The cesarean delivery rate is increasing worldwide, with dramatic increase in the primary cesarean delivery leading to potential risks in subsequent pregnancies with emergency peripartum hysterectomy for placenta accreta and rupture uterus. Achieving a healthy future pregnancy was the main reason for seeking new methods that can optimize uterine wound healing following CS. Thus, many previous attempts to compare the efficacy of new surgical techniques, or new suture types on human uterine wound healing were done. Nonetheless, testing pharmaceuticals for enhancing uterine scar healing was only performed in animal models.

In this study, we investigated the effectiveness of alpha lipoic acid compared to a placebo on the healing of uterine CS scar; ALA has potent antioxidant and anti-inflammatory effects, which achieved better uterine CS healing scar in rat models. It increased uterine tissue thickness with higher α-SMA and VEGF levels in scarred uterine tissue [9].

Moreover, ALA has a preventive effect on post-operative adhesions through its potent antioxidant effect [22]. Previous reports suggested that reactive oxygen species were involved in post-operative adhesions. Local hypoxia at the surgical area produces an ischemia/reperfusion process leading to decreased free radical scavenger levels. The resultant increase in the free radical activity of superoxide anions, xanthine oxidase and MDA induces adhesions by cellular membrane damage [23].

In the present study, the average age of cases in the intervention and the placebo groups was 25.3 ± 5.1,

