Comparative study of (Leuko-off Coded herbal formulation) vs. Metronidazole (Allopathic medicine) for bacterial vaginosis and trichomonal infections

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Abstract

Vulvovaginitis is one of the common problems that women's have to face in their lifetime. The women are more susceptible of these infections and that they are increasingly vulnerable to infection from the anatomic as well as hormonal point of view. Bacterial vaginosis and trichomoniasis are common examples that occur after the change in the vaginal ecosystem. Single-line therapy is often inadequate and recurrence is common. So there is a need of treatment, which should be safe and affective. A random controlled clinical trial was conducted to compare the anti-bacterial and anti-trichomonal activity and safety of coded herbal medicinal treatment Leuko-off with Metronidazole. All subjects were clinically studied and completed the assigned therapy during the period May 2001 to June 2004. The clinical evaluation was carried out on 45 patients of ages between 14-48 years with the complaint of vaginal discharge at Department of Gynecology and Obstetrics in Shifa-ul-Mulk Memorial Hospital for Eastern Medicine at Hamdard University, Hamdard Matab Aram Bagh in Karachi and Civil Hospital, Karachi.

Objective of Study: To investigate the efficacy and safety of coded herbal medicine “Leuko-off” for the treatment of bacterial vaginosis and trichomonal infections and provide a comparison between herbal medicine and current allopathic treatment “Metronidazole” for bacterial vaginosis and trichomonal infections.

Conclusion: Consequently the generated data offered support to the null hypothesis (when P>0.05) hence the null hypothesis was rejected on the basis of statistical findings with regard to efficacy, safety, drug compliance and cost affectiveness (P<0.05).

Key words: Vaginal trichomoniasis, Bacterial vaginosis, Female outpatients, Vaginal microbiological ecosystem, Metronidazole.

Introduction

Bacterial vaginosis and trichomoniasis are the most common cause of vaginitis among women of child bearing age. The incidence of bacterial vaginosis varies, with higher reported rates (33% to 64%) for women attending clinics for sexually transmitted diseases. Bacterial vaginosis and trichomoniasis are not uncommon during pregnancy and has been observed in 16% to 29% of pregnant women.

The vagina makes an ideal reservoir for infected body fluids and is likely to experience minute tears and abrasions due to intercourse, allowing entry for pathogenic organisms. Both endogenous and exogenous hormones affect vulnerability to certain infections through promotion of cervical ectopy, which increases the exposure of susceptible columnar epithelium to potential pathogens. The vaginal epithelium in healthy adults woman undergoes constant desquamation and the discharges of vaginal origin are characterized chiefly by the presence of epithelial cells. The vaginal secretions are largely estrogen dependent and the amount of normal vaginal secretion varies with age and time of the menstrual cycle, with a physiological increase at ovulation, in the premenstrual phase, during pregnancy etc. In addition to these physiological variations, various microbes such as Trichomonas, Candida, Gardnerella vaginalis, Bacteroides, Mobiluncus, Gonococcus and other non-specific organism, which result is increase vaginal secretion, may infect the vagina pathologically.

Gardnerella vaginalis, Bacteroides, Mobiluncus, and Mycoplasma hominis are found in the vagina of women with bacterial vaginosis whereas trichomoniasis is caused by a single-celled protozoan parasite called Trichomonas vaginalis.
naerobic vaginitis or *Gardnerella*-associated vaginitis. The occurrence of symptoms is not based only on the over growth of organisms, but involves a combination of the virulence of the organism and the host response to infection. The primary symptom of bacterial vaginosis is an abnormal, odorous vaginal discharge. The fish-like odor is noticeable especially after intercourse. The odor results primarily from metabolic by-products of anaerobic bacteria. The odor is stronger during menses and after sexual intercourse because of the alkalinity of blood and semen. Vulvar pruritus or irritation is not common with bacterial vaginosis, but may occur (approximately 15% of cases). The discharge is usually thin, milky white or dark or dull gray, homogeneous, and adherent to the vaginal wall. Usually little or no inflammation of the vaginal epithelium is associated with the disease.

The symptoms in trichomoniasis include a heavy, yellow-green or gray vaginal discharge, discomfort during intercourse, vaginal odor, and painful urination. Irritation and itching of the female genital area, and on rare occasions, lower abdominal pain also can be present. The pH of the vaginal discharge is usually greater than 4.5. Cervicitis (strawberry cervix), although seen in fewer than 25% of patients, is suggestive of trichomoniasis. The symptoms in men, if present, include a thin, whitish discharge from the penis and painful or difficult urination.

