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Original article

Efficacy of *Sphaeranthus indicus* and cream of *Lawsonia inermis* in cervical erosion with cervicitis

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Abstract

Aim: To compare the efficacy and safety of *Sphaeranthus indicus* Linn, and cream of *Lawsonia inermis* Linn and *Plumbi oxidum* with placebo in the healing of erosion and relief of symptoms in cervical erosion with cervicitis.

Materials and methods: A randomized placebo controlled single blind study was carried out in the Department of Gynecology at the National Institute of Unani Medicine. Clinically diagnosed patients ($n = 45$) were randomized to the test ($n = 30$) and control ($n = 15$) groups. The inclusion criteria were the married patients aged 18–40 years with symptoms of cervical erosion associated cervicitis. The exclusion criteria were the unmarried, pregnant and lactating patients; use of oral or intrauterine contraceptive devices, sexually transmitted diseases and systemic diseases. In the test Group, *Safoof Mundi* (Flower of *S. indicus* Linn) was administered 6 g orally in three divided doses and 5 g cream of *Henna* (leaves of *L. inermis* Linn) with *Murdarsang* (*P. oxidum*) was applied intra-vaginally twice daily for 9 weeks. The placebo was given for the same duration. The outcome measures were to assess healing of erosion and relief of symptoms. The results were analyzed by Fisher exact and Student '*t*' test.

Results: In the test group, 8 (26.7%) patients demonstrated complete healing of erosion, where as none of the patient had healing in the control group with $P < 0.05$, statistically significant.

Interpretation and conclusions: The test drug formulations were found to be effective in healing and relieving the symptoms of this disease. Further, the effectiveness should be evaluated in large sample size with computerized planimetry.

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Keywords: Cervical erosion with cervicitis; Sexually transmitted disease; *Sphareanthus indicus* Linn; *Lawsonia inermis* Linn; *Plumbi oxidum*; Randomized placebo controlled trial

Introduction

Gynecological health is an important component of women's health. The women of fertile age (15–44 years) constitute 19% of the total population in India [1] and cervical erosion is a common finding on routine pelvic examination during this period [2]. Cervical erosion is an anachronistic term [3] of cervical ectopy. It is the presence of endocervical columnar epithelium on ectocervix [4] and thus, the multilayered squamous epithelium typically found on exocervix is replaced [5]. The hormones cause an increase in fibro musculature of the cervix, hyperplasia of the columnar cells and stromal edema [6]. After its development, healing occurs by a process of squamous metaplasia [5]. The chronic cervicitis can lead to recurrent cervical erosion or erosion can be associated with cervicitis [7]. The cervical columnar epithelium is thinner and substantially more friable and liable to disruption than the stratified squamous epithelium of the vaginal walls, making the cervix more vulnerable to trauma or disruption that may potentially increase a woman's risk of becoming infected by HIV [8] and HPV [9] during intercourse. In addition, the cervix is far more susceptible to infections by other sexually transmitted pathogens including herpes simplex virus type 6 [10]. It is also the principal site of infections for *Chlamydia trachomatis* [11] and *Neisseria gonorrhea*. It is reported that higher frequency of chlamydial infection in subjects with bacterial vaginosis could be mediated through cervical erosion [12]. Apart from these, symptoms such as increased vaginal discharge, dyspareunia, lower abdominal pain and so on cause discomfort in a woman and affect the quality of life. Hence, there is a strong tendency towards treating

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cervical erosion associated with cervicitis to hasten the process of healing, (squamous metaplasia) so that sexually transmitted diseases and recurrent cervicitis can be prevented. The therapeutic options in conventional medicine include surgical interventions such as thermal cauterization, cryosurgery and laser vaporization along with antibiotics. All these procedures have got their own side effects. Therefore, the world is turning towards the alternative system of medicine for treatment of many chronic diseases. The Unani drugs have been in use for a long time and are effective. In Unani system of medicine many single and compound drugs, which have various medicinal properties such as *Muhallil* (resolvent), *Musaffi khoon* (blood purifier), *Qabiz* (astringent), *Mujaffif* (desiccant), *Mundamil qurooh* (cicatrizing), and *Muaddil* (alterative) are used orally or locally to treat this disease. The efficacy and safety of the powdered *Mundi* orally and a cream of *Henna* and *Murdarsang* locally in the cervical erosion associated with cervicitis have not been validated and documented till date. Therefore, an attempt was made to validate the efficacy and safety.

