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The Effect of *Hypericum perforatum* on the Wound Healing and Scar of Cesarean

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Abstract

Objective: The aim of this study was to determine the effects of *Hypericum perforatum* on cesarean wound healing and hypertrophic scar.
Design: This was a randomized, double-blind clinical trial study.
Setting: The study was conducted in Samen-Ol-Aemmeh (Pbuh) Hospital in Mashhad, Iran.
Subjects: The subjects included 144 women with surgical childbirth who had eligible criteria.
Intervention: The participants were randomly assigned to three groups. The treatment and placebo groups applied *H. perforatum* or placebo ointment 3 times a day for 16 days based on consecutive coded ointments. The control group remained without any intervention postoperatively.
Assessment: Wound healing was assessed on the 10th day postcesarean using the REEDA scale (REEDA stands for redness, edema, ecchymosis, discharge, and approximation), which had criteria including redness, edema, ecchymosis, discharge, and approximation. On the 40th day, the degree of scarring was assessed using the Vancouver scar scale including pigmentation, height, pliability, and vascularity. The subjects were also asked some questions about pain by using the Visual Analogue Scale and pruritus of scar.
Results: The mean age of all the study subjects was 23.50 ± 4.03 and mean parity was 1.23 ± 0.48. There were significant differences in wound healing on the 10th day ($p < 0.005$) and scar formation on the 40th day postpartum ($p < 0.0001$) between treatment group with placebo and control groups. However, the placebo group had no differences in wound healing ($p = 0.93$) and scar formation ($p = 0.11$) with the control group. In addition, significantly lower pain and pruritus were reported by the treatment group compared with the placebo and control groups on the 40th day postpartum.
Conclusions: Topical application of *H. perforatum* is safe and can facilitate cesarean wound healing and minimize formation of scar and its pain and pruritus.

Introduction

Delay in healing of cesarean wound and formation of visible scar are common symptoms of maternal morbidity after cesarean section.[1]

Pregnancy is possibly associated with altered healing of wound including development of hypertrophic scarring.[2] Wound complication rates following cesarean delivery vary from 2.5% to as high as 34%.[3,4]

Basically, factors that prolong the wound healing process predispose to hypertrophic scar formation.[5] These scars represent an abnormal, exaggerated healing response after skin injury,[6] and may cause pain, pruritus, contractures, hindrance to movement and other functional impairments.

In addition, cosmetic deformities and psychological stress cause patient dissatisfaction.[6,7] Despite recent scientific progresses, hypertrophic scars have remained the major medical problems and prevention of hypertrophic scars remains the best strategy.[8] A few therapeutic approaches to scar management have been reported such as radiation, laser therapy, cryotherapy, intralesional injections of corticosteroid and cryosurgery.[6,8] Many of them are associated with high rates of recurrence and can be expensive or painful.[9] Topical therapies have become increasingly popular because of their

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ease of use, comfort, noninvasiveness, and relatively low cost. Pressure therapy, vitamins A and E, silicon gel sheeting and ointment, onion extract, and imiquimod 5% cream prevent and treat hypertrophic scars.[6]

The use of herbal and alternative medications is globally increasing.[10] *Hypericum perforatum* has long been used both orally and topically for healing of wounds in the folk medicine of various countries.[11]

Lavagna and coworkers (2001) in a clinical study demonstrated that oily extract of *H. perforatum* promotes healing of surgical wound from childbirth with cesarean section.[12]

In experimental studies with rats, the healing of incision, excision, and dead space wounds has been reported to be increased by oral administration of a tincture of *Hypericum* species.[13,14]

The genus *Hypericum L*. belongs to the family of Hypericaceae (Clusiaceae, Guttiferae) and contains about 370 species in the temperate regions and tropical mountain.[15,16]

Around 19 species of the genus are found in Iran, among which *H. perforatum L*. is endemic to the country. The Persian names of the plant are *Gol-raei* and *Hofariqoun*.[17,18]

H. perforatum (*St. Johns wort*) is an important medicinal plant with a vast range of therapeutic effects such as depression, anxiety, anti-inflammatory, antimicrobial, antioxidant agent, and wound healing effects.[19,20]

Basically, natural remedies are perceived by many people as being natural and safe.[10] In Islamic and Iranian traditional medicine, *H. perforatum* is used for wound healing,[20–22] but often there is limited clinical research supporting this practice. This research was conducted to determine the effects of the ointment made of *H. perforatum* on cesarean wound healing and hypertrophic scar in women with surgical childbirth at Samen-ol-Aemmeh (pbuh) Hospital in Mashhad.