According to WHO estimates, more than 80% of people in developing countries depend on traditional medicines for their primary health needs. The medicinal plants stand out in the frequency of utilization with which they are prescribed for gynecological complaints, specifically for vaginal discharge. The literature search obtained from NAPALERT data (Natural Product Alert Database, University of Illinois at Chicago) revealed that many plants are used for the treatment of bacterial vaginosis and trichomoniasis. Out of the list plants such as *Berberis aristata*, *Acacia arabica*, *Butea morosperma* and *Salvia malabarica* has been selected to formulate a coded herbal formulation designated as leuko-off.

**Level of Significance:**

This is the set standered to decide the cut-off value between treatment groups when comparing the two groups. If the result are significant at this set level ($\alpha = 0.05$) the null hypothesis will be rejected.

**Materials and Methods**

**Subjects:** The study was conducted on the patients of ages between 14-48 years. The trial was conducted on 45 patients irrespective of socio economic status and attending gynecological out patient department in given hospitals and clinics.

**Study design:** The study was based on an experimental, randomized, clinical trial. The study had been conducted according to the principles of good clinical practice i.e., an informed consent was obtained from the patients before enrollment and proper history and clinical examination were recorded on each follow up. The study was carried out between May 2001 to June 2004.

A randomized experimental design was employed to test the hypotheses, therefore, by manipulating the independent variable (IV) any effects on the dependent variables (DV) could be monitored. The variables were as follows: To test Experimental Hypothesis ($H_1$) and independent variables.

**Setting:** The study was conducted in the Department of Gynecology and Obstetrics at Shifa-ul-Mulk Memorial Hospital for Eastern Medicine at Hamdard Matab Aram Bagh in Karachi and STD clinic in the Department of Gynecology of Civil Hospital, Karachi.

**Sample Selection:** In this study only those patients were selectively enrolled, who were carefully diagnosed to have vaginal trichomoniasis or bacterial vaginosis through clinical history and laboratory investigations. Any abnormal secretion was collected on a sterile swab and the samples sent for microscopy and culture. Diagnosis was based on the typical signs and symptoms, wet mount prepartion and microscopy of discharge, Gram’s staining and high vaginal swab culture. Haemoglobin, ESR, urine (routine and microscopic) was also carried out.

All participants were randomly allocated in test or controlled group. The randomization will be stratified on study site and (with random sequences of block sizes) within study site to ensure that the assignment sequence is not predictable and to ensure that balance between test and control group is maintained within each study site over the entire period of participant recruitment. Study sites will computerize randomization system to obtain the accurate distribution. After the baseline assessment, patients were randomized individually to one of the two treatment groups. Randomization was done with sealed opaque envelopes that contained group designations, which were generated randomly.
by computer with Microsoft Access 97 (Microsoft Corporation, Seattle, WA). Then the patients were divided in to two groups viz control group and test group. Control group received allopathic treatment Metronidazole (Flagyl 500 mg tablets twice a day for seven days) Test group received herbal medicine Leuko-off suppository (one suppository per night for three weeks containing 2.7 gram Leuko-off powder) for all the patients having bacterial vaginosis and trichomonas infections. All participants were observed for follow-up visits over the course till the improvement.

All the patients were called for per speculum examination and per vaginal examination for observation of the discharge from vagina. Finally vaginal swab was collected for culture (HVS) when the clinical picture shows the complete improvement to access the efficacy of the trial and confirmation of the eradication of pathogenic organisms from the genital tract. Same parameters were followed in control group.

Assessment: The proportion of improvement responses for bacterial vaginosis and trichomonas represented the primary efficacy variable. Adverse events reported by patients were recorded at each follow-up visits, classified by severity was the secondary variable of the study. The relationship of each event to the study drug was also assessed. The safety outcome measure was the incidence of treatment-emergent adverse events in both groups. A high vaginal swab specimen (HVS) for routine culture and microscopy was obtained prior to the treatment. Identification of causative organism and testing for aerobic susceptibility to all study drugs by disk performed according to national Committee for Clinical Laboratory standard procedures. A urine detailed report (urine D/R), complete blood picture (CBC) and erythrocyte sedimentation rate (ESR) were also performed at the time of enrollment.

Inclusion Criteria

Persons may be included in the trial if they meet the following criteria.

* Female patients between the age of 14-48 years having the normal reproductive cycles.

* Patient suffering from bacterial vaginosis and trichomoniasis and being diagnosed through high vaginal swab culture (HVS).

* Only clinically diagnosed cases of bacterial vaginosis and trichomoniasis after microscopy and high vaginal swab (HVS) were included.

* Verbal consent and willing and able to participate in all scheduled study visits and tests.

* Patients living in Karachi, Pakistan.

* All socio-economical classes including lower, middle and higher.

Exclusion Criteria

The cases suffering from vaginal discharge were excluded as follows.

* Patients suffering from non-infective vaginal discharge.

* Patients suffering from other vaginal discharge for example vaginal candidiasis, allergic and irritative vaginitis and senile vaginitis.

* Patients with concurrent physical illness as associated diseased such as uncontrolled hypertension and diabetes.