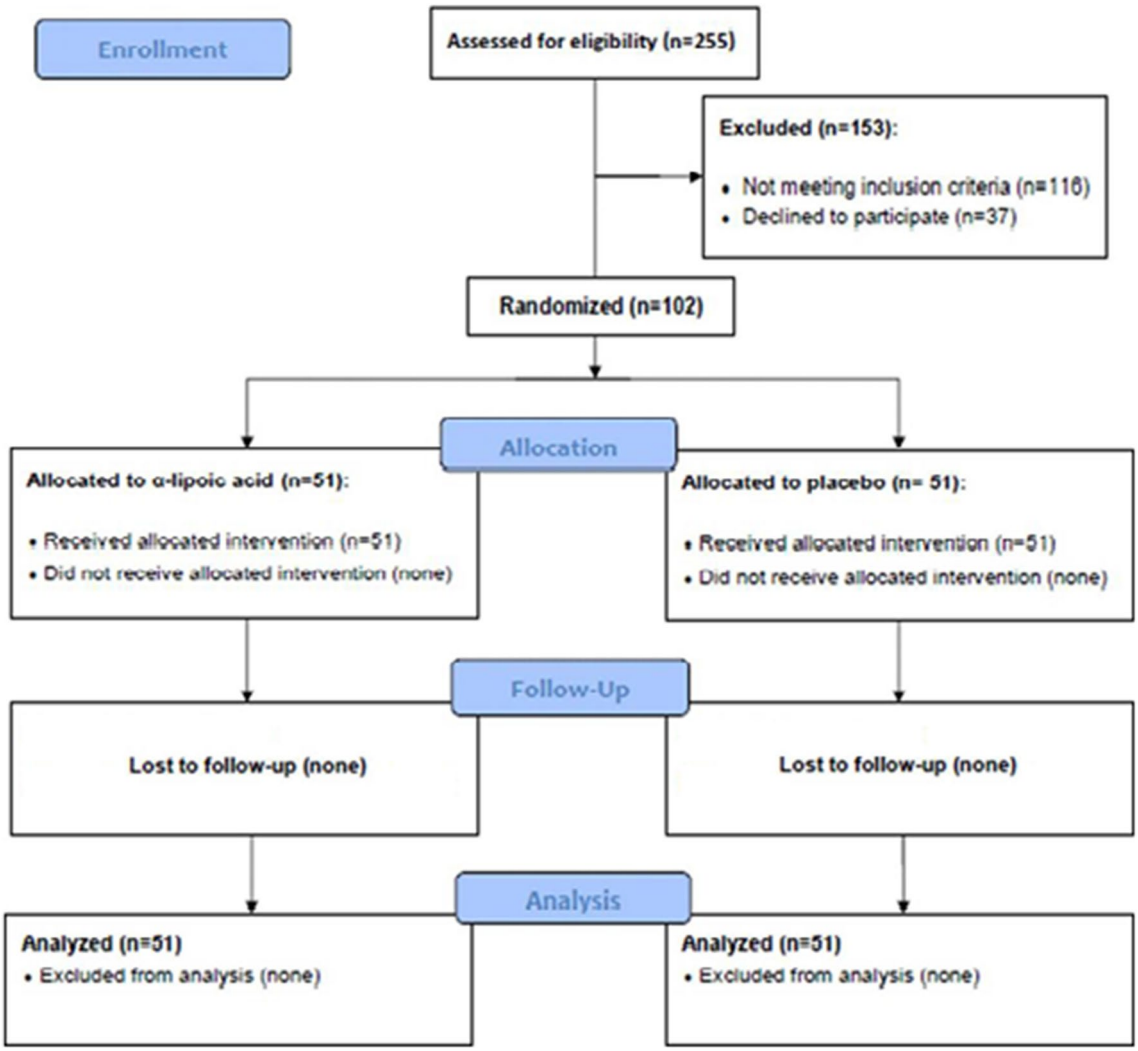

Fig. 2 Flow diagram of the progress through the phases of the trial

Table 1 Clinical characteristics of the participants

Variables	Study group ($n=51$)	Placebo group ($n=51$)	P value
Age (years)	25.3 ± 5.1	25.1 ± 5.4	0.850
Weight (kg)	69.8 ± 9.3	69.3 ± 9.0	0.755
Height (cm)	161.7 ± 8.7	162.3 ± 8.1	0.716
BMI (kg/m^2)	26.7 ± 3.1	26.2 ± 2.6	0.429
Parity			
PG	21 (41.2%)	16 (31.4%)	0.152
P1	10 (19.6%)	9 (17.6%)	
P2	9 (17.6%)	10 (19.6%)	
P3	8 (15.7%)	9 (17.6%)	
P4	3 (5.9%)	7 (13.7%)	

Data are mean ± SD or number (%)

25.1 ± 5.4 years, respectively. Women with advanced maternal age were excluded from this study and matching both groups regarding age was intended to eliminate age as a cofounder factor affecting the healing process.

In the current study, 49.8% of the women in intervention group were parous (P1–4) while 69.6% were parous (P 1–4) in control group.

As shown in Table 2, among the placebo group the scar niche was detected in 80.4%. Niche depth was 3.75 ± 1.98 mm, niche width was 3.64 ± 1.92 mm, and residual myometrium was 8.63 ± 2.52 mm.

These findings were in accordance with a study by Voet et al. [24] who reported that a niche was present in 64.5% of women 6–12 weeks after primary cesarean section, niche depth was 4.77 ± 2.64 mm, and residual myometrium was 8.59 ± 3.75 mm; the higher incidence of scar niche in our study may be due to performing SCSH only 6 weeks

Table 2 The CS scar-related measurements in the two groups

	Placebo group	Study group	95% CI	*P* value
Incidence of scar niche *n* (%)				
No niche	10 (19.6%)	20 (39.2%)	−0.388, −0.0037	0.030*
Niche	41(80.4%)	31 (60.8%)		
Anterior myometrial thickness (mm)				
Mean ± SD	12.37 ± 2.07	13.18 ± 1.96	−1.6, −0.02	0.046*
Range	8–16	10–16		
Thickness of residual myometrium (mm)				
Mean ± SD	8.63 ± 2.52	11.57 ± 2.12	−3.85, −2.3	0.000*
Range	5–16	8–16		
Depth of scar niche (mm)				
Mean ± SD	3.75 ± 1.98	1.61 ± 1.42	1.46, 2.82	0.000*
Range	0–6	0–4		
Width of scar niche(mm)				
Mean ± SD	3.64 ± 1.92	1.49 ± 1.39	1.49, 2.81	0.000*
Range	0–5.8	0–4.4		
Healing ratio (%)				
Mean ± SD	69.49 ± 16.36	87.89 ± 10.46	−23%, −13%	0.000*
Range	50–100	71–100		
Intrauterine adhesions	0 (0%)	0 (0%)	–	–
Shape of scar niche *n* (%)				
Irregular	16 (31.4%)	0 (0.00%)	–	0.000*
Linear	2 (3.9%)	13 (25.5%)		
Triangular	23 (45.1%)	18 (35.3%)		
No niche	10 (19.6%)	20 (39.2%)		

Data are mean ± SD or number (%)

*Statistical significance

Table 3 Event rates and improvement criteria of ALA use on CS healing

Event rates	Proportion of scar niche	
Control event rate	80.39%	
Experimental event rate	60.78%	
Improvement criteria	Point estimate	95% CI
Absolute risk reduction	19.61%	(0.0190–0.3578)
Relative risk reduction	24.39%	(0.0236–0.4451)
Number needed to treat	5	(3–53)

Table 4 Occurrence of drug complications or discontinuation in both study groups

Variables	Study group (*n* = 51)	Placebo group (*n* = 51)	*P* value
Discontinued drug	0/51 (0.0%)	0/51 (0.0%)	1.000
GIT upset	3/51 (5.8%)	2/51 (3.9%)	0.647

Data are proportion and percentage (%)

after CS and defining the niche as any defect in the anterior myometrium related to the scar.