Methods

Research design

This randomized, double-blind clinical trial was approved by medical Research Ethics Committee of Mashhad University of Medical Sciences and was in compliance with the Helsinki Declaration.

Subjects

One hundred forty-four women with surgical childbirth who had eligible criteria including lower segment cesarean section, age range 17–35 years, term pregnancies, first cesarean section and had no scars from prior abdominal surgery, and no history of medical and obstetrical problems were recruited; they were given both verbal and written information regarding the study. Signed informed consent was obtained prior to entry. Some variables before cesarean controlled and recorded include: duration of labor and membrane rupture, dilatation of cervix at time of cesarean delivery, postoperative hematocrit, operative time, and birth weight.

Ointment preparation

The *H. perforatum* used in this study was provided by the Gol-Daru Company (Isfahan, Iran). Oily extract of this plant was prepared from flowering tops of plants. The fresh plants were dried, crushed, and macerated in grapeseed oil (1 part plant powder in 3 parts oil) for 1 week. The macerate was placed in a microwave oven for 15 minutes. The prepared extract was clarified by filtration. For preparation of sterile ointment, the oily extract was sterile filtered via 0.45-μm membrane filter. The petroleum jelly base was sterilized by dry heat (160°C, 90 minutes). Mixing (20% oily extract + 80% petroleum jelly)[12] and filling in presterilized tubes were performed in aseptic condition under high-efficiency particulate arresting filters. Placebo ointment was similarly prepared, except for oily extract.

Treatment procedures

Cesarean delivery was done by only 2 obstetricians, who had the same obstetric experience. In all subjects, fannestiel skin incision and transverse incision in the lower uterine segment were made, and then the skin was closured with plastic suture.

One (1) gram cefazolin was given intravenously every 6 hour for 4 doses and then 500 mg of cephalexin orally 4 times a day for 7 days.

Participants were randomly allocated into 3 groups. Twenty-four (24) hours after cesarean, patients in the treatment and placebo groups began to apply *H. perforatum* or placebo ointment 3 times a day and continued it for 16 days. The randomization was based on consecutive numbering and ointments were coded by a staff member in the pharmaceutics laboratory of the pharmacy faculty. Except for him, none of the members of the research team knew who had received the intervention when assessing at the 10th and 40th days.

The control group remained without any intervention postoperatively.

Assessments

Wound healing was assessed on the 10th day postcesarean using the REEDA scale (REEDA stands for redness, edema, ecchymosis, discharge, and approximation). Each characteristic is scaled from 0 to 3, and the ratings for the five characteristics are added to obtain the score. A total score range from 0 to 15 and score of 0 reflects normal skin. We chose the REEDA scale because it has been shown by Davidson (1974) and Hill (1990) to be valid for the measurement of wound healing.[23,24] BMI was also measured in this day.

The degree of scarring was assessed by an experienced plastic surgeon on the 40th day using the Vancouver scar scale (VSS). The VSS consists of four variables including pigmentation, height, pliability, and vascularity. Pliability has six scores and other variables have four possible scores. A total score ranges from 0 to 14, whereby a score of 0 reflects normal skin. Baryza (1995) and Nedelec (2000) established validity and reliability of VSS in scar measurement.[25,26] Pain of the incision site was assessed on the 40th day using visual analogue scale, which has demonstrated its validity and reliability in many studies.[27,28] Also some questions were asked about pruritus and patient satisfaction regarding scars.