* Known cases of cervical, vaginal and uterine malignancies.

* Patients having the history of post coital and intermenstrual bleeding.

* Patient belonging to area outside Karachi because of inherent difficulty in follow up.

RESULTS

The present study is to investigate formulated herbal medicine Leuko-off for the treatment of bacterial vaginosis and trichomoniasis. The clinical screening of anti-trichomonal and anti-bacterial activity between Leuko-off and Metronidazole was carried out to determine the efficacy and side effects to wards this malaise. These evaluations were based on clinical and laboratory findings so as to ascertain the rate of inhibition on microorganisms.

In this study a total of 50 patients were initially screened and randomized, of whom the intent-to-treat population enrolled at 4 centers: 30 were treated with herbal medicine and 15 were treated with allopathic medicine. Remaining patients were lost during follow up. This loss was distributed evenly between the treatment groups. The demographic and baseline characteristics of the intent-to-treat group were comparable for the herbal medicine and allopathic medicine treatment. Consequently, a total 45 of patients completed the final
assessment, including the blood and high vaginal swab sampling.

Patient Characteristics

There were no significant differences in the mean age (32.67 + 9.08 vs. 32.23 + 8.63 (Table 2) values between the treatment groups at the start of the clinical trial. All the patients were distributed in 5-class interval ranging from ranging from age 14 to 48 years. The mean age of the married women’s were 33.36 vs. 33.52 and mean age of the single patients were 23.00 vs. 20.67.

Table 1 and Table 2

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment Group</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n)</td>
<td>Test (n)</td>
</tr>
<tr>
<td>14-20 years</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21-27 years</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>28-34 years</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>35-41 years</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>42-48 years</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>30</td>
</tr>
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Table 2: Martial Status by Treatment Group

<table>
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<tr>
<th>Martial Status</th>
<th>Treatment Group</th>
<th>Mean</th>
<th>Number (n)</th>
<th>Std. Deviation</th>
<th>Sum</th>
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<tr>
<td>Married</td>
<td>Control</td>
<td>33.36</td>
<td>14</td>
<td>9.01</td>
<td>467</td>
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<tr>
<td></td>
<td>Test</td>
<td>33.52</td>
<td>27</td>
<td>8.11</td>
<td>995</td>
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<tr>
<td></td>
<td>Total</td>
<td>33.46</td>
<td>41</td>
<td>8.31</td>
<td>1372</td>
</tr>
<tr>
<td>Single</td>
<td>Control</td>
<td>23.00</td>
<td>1</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>2.67</td>
<td>3</td>
<td>1.15</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21.25</td>
<td>4</td>
<td>1.50</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>Control</td>
<td>32.67</td>
<td>15</td>
<td>9.08</td>
<td>490</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>32.23</td>
<td>30</td>
<td>8.63</td>
<td>967</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>32.38</td>
<td>45</td>
<td>8.68</td>
<td>1457</td>
</tr>
</tbody>
</table>

Treatment Assignment and Follow-up

All subjects were clinically studied and completed the assigned therapy during the period May 2001 to June 2004. Results presented below represent an intention-to-treat analysis vaginal discharge history and examination were performed. The clinical evaluation proforma of vaginal discharge was filled at the time of enrollment in both treatment groups. Patient’s baseline demographic variables for vaginal discharge history and speculum examination were summarized for each treatment group. As depicted in Table 3, patient characteristics were equally balanced between the test and control groups. The two treatment groups did not differ significantly (all p<0.05) from each other at any time point. The color of discharge was significantly related to infection (p=0.000). The most common vaginal discharge color was the Milky white (26 out of 45 patients) of the complaints.

Effects of Therapy on Vaginal Pathogens

Pathogens decreased dramatically in both treatment groups after therapy (table 4). The rates of complete elimination of vaginal pathogens clearance were same in the herbal treatment group at all times after treatment and it revealed that the efficacy of herbal treatment is as effective as the allopatic treatment (P = 0.058). The total duration of treatment of patients for both treatment groups was four weeks however, in control group treatment was completed in two weeks. The clinical success rates on the basis of self-assessment of patient regression of complaints and physician examination at 1st
follow-up and 2nd follow-up were equal (p > 0.05).

Table 4 and Figure

Table 4: Pathogens after treatment

<table>
<thead>
<tr>
<th>Pathogens After Treatment</th>
<th>Treatment Group</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>Bacteroides spp</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Gardnerella</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No growth</td>
<td>7</td>
<td>24</td>
<td>31</td>
</tr>
</tbody>
</table>

Pathogens after Treatment

Clinical failures or HVS positive culture after treatment no improvement occurred in 6/30 patients (20.3%) receiving herbal medicine and in 8/15 patients (53.3%) receiving allopatic medicines (table 4). Clinical success rates for those with mild to moderate infections and those with severe infections were similar in both treatment groups. For the overall, clinical success was observed in 24/30 patients (80%) of cases in herbal-treated patients and in 7/15 (46.6%) of cases in allopatic-treat ed patients.

