

Role of Lukol Syrup in Relieving the Symptoms Associated with Leucorrhoea: A Randomized, Double Blind Placebo Controlled Clinical Study

Dr. Cordelia Praveen, MD, DGO,

Dr. Ezhilarasu Children & Speciality Hospital, 7/33 Natarajapuram Street, Meenakshipuram, Nagercoil-629002

Corresponding Author

Dr. D. Palaniyamma, MBBS., MD., Medical Advisor, R&D, The Himalaya Drug Company, Makali, Tumkur Road, Bangalore 562 162, India

Abstract: *Vaginal discharge in the reproductive age group is the most common complaint encountered everyday both by gynecologists and general practitioners. The present study was conducted to evaluate the clinical efficacy and safety of Lukol Syrup in relieving symptoms associated with Leucorrhoea. Seventy women aged more than 30 years of age with symptoms of leucorrhoea enrolled in the study based on the selection criteria. All the subjects were randomized to Lukol Syrup (Group A) and placebo group (Group B) using random number table. Subjects in the Lukol Syrup group received Lukol Syrup at a dose of 2 teaspoonful twice daily for 4 weeks and subjects in the placebo group received similar looking placebo at the same dose for 4 weeks. All subjects were followed at weeks 2 and 4 for the presence or absence of symptoms. The predefined primary efficacy endpoints were relief from the symptoms of leucorrhoea and safety of the formulation. The secondary outcome was to evaluate efficacy on the organism causing Leucorrhoea and compliance to the study medication. This clinical study clearly shows that significant symptomatic relief was observed with Lukol Syrup in individuals with leucorrhoea. There were no adverse effects either observed or reported during the clinical study and compliance to the treatment was satisfactory. In terms of the microbiological examination, there was a trend towards improvement in individuals with Candida albicans and significant improvement in individuals with Trichomonas vaginalis. Therefore, it may be concluded that, "Lukol Syrup" is effective and safe in relieving the symptoms of leucorrhoea.*

Keywords: Leucorrhoea, Lukol Syrup

1. Introduction

Excessive vaginal discharge is most often seen in women of reproductive age group. It can be due to vaginitis with inflammation of vaginal mucosa caused by trichomonas vaginalis or yeast like fungus candida. Nonspecific vaginitis also known as bacterial vaginosis is characterized by absence of inflammation of the vaginal wall.

Vaginal discharge in the reproductive age group is the most common complaint encountered everyday both by gynaecologists and general practitioners. Symptomatic vaginal discharge is caused by inflammation due to infection of the vaginal mucosa. It occurs in 1-14% of all women in the reproductive age group¹ and is responsible for 5-10 million OPD visits per year throughout the world. The prevalence of vaginal discharge in India is estimated to be 30%¹. Abnormal vaginal discharge also predisposes to significant morbidity in the form of pelvic inflammatory diseases, infertility, endometriosis, urethral syndrome, pregnancy loss, preterm labour, to enumerate a few. Most common cause of symptomatic vaginal discharge is bacterial vaginosis (33-47%)², followed by candidiasis (20-40%) and trichomoniasis (8-10%)^{3,4}. These three conditions account for 90% of all etiologies of abnormal vaginal discharge. Multiple infections can also coexist³.

Successful management of symptomatic vaginal discharge lies in the diagnostic approach. The traditional approach to diagnosis is through laboratory diagnosis of the aetiological agent(s). This approach is expensive and not available at all

health centres or dispensaries. Most of the times a presumptive diagnosis is made based on the nature of the discharge. Diagnosis using clinical criteria often leads to misdiagnosis as the components are subjective and depend upon the acuity of the clinician and the availability of equipment. Therefore etiological diagnosis by isolation and identification of the causative agent provides reliable information for delivering proper treatment and avoid complications. Vaginal Trichomoniasis and candidiasis are diagnosed by wet mount, and culture.