Materials and methods

The research question was whether the test drugs were safe and effective in healing of erosion and relieving the symptoms in cervical erosion with cervicitis. The hypothesis of this study was to compare the effectiveness and safety of Unani drugs in healing of erosion and relieving the symptoms in cervical erosion with cervicitis with placebo control.

Design

A prospective, single center, randomized placebo controlled, single blind, pre-evaluation and post-evaluation studies were conducted in the Outpatient department of Amraze Niswan (Gynecology) at the National Institute of Unani Medicine, during April 2007–April 2008. This study was started after the approval by institutional ethical committee. As per the recommendation of ethical committee members, the sample size in Placebo control group was reduced to 15 patients, whereas in the test group sample size was 30 patients. The intervention was given for 9 weeks. The data was analyzed from baseline after completion of the treatment.

Participants

The written consent was obtained from the patients, who fulfilled the inclusion criteria. They were evaluated through the complete history and physical examination. The inclusion criteria were married women aged 18–40 years with symptoms that were attributed to erosion like white discharge, low backache, low abdominal discomfort, dyspareunia, postcoital bleeding, vulval itching, dysmenorrhoea and menstrual disorders. The exclusion criteria were unmarried, pregnant and lactating women, patients with genital tract lesions like fibroid and carcinoma, using oral or intrauterine contraceptive devices, with any systemic illness like hypertension, diabetes mellitus, sexually transmitted diseases or tuberculosis.

The pelvic examination was performed to evaluate the *Takkul wa iltehabe unqur rehm* (cervical erosion with cervicitis) related sign like vaginal discharge, bleed on touch, and to note the state of cervix, its position, direction, consistency, irregularity, or any other abnormalities. The grade of cervical erosion was assessed by direct visualization. The extent of erosion was graded as 0, 1, 2 and 3 according to method of K. Yang et al. which are as follows: Grade 0: No erosion; Grade I: Covering one third of the cervix; Grade II: From one third to two third of the cervix; and Grade III: Over two third of the cervix [13]. The subjective parameters of white discharge, low back ache, lower abdominal pain, vulval itching, dyspareunia and urinary symptoms associated with cervical erosion with cervicitis were assessed by grading them according to severity as 0 (absent), 1 (mild), 2 (moderate) and 3 (severe).

The baseline clinical laboratory investigations such as haemoglobin percentage, total leucocytes count, differential leucocytes count, erythrocyte sedimentation rate, VDRL and Random blood sugar were done to exclude general diseases. To exclude the pelvic pathology, Ultrasonography, and Pap smear were done. To assess the safety of drugs, blood urea, serum creatinine, SGOT, SGPT, and Alkaline phosphatase were done before and after trial. At every follow up during three months of study period progression or regression of symptoms and signs were recorded in the case record form.

Intervention

The patients were randomly allocated to the test ($n = 30$) and control groups ($n = 15$) with lottery method.

Preparation of cream of *Henna* and *Murdarsang*: The ingredient to make the cream were water – 34%, *Neem* oil – 62%, bee wax – .5%, liquid paraffin – 3.5%, parabin – 0.04 g, Borax – 0.04 g, *Henna* aqueous extract – 9.75 g, and litharge – 2.5 g. The cream was formed as oil in water emulsion. The standard formula for cream was used. The concentration of *Henna* for clinical application was selected as 50% w/v and *Litharge* as 1.25% w/v as calculated from Hamdard pharmacopoeia of Eastern medicine [14].

In the test group, 6 g powder of Flower of *Mundi*, filled in 500 mg capsule was administered orally in three divided doses and intra-vaginally 5 g cream Dose of Cream of *Henna* Leaves with *Murdarsang* was applied twice daily for 9 weeks (from day 5 to day 28 of menstrual cycle for three consecutive months). The control group received orally, roasted wheat flour and locally, base (Bee wax) of cream per vaginum as the placebo in the same dose as that of the test drugs.

Outcome

The outcome measures were to assess healing of erosion and relief of symptoms. The patients each in the test and the control group were assessed on day one before starting the treatment and after administration of the test drugs or the placebo control for 9 weeks.

The cervical erosion was considered cured when the cervix had become smooth and glossy, and erosion had disappeared,

where as not cured, when there was no reduction in the grade of cervix erosion or no change after treatment.

Statistical analysis

The results were analyzed statistically using Graph Pad Instat version 3.00 for window (Graph Pad Software, San Diego, CA, USA) at the completion of the study taking in account the relief of symptoms and healing of the erosion. The descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented on Mean ± SD and results on categorical measurements were presented in number (%). Significance was assessed at 5% with 95% confidence interval. The following assumptions on data was made samples drawn from the population should be random.