The overall evaluation was mainly based on the efficacy of drugs in reducing vaginal discharge in term of objective symptoms. The Leuko-off produced a better result than allopatic medicines, which showed an overall cure rate of 80% versus allopatic treatment 46.6% however according to chi-square test the both treatment didn’t not differ in their efficacy.

Safety Evaluations

All the patients enrolled in the study were evaluated for safety. Adverse effects observed after administration of medicine are summarized in Table 5. The majority of adverse events were assessed as mild in severity. Adverse events categorized by the Physician (researcher) as possibly or definitely drug related were reported in 0/35 patients (0%) receiving herbal medicine and in 8/15 patients (53.3%) given allopatic medicine.

Dark urine (20%) and digestive upset (20%) were the most common drug-related events among allopatic medicine and there were no side effects seen in herbal group (0%)recipients. Overall side effects (p < 0.000) were greater in control treated participants than in test participants. No severe or serious adverse side effects were observed that interfere activities of daily living.

The hepo-toxic and nephro-toxic adverse actions were also checked in both groups after the end of treatment. Serum glutamic-pyruvic transaminase (SGPT), urea and creatinine values were recorded for this purpose. Comparison of data recorded by participants relating to these variables showed highly significant differences between test and control groups for measurements hepato-toxicity (p = 0.003) and nephro-toxicity (p = 0.011).

Table 5, 6, 7 and Figure

Table 5: Side Effects on Patients Self Assessment

Observed Side-effects | Treatment Group | Total | p value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive Upset</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Impaired Taste and Smell</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dark Urine</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>No Complaints</td>
<td>7</td>
<td>30</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 6: Hepato-toxicity and nephro-toxicity analysis

<table>
<thead>
<tr>
<th>Laboratories Values after Treatment</th>
<th>Treatment Group</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>SGPT Normal</td>
<td>11</td>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>Elevated</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Urea Normal</td>
<td>14</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>Elevated</td>
<td>1</td>
<td>0</td>
<td>01</td>
</tr>
<tr>
<td>Creatinine Normal</td>
<td>12</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Elevated</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
Drug Compliance and Cost Effectiveness

The aforementioned studies attempted to assess the remarks of the patients for compliance of the treatment and cost effectiveness of both medications used for the treatment of vaginal discharge as mentioned in table 7. Most of the women were satisfied with the treatment and had an option that they would prefer a similar treatment was on the higher side however only 16.6% patients estimated in test group and this showed highly significant difference among the groups (p = 0.000). Similarly the duration of treatment was short in control group and long among test group (p = 0.088).

Consequently the generated data offered support to the null hypothesis (when p>0.05) hence the null hypothesis was accepted on the basis of statistical findings in regard to efficacy whereas null hypothesis were rejected in case of safety and drug compliance and cost effectiveness.

DISCUSSION

Vaginitis is most often a polymicrobial infection. The use of allopathic drug combination has been considered as one of the affective chemotherapy. But this is not feasible, as besides being most cost prohibitive, they are not without side effects. The coded herbal formulation Leuko-off contains herbs, which are known for its wide range of clinical use in indigenous medicine. It has been proved that these herbs exert profound antibacterial and antitrichomonal properties. Beside all this herbal formulation have Berberis aristata, which was found to possess significant anti-inflammatory properties on acute, sub-acute and chronic type of inflammation.

This multi-center trial demonstrated that herbal medicine was as effective as the allopathic medicine in the management of patients with bacterial vaginosis and trichomoniasis. Among herbal treatment resulted in a 80% clinical cure or improvement rate, which is almost equal to that achieved with allopathic therapy 46.6% clinical success rate. The response rate of microbiological status before and after treatment suggests that Leuko-off has the same efficacy as allopathic medicine (p>0.05).

In selecting an antimicrobial agent(s) for the treatment of infective vaginal discharge, the practitioner must consider not only documented efficacy but also the adverse-events profile of the medicinal agent and the cost of therapy. In this multi-center study, Leuko-off was well tolerated and had a rate of drug related adverse events less than that to that of patients treated with Metronidazole (p=0.000). Dark urine and digestive upset were the most commonly reported adverse events in control group while no side effects reported in test treatment group.

Conclusion

Based on the statistical result of present clinical trial it can be concluded that:

* Leuko-off is of same value in the treatment of bacterial vaginosis and trichomoniasis in comparison with Metronidazole.

* There was less untoward manifestation associated with the use of Leuko-off medication and this is found a good acceptability by most of the treated patients.

* Leuko-off has added benefit of safety in term of hepato toxicity and nephro-toxicity.

Acknowledgement

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References