Statistical Analysis

The data were analyzed using SPSS (version 11.0; SPSS Inc., Chicago, IL) and a value of $p < 0.05$ was considered significant. The results were expressed as mean ± standard devia-

Table 1. Baseline Data

Characteristic	*Groups*			*Result of one-way ANOVA test*	
	Treatment (n = *47*)	*Placebo* (n = *44*)	*Control* (n = *34*)	F	p-*value*
Duration of membrane rupture (hours)	2.13 (4.29)	1.91 (4.42)	1.88 (3.40)	0.046	0.96
Dilation of cervix at time of cesarean (cm)	3.00 (2.68)	3.22 (3.11)	3.27 (2.54)	0.085	0.92
Maternal postoperative hematocrit (%)	39.88 (3.50)	40.26 (4.81)	39.61 (3.08)	0.27	0.76
Operative time (minutes)	21.62 (4.64)	21.52 (3.51)	22.29 (4.28)	0.38	0.69
Birth weight (g)	3223.83 (388.97)	3318.86 (390.74)	3371.18 (505.10)	1.27	0.28
Duration of hospitalization (hours)	49.15 (120.8)	46.59 (10.58)	51.03 (12.13)	1.63	0.26
BMI (kg/m^2)	28.22 (2.71)	27.47 (2.57)	27.69 (2.72)	0.29	0.74

Data represent mean (standard deviation).
ANOVA, analysis of variance; BMI, body–mass index.

tion, and statistical differences between groups were determined by one-way analysis of variance. Kruskal-Wallis was used to determine difference between three groups in REEDA and Vancouver scar scale. If there was any significant difference between any of the three groups, the Mann–Whitney test was performed to compare the two groups. Chi-square test was used to compare the noncontinuous data.

Results

Of the 418 women assessed for eligibility, 274 were excluded for not meeting the inclusion criteria or they refused to participate.

The remaining 144 women were randomized into three groups. Nineteen (19) subjects failed to complete the study on the 10th day and 9 failed on the 40th day postcesarean due to either noncompliance with protocol or were lost to follow-up.

The mean age of all the study subjects was 23.50 ± 4.03 years and the mean parity was 1.23 ± 0.48; there was no difference in mean age and parity between the three groups. Some variables that were compared to test the homogeneity produced by random allocation had no statistically significant difference between the three groups (Table 1).

A lower score was observed on the 10th day postpartum in total and four of five criteria of the REEDA scale including redness, edema, discharge, and approximation of the wound edges in the treatment group, but there was no difference in ecchymosis (Table 2).

Overall, statistically significant difference in wound healing was observed between treatment group with placebo ($p < 0.002$) and control groups ($p < 0.008$), but there were no significant difference between placebo and control groups ($p = 0.93$).

A lower score of scar based on the VSS was observed on the 40th day postpartum in the treatment group. Pigmentation, height, and pliability of scar were the most distinguishable features that caused the lower score in the treatment group. The vascularity of scar was lower in the treatment group, but the difference was not significant (Table 3).

However, there was a significant difference in scar formation between the treatment group compared to the placebo and control groups ($p < 0.0001$), but there was no significant difference between the placebo and control groups ($p = 0.11$).

A lower wound pain score was observed on the 40th day postcesarean in the treatment group ($p < 0.0001$).

Also on the 40th day, significantly fewer patients were reported to have pruritic scar in the treatment group ($p < 0.0001$).

Patient satisfaction with scar was 90% in treatment group, 76% in the placebo group, and 68% in the control group, and there was a significant difference among the three groups ($p < 0.03$).

One patient in the group that received *H. perforatum* ointment discontinued the study because of irritation in the surgical site, which resolved without medical intervention.

Discussion

The positive effect of *H. perforatum* ointment on wound healing and reduction of scar formation is shown in our clinical trial study.