Many theories were proposed to explain the pathogenesis of CS defects. These theories can be categorized into two main levels: surgery-related and patient-related factors. The cervical location of CS incision, single-layer endometrial saving closure technique or use of locking

sutures, surgical activities that may induce adhesion formation, and patient-related poor wound healing and defective angiogenesis all contributed to the occurrence of CS niche [25]. Sholapurkar explained the CS niche development by the ischemic necrosis of the myometrium at the uterine incision edges caused by improper uterine incision closure techniques [26].

We detected scar niche in 60.8% of our study group and in 80.4% of the placebo group. The incidence of the niche was significantly decreased with the ALA administration with a relative risk 0.756 (95% CI 0.584, 0.979). The absolute and relative risk reduction of forming a niche was 19.61% and 24.39%, respectively. The number of women needed to treat was five to avoid one niche formation.

The depth of scar niche was 1.61 ± 1.42 in the study group compared to 3.75 ± 1.98 in the placebo group. The width of scar niche was 1.49 ± 1.39 in the study group compared to 3.64 ± 1.92 in the placebo group. The residual myometrial thickness was 11.57 ± 2.12 mm in the study group and 8.63 ± 2.52 mm in the placebo group. The healing ratio of the study group was more than in the placebo group ($87.89 \pm 10.46/69.49 \pm 16.36$, respectively); these results showed that the healing in our study group was much better than in the placebo group.

Regarding the shape of scar niche, there was a significant difference between both groups. The triangular niche was the most common shape in both groups (45.1% and 35.3% in placebo and study groups, respectively). The linear shape was 25.5% in the study group, 3.9% in the placebo group, while the irregular shape was only in the placebo group (31.4%). However, the clinical significance of the different niche shapes remains unexplored and can be the scope of future studies.

Previous reports showed that most niches had a semicircular (50.4%), and 31.6% were triangular. However, these different patterns did not relate to postmenstrual spotting [20].

To the best of our knowledge, few pharmacological interventions were evaluated in rat models with good outcomes on uterine scar healing such as basic fibroblast growth factor [27], and Resveratrol [28].

In clinical trials in women, the aim of research has been to assess the effect of different wound closure techniques on uterine scar healing with controversial results. Previous RCT reported a lower frequency of a niche in women treated by full thickness suturing (including the endometrial layer) in comparison with split thickness suturing (excluding the endometrial layer) [29]. Another study evaluated the effect of locked and unlocked sutures of the uterus on the healing which showed that the thickness of the niche and the percentage of thinning of the scar region were significantly less in the unlocked group ($P = 0.002$, $P = 0.000$) because unlocked method caused less ischemic damage to the myometrium [30].

However, in a recent study, there were no significant differences in the niche incidence ($P = 0.52$), which was 40% in the single-layer unlocked group, 32% in the single-layer locked group and 43% in the double-layer closure group. The mean niche depth was 3.0 ± 1.4 mm after single-layer unlocked closure, 3.6 ± 1.7 mm after single-layer locked closure and 3.3 ± 1.3 mm after double-layer closure ($P = 1.0$) [31]. Hereby, we performed a double-layer unlocked closure of the uterine wound for all participants in our study.

To date, there are no sufficient data regarding the safety of ALA in breastfeeding women. However, a previous study showed that ALA was safely used in postpartum pain treatment [15]. Also its safety in pregnancy was presented by a retrospective study by Parente and colleagues which included 610 pregnant women receiving oral ALA for at least 7 weeks during gestation [32]. ALA was used in many obstetric indications as preventing preterm labor [33], peripheral neuropathy in pregnant women [13], threatened miscarriage and sub-chorionic hematoma, gestational diabetes [14].

Conclusion

Based on the results of this study, the administration of oral ALA for 6 weeks postpartum in women after primary CS with hysterotomy closure using double-layer closure of the myometrium with non-locking continuous sutures decreased the incidence and size of CS scar defects, and improved the healing process as assessed by saline contrast sonohysterography.

Strengths and limitations

To our knowledge, this study is the first randomized placebo-controlled trial on a therapeutic formulation to improve uterine wound healing after CS in human. All previous studies targeted the use of different suture materials and surgical techniques with conflicting results.

However, our study had several limitations; importantly it was performed at a single center on a small sample size with none of the cases showed large defects. Future multi-center study on a bigger sample size is required. Moreover, long-term follow-up is strongly recommended to assess whether the effect of oral ALA will minimize uterine scar-related complications during future pregnancies with an assessment of its effect of intra-abdominal adhesions and its impact on reducing long-term complications of CS e.g., abnormal bleeding, chronic pelvic pain, and dyspareunia.

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Compliance with ethical standards

Conflict of interest The authors declared no conflicts of interest with respect to the authorship and publication of this article.

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