The Fisher exact test and Student '*t*' test was used to find out the significance of the study parameters on categorical and continuous scale respectively. The Mann–Whitney and Kruskal Wallis tests were used to find the comparison of the symptoms. Analysis of data was on an intention-to-treat basis.

Results

A total number of 120 patients were screened for cervical erosion with cervicitis during the study period. Forty eight patients were subjected to preliminary investigations and out of them three were excluded. To observe the efficacy and safety, statistical analysis of different parameters were evaluated before and after the trial.

The socio-demographic (literacy status, socioeconomic status, parity, age at marriage) characteristics and investigations of the test and control groups are shown in Table 1. It was found that the parameters were statistically not significant. ($P > 0.05$) Thus, the groups were homogenous in terms of biochemical parameter and age before intervention (Table 1).

Table 1
Socio-demographic characteristics and investigations of test and control groups before treatment.

Characteristics	No. of patients	
	Test group $n = 30$	Control group $n = 15$
Age (years) (range)	21–40	20–40
Literacy status		
Illiterate	15(50)	05(33.33)
Primary School	04(13.33)	02(13.33)
Middle school	06(20)	02(33.33)
High school	04(13.33)	06(40)
Intermediate	01(13.33)	0
Graduate or above	0	0
Socioeconomic Status		
Upper	0	0
Upper middle	11(36.67)	07(46.67)
Lower middle	05(16.67)	07(46.67)
Upper lower	13(43.33)	01(6.67)
Lower	01(13.33)	0
Parity		
Nulliparous	01(13.33)	0
1	06(20)	01(6.67)
2	10(33.33)	06(40)
≥3	13(43.33)	08(53.33)
Age of marriage		
<20 (years)	25(83.33)	10(66.67)
20–24	05(16.67)	05(33.33)
Investigations		
Hb%	11.45 ± 0.24	11.36 ± 0.27
ESR	25.16 ± 2.2	25.66 ± 4.90
SGOT	24.4 ± 1.83	24.66 ± 2.94
SGPT	25.6 ± 2.01	23.26 ± 1.81
Alkaline phosphatase	97.86 ± 4.87	94.26 ± 5.66
Blood urea	21.63 ± 0.90	25.8 ± 1.37
Serum creatinine	0.67 ± 0.02	0.77 ± 0.02
Cytological pattern		
Normal	03(10)	01(6.67)
Mild inflammatory	13(43.33)	07(46.67)
Moderate inflammatory	06(20)	02(13.33)
Dense inflammatory	8(26.67)	05(33.33)

Test used: unpaired '*t*' test for investigations, $P > 0.05$, considered not significant. Data are shown as Mean ± SD and number (percentage).

Therapeutic outcome

In the test group, out of 30 patients of cervical erosion with cervicitis, 8 (26.7%) patients were cured completely and in the control group none of the patients were cured. The data was analyzed by Fischer exact test and the comparison revealed that the difference in the cure was significant ($P < 0.05$) (Table 2).

Efficacy of the test drugs and placebo on grade of erosion:

The data was statistically analyzed using Kruskal Wallis test and post hoc Dunn pair comparison test. The median rating score after treatment in the test group when compared with median rating score before treatment in control and median rating score after treatment in control was found to be significantly reduced ($P < 0.05$) (Table 3).

Effect of test drugs and placebo on subjective parameter

The most common symptom in the present study was white discharge. The median rating score for white discharge and other symptoms are in the test group after treatment [0(0, 0)] was significantly reduced ($P < 0.001$) when compared to median rating score with range before treatment of the test and control group. The median rating score of other symptoms are summarized (Table 4).

Table 2
Therapeutic outcome of test drug formulations and placebo on cervical erosion with cervicitis.

Results	No. of patients	
	Cured	Not cured
Test group ($n = 30$)	08(26.66%)[a]	22(73.33%)
Control group ($n = 15$)	Nil(0%)	15(100%)
Total	30	15

Data presented: number (percentage).
Test used: Fischer exact test
[a] $P < 0.05$, considered significant.

Table 3
Efficacy of test drug formulations and placebo on grade of erosion.

Results	No. of patients	
	Before treatment	After treatment
Test group ($n=30$)	2(1, 3)	1(0,2)[a]
Control group ($n=15$)	2(1, 3)	2(1,3)

Data presented: median (Min, Max).
Test used: Kruskal Wallis test with Dunn compared all pairs of column.
[a] $P<0.05$ with respect to after treatment control.