Despite the ability to treat reproductive tract infections, Leucorrhoea remains the major world wide public health problem in women. Several modern medicines are available to alleviate the symptoms of Leucorrhoea. Oral metronidazole is associated with anorexia, nausea, vomiting and skin rashes. It crosses the blood brain barrier and may cause dizziness, convulsions and peripheral neuropathy. Transient leucopenia and disulfiram like action has been seen with metronidazole. 10 to 30% of patients treated with the drug had Candidiasis three weeks later. Hence metronidazole should not be used unless definitely indicated. Antifungal therapy is associated with renal and hepatic complications, hypersensitivity reactions, nausea and vomiting, flatulence and rarely angioedema. Blanket therapy and combination therapy for treatment of vaginal infections is not preferred without proof of infections⁵.

Several traditional and complimentary agents are known to relieve symptoms of Leucorrhoea and are being continuously researched. Lukol syrup is one such formulation, with potent herbs known to be effective in Leucorrhoea. The present

clinical study is aimed to evaluate the safety and efficacy of Lukol Syrup.

Aim:

The present study was planned to evaluate the clinical efficacy and safety of Lukol Syrup in relieving symptoms associated with Leucorrhoea

2. Study Design

This study was a randomized double blind placebo controlled clinical study. The study protocol, case report forms, regulatory clearance documents, product related information and informed consent form were submitted to the Ethics Committee and were approved by the same.

3. Materials and Method

Seventy women aged more than 30 years of age with symptoms of leucorrhoea attending the outpatient at Dr. Ezhilarasu Children & Specialty Hospital, 7/33 Natarajapuram Street, Meenakshipuram, Tamil Nadu, India were included in the study. Detailed history was obtained and general examination of the patients was carried out to exclude patients suffering from systemic disorders. Also subjects with pre-existing systemic disease necessitating long-term medications, endocrinal disorders, subjects with known history or present condition of allergic response to similar medications and those who refused to give informed consent, were excluded from the study. Pregnant and lactating women were also excluded from the study. Pelvic examination was done to exclude pelvic pathology. Speculum examination was done to exclude lesions of the cervix and vagina and the discharge was examined microscopically to rule out specific cervicitis or vaginitis. –Pap” smear was done on patients aged 35 and more to exclude early malignancy. The demographic details of the study have been presented in table 1.

All the subjects were randomized to Lukol Syrup (Group A) and placebo group (Group B) using random number table. Subjects in the Lukol Syrup group received Lukol Syrup at a dose of 2 teaspoonful twice daily for 4 weeks and subjects in the placebo group received similar looking placebo at the same dose for 4 weeks. All subjects were followed at weeks 2 and 4 for the presence or absence of symptoms.

4. Primary and Secondary Outcomes

The predefined primary efficacy endpoints were relief from the symptoms of leucorrhoea. Assessment parameters included itching in vulva and vagina, pain in vulva and vagina, painful coitus, backache, loss of appetite, constipation, weakness, abdominal pain and vaginal discharge and safety of the formulation. The secondary outcome was to evaluate efficacy on the organism causing Leucorrhoea namely Candida and Trichomonas and compliance to the study medication.

Adverse Events

All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset,

duration, and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as –Unrelated” (follows a reasonable temporal sequence from the administration of the drug), –Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and –Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they so desired without assigning reasons. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non compliance were noted.

5. Statistical Analysis

Results were analyzed statistically by Mann Whitney test for evaluation of Lukol Syrup in symptoms of leucorrhoea. Effect of Lukol Syrup for the evaluation of clinical parameters were analyzed statistically using Repeated measures of ANOVA with Tukey’s Multiple Comparison post hoc test and the effect of Lukol Syrup for the evaluation of haematological and biochemical parameters were evaluated using Paired t test. For the evaluation of Lukol Syrup on microbiological examination, statistical analysis was conducted using Fisher’s exact test. There was 95% confidence interval with 5% level of significance for two-tailed p value. Analysis was performed using Graphpad prism software Version 4.03 for Windows, GraphPad Software, San Diego, California, USA.

6. Results

A total of 70 subjects were enrolled in the study. The demographic details of the subjects at entry are listed in Table 1.