Table 2. Assessment of the Wound Healing by the REEDA Scale on the 10th Day Postpartum

Variable of REEDA scale	*Groups*			*Result of Kruskal-Wallis test*	
	Treatment (n = *47*)	*Placebo* (n = *42*)	*Control* (n = *34*)	χ^2	p-*value*
Redness	0.11 (0.31)	0.36 (0.49)	0.35 (0.49)	9.56	<0.008
Edema	0.06 (0.25)	0.05 (0.21)	0.21 (0.41)	6.53	<0.04
Ecchymosis	0.02 (0.14)	0.00 (0.00)	0.00 (0.00)	1.66	0.44
Discharge	0.00 (0.00)	0.20 (0.59)	0.21 (0.54)	7.22	<0.03
Approximation	0.00 (0.00)	0.16 (0.37)	0.03 (0.17)	10.45	<0.005
REEDA	0.19 (0.50)	0.75 (1.08)	0.79 (1.17)	10.51	<0.005

Data represent mean (standard deviation).
REEDA, redness, edema, ecchymosis, discharge, and approximation.

Table 3. Assessment of the Hypertrophic Scar by the VSS on the 40th Day Postpartum

	Groups			Result of Kruskal-Wallis test	
Variable of VSS	*Treatment* (n = *44*)	*Placebo* (n = *40*)	*Control* (n = *32*)	χ^2	p-*value*
Pigmentation	1.91 (1.05)	2.58 (0.68)	2.62 (0.71)	15.72	<0.0001
Height	0.41 (0.50)	0.73 (0.55)	0.84 (0.37)	15.21	<0.0001
Pliability	0.98 (0.63)	1.60 (0.59)	1.84 (0.63)	30.03	<0.0001
Vascularity	0.02 (0.15)	0.15 (0.36)	0.16 (0.37)	4.95	0.08
Vancouver	3.32 (1.54)	5.03 (1.29)	5.50 (0.92)	43.23	<0.0001

Data represent mean (standard deviation).
VSS, Vancouver scar scale.

Wound healing activity of *H. perforatum* has been demonstrated in previous experimental and clinical studies.

In an experimental study with rats, Rao and coworkers (1991) demonstrated the effectiveness of oral *H. perforatum* in wound healing.

The phytochemical analysis of the flower extract showed the presence of tannins, hyperin, hypericine, hyperforin, amentoflavone, flavonoids, and xanthones in this plant.

It has demonstrated that amentoflavone and hypericine have anti-inflammatory effects.[19]

In a laboratory study, it was observed that hyperforin inhibits the growth of all Gram-positive bacteria that infect and delay the healing process.[19,29]

In a clinical study, it was demonstrated that oily extract of *H. perforatum* promotes healing of cesarean wound as a result of the increase in epithelial reconstruction and reduction in surface perimeter area.[12]

This observation agrees with our study that shows the effect of *H. perforatum* extract on wound healing and the reduction of scar formation.

Therapeutic modalities for the prevention and management of scar have been postulated to act in one of three ways: (1) correction of abnormal collagen metabolism, (2) alteration of the immune response, and (3) manipulation of the mechanical properties of wound repair.[30]

The granulation tissue of the wound is primarily composed of fibroblast, collagen, edema, and small new blood vessels.[31]

Fibroblast cells play an important role in the proliferative phase of wound healing, which results in scar formation; also, they are involved in the syntheses of collagen and other adhesion molecules.

The presence of flavonoids and xanthones in *H. perforatum* caused an increase in the percentage of polygonal fibroblasts, stimulation of collagen synthesis, and influenced epithelial cell proliferation and migration.[11]

Flavonoids are known to reduce lipid peroxidation not only by prevention or slowing the onset of cell necrosis, but also by improving vascularity. It is believed that any drug that inhibits lipid peroxidation increases the circulation of wound and strength of collagen fibers, and prevents cell damage by promoting DNA synthesis.[32,33] Therefore, the reason for clinical response in this study seems to be supported by these concepts.

Our results showed less pain and pruritus in the surgical site in the treatment group compared with the placebo and control groups.

This difference could be due to less postcesarean scar in this group, because these scars can be pruritic and painful.

Less scar and its pain and pruritus probably lead to better overall patient satisfaction in treatment group in our study.

However, further studies are suggested to compare the efficacy of *H. perforatum* ointment with other complementary medicine products on cesarean wound healing and scar formation.

Conclusions

The results of our clinical study demonstrated that *H. perforatum* ointment can effectively facilitate cesarean wound healing and minimize formation of scar and also its pain and pruritus without any important side-effects.

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Disclosure Statement

No competing financial interests exist.

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