Discussion

This study demonstrates that the test drug formulations were effective in healing of erosion and relieving the symptoms than those compared to the placebo. The laboratory investigations were within normal range before and after treatment showing that these drugs were safe.

Till date, none of the studies in the Unani system of medicine had evaluated or documented the efficacy and safety of the test drugs formulation in healing of erosion and relieving of symptoms in cervical erosion with cervicitis. Thus, it is difficult to correlate the finding with other clinical studies but it validates the claim made by the Unani Scholars. According to the Unani Scholars, *Takkul wa ilethabe unqur rehm* is caused by *Ufunat* and dominance of *Khilt dam* or *Safra* (blood or bile humour) [15], which belongs to *Warme har* disease and it should be treated with *barid* (cold) *wa yabis* (dry) drugs [16]. The temperament of *Mundi*, *Henna*, *Neem* and *Murdarsang* is *Barid wa Yabis,* thus, it is presumed that these drugs have rectified the *warm har* or dominance of *Khilt dam. Neem* and *Mundi* are useful in *Safravi Amraz*. Moreover, *Henna, Mundi* and *Neem* are having *Musaffi Khoon* (blood purifier) and *Muhallil* property, which is useful in *Warm Rehm* (uterine inflammation) and *Sailanurehm* (leucorrhoea). *Henna, Neem* and *Murdarsang* are also used for healing the wound and ulcers. *Neem* and *Henna* are having *Dafe taffun* (antiseptic), *Muhallil* (anti-inflammatory) properties, and *Murdarsang* is having *Muhallil*, *Mundamile qurooh* (ulcer healing) and *Munbite laham* properties [16]. Unani Jargon is used to specify the action of each drug, hence, it is assumed that the temperament and properties of the test drugs have caused healing of cervical erosion and relieve the sign and symptoms related to cervicitis.

Furthermore, the cervical erosion causes increase in pH, which is a risk factor for bacterial vaginosis and sexually transmitted diseases. [17] If pH of the ectocervix is lowered it stimulates the sub columnar cells to undergo metaplasia [18] and also most likely destroys the buffering action of mucus that protects columnar cells [11]. The cream made of *Henna* and *Murdarsang* used for local application had acidic pH, consequently, it is hypothesized that these drugs has stimulated the cells to undergo metaplasia there by causing healing of erosion and preventing further infections. The pharmacological studies also reported that *Henna* leaves in the form of ointment have better efficacy in wound healing [19].

Table 4
Efficacy of test drug formulations and placebo on symptoms of cervical erosion with cervicitis.

Symptoms	No. of patients			
	Test group $n=30$		Control group $n=15$	
	BT	AT	BT	AT
White discharge	2(1,2)	0(0,0)[a]	1(1,2)	1(0,2)[a]
Low back ache	2(0,2)	0(0,2)[a,b,c]	2(0,2)	1(0,2)
Lower abdominal pain	1(0,2)	0(0,1)[a,b,c]	1(0,2)	1(0,2)
Vulval itching	1(0,2)	0(0,1)[a,b,c]	1(0,2)	1(0,2)
Dyspareunia	0(0,2)	0(0,0)[a,b,c]	0(0,1)	0(0,1)
Urinary symptoms	0(0,2)	0(0,0)	0(0,1)	0(0,1)

Data presented: median (Min, Max).
Test used: Kruskal Wallis test with Dunn compared all pairs of column test.
[a] $P<0.001$ compared with respect to before treatment control.
[b] $P<0.001$ compared with respect to before treatment test.
[c] $P<0.001$ compared with respect to after treatment control.

Efficacy of the test drugs and placebo on the subjective parameter

The test drugs were most successful in managing white discharge (*Sailanurrehm*) as all 30 patients presenting with vaginal discharge were having no discharge after the treatment. The other associated symptoms of cervicitis such as low backache, lower abdominal pain, vulval itching, and dyspareunia were significantly relieved.

The amelioration in these symptoms is attributed to *Musaffi khoon*, *Muhallil*, *Dafe taffun*, *qabiz* (astringent), and *Mujaffif qurooh* properties of the test drugs [16]. *Gul Mundi* is having *Musaffi*, and *Muqawwi* properties; moreover, in the classical text it has been mentioned that orally, it is useful in *Salain ur Rehm*, *Amraze Safravi* (Abnormal vaginal discharge) and *Warme Rehm* (Inflammation of uterus). Added why sphaeranthus is given orally and not locally. It is also mentioned in textbook of gynecology that oral drugs should be given in cervicitis. For healing erosion local drugs were used [16]. *Neem* is having *Dafe Taffun*, *Muhallil*, *Musakkin*, and *Musaffi* properties and it is also useful in *Amraze Safravi*. *Mudarsang* is having *Mujaffife Qurooh*, *Muhallil* and *Munbite Laham* properties. Unani Scholars mentioned that one of the main causes of *Sailanurrehm* (vaginal discharge) is *Zoafe quwate ghazia* of uterus that leads to this disease and it is theorized that *Barid wa Yabis mizaj* of drugs tones up this *Quwat* [15] and thereby rectifying the quality and quantity of *Khilt dam*. Further, astringent drugs have been reported to decrease the secretions, which may have inhibitory effect.

Forty one out of 45 Pap smears were found to have inflammatory cytological smears where as only 4 were observed as having normal cytological pattern. The high percentage of inflammatory smear in patients with cervical erosion with cervicitis was observed. This shows that cervical erosion though being a physiological condition but makes the cervix more vulnerable to trauma or disruption since the cervical columnar epithelium is thinner and substantially more friable and liable to disruption than the stratified squamous epithelium of the vaginal walls [8,9]. It has been also reported that the cervical erosion is not supposed to be caused solely by estrogenic hormonal changes but inflammation and trauma have also been implicated in the eti-

ology [20]. Furthermore, It has been pharmacologically proven that *Mundi*, [21] *Henna*, [22] *Neem* [23] are having antimicrobial and anti-inflammatory properties [21] that have inhibited the growth of organism and decreased the inflammation respectively.

In the present study, Kuppuswamy's scale was used to evaluate the association between the cervical erosion associated with cervicitis and socioeconomic status. It was observed that the high occurrence of this disease was seen more in lower middle class and low class than that in upper middle class and upper class (Table 1). This significant association may be correlated directly to general hygienic standard of the patient. It is in consonance with earlier study reports. [2] The lower socioeconomic status and illiteracy are prime causes of early marriage, apart from childbirth at young age, repeated pregnancies, unhygienic living standard, and gynecological infections. All these conditions lead to recurrent trauma and ultimately result in changes in cervical epithelium and cervical erosion (Table 1).

In most of the patients the age at marriage was less than 20 years (Table 1). A significant association between early age marriage and occurrence of cervical erosion with cervicitis may be due to more active sexual life, childbirth at a young age and high parity. The significant association between this disease and parity was also observed. The higher number of patients with cervical erosion with cervicitis was with three or more than three children (Table 1). The effect of parity may be explained by an increase in fibro-musculature stromal edema and hyperplasia of columnar epithelium probably resulting from hormonal changes and trauma [4]. This finding is also in consonance with previous study reports [2].

The patients were followed up for three months after completion of the trial of the disease to observe the recurrence. However, no recurrence of this disease was found in the patients who got relieved completely of symptoms and signs of cervicitis with healing of cervical erosion except in one case. The patients who had relieved of symptoms and signs with partial healing of erosion also did not complain the recurrence of symptoms. On clinical examination there was no increase in the grade of erosion in the test group. In the control group there were no changes in the symptoms related to cervicitis and grade of erosion.

The strength of the study: It is first of its kind of single blind, randomized placebo controlled trial to validate and document the effectiveness of the test drugs. Moreover, though the response was seen in 26.67% patients, it is appreciable since, there are only surgical interventions in the conventional medicine.

The limitations of this study were single blind, unequal sample size; the effect of the test drugs was assessed only by the direct visual assessment method, and sample size, and power of the study was not calculated statistically because of paucity of time. The computerized planimetry for exact measurement of cervical erosion or direct visual assessment by application of 5% acetic acid could not be employed. Therefore, further studies by using these precise methods for measuring cervical erosion and also double blind, randomized standard controlled clinical studies involving large number of patients are recommended.

Conclusion

The cervical erosion with cervicitis is considered as a potential risk factor for sexually transmitted diseases. In addition, the symptoms related to cervicitis cause discomfort to the women and affect the quality of life. Therefore, it must be treated with due care. This study proves that the formulations were found to be safe and effective in healing of erosion as well as relieving the symptoms and signs related to cervicitis than compared to the placebo. The study also validated the claim of the *Unani* physicians. Further, the efficacy of the test drugs should be evaluated by the exact measurement of cervical erosion by the computerized planimetry in double blind, randomized standard controlled studies.

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Conflict of interest

None.

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