The subjects treated with Lukol Syrup, reported reduction in leucorrhoea symptoms summarized in Table 2. The reduction in the symptoms was seen from week 2 onwards, till the end of the study. There were no clinically significant adverse reactions, either reported or observed, during the entire study period and overall compliance to the treatment was good.

The evaluation of various parameters on the effect of Lukol Syrup has been depicted in table 2. For itching in vulva and vagina and pain in vulva and vagina the change in the values from baseline to each follow up is considered. For itching in vulva and vagina, the change in the value from baseline was 1.14 ± 0.43 at week 2 and 1.63 ± 0.65 at week 4. The change in the level of significance was found to be $p < 0.0362$ at week 2 and $p < 0.0097$ at week 4 respectively. Similarly for pain in vulva and vagina, the change in the values from baseline were 0.43 ± 0.56 at week 2 and further change in the value at week 4 was 0.46 ± 0.61 . The change in the level of significance from baseline to the end of the treatment was

found to be $p < 0.0322$ and $p < 0.0303$ at weeks 2 and 4 respectively.

Change in the value for loss of appetite was observed with 0.71 ± 0.79 on day 1 with a significance of $p < 0.022$ in the Lukol group. Reduction in the other symptoms of leucorrhoea like painful coitus, backache, constipation, abdominal pain and vaginal discharge was observed from week 2 onwards in the Lukol group as compared to placebo but were not found to be statistically significant.

Evaluation of the effect of Lukol Syrup on clinical parameters and haematological and biochemical parameters showed that all the parameters were found to be within the normal limits before and after treatment in both the groups demonstrating the safety of Lukol syrup. .

Microbiological evaluation of the effect of Lukol Syrup before and after treatment was evaluated in table 3. *Candida albicans* was present in 15 subjects before treatment in Lukol group. Whereas, in the placebo group *Candida albicans* was present in 12 subjects before treatment. After 4 weeks of treatment with Lukol Syrup, there was marked reduction in the number of subjects with 8 subjects continuing to have *Candida albicans*, however, the significance was missing in the Lukol group. In the placebo group, 10 subjects still persisted with *Candida albicans* after treatment. *Trichomonas vaginalis* was present in 12 subjects in the Lukol group and 13 subjects in the placebo group before treatment. At the end of treatment, there was a significant ($p < 0.0224$) reduction with only 5 subjects continuing to have *Trichomonas vaginalis* in the Lukol group as compared to placebo.

Overall impression to the treatment was evaluated by interviewing the patient and was presented in table 4. Out of 35 patients, 3 patients were cured, 16 showed marked improvement, 11 showed moderate improvement and 5 patients showed slight improvement to Lukol Syrup. Whereas, in the placebo group, 1 patient showed marked improvement, 12 patients showed moderate improvement, 4 patients showed slight improvement, 12 patients showed no change and for 6 patients symptoms became worse. The investigator response to the treatment had shown that in the Lukol group, 5 patients were cured, 16 patients showed marked improvement, 12 patients showed moderate improvement and 2 patients showed slight improvement to treatment. Whereas, in the placebo group the investigator response to the treatment showed 2 patients with marked improvement, 12 patients with moderate improvement, 5 with slight improvement, 12 showed no change and 4 patients with symptoms became worse at the end of the treatment.

In a series of 70 cases of leucorrhoea, oral treatment with Lukol Syrup gave good results with significant reduction of symptoms within 2 weeks of treatment. Lukol Syrup was well tolerated and produced no toxic effects. Two patients from the placebo group were withdrawn from the study due to personal reasons. There were no adverse effects either observed or reported during the clinical study and overall compliance to treatment was found to be good.

Table 1: Demographic data at entry (n=70)

	Lukol Syrup	Placebo
No. of subjects	35	35
Age (Mean±SD)	31.35 ± 2.65	34.62 ± 7.02

Table 2: Efficacy of Lukol Syrup in symptoms of Leucorrhoea

Parameters	Duration	Lukol Syrup	Placebo	Significance
Itching in Vulva and Vagina [#]	Week 2	1.14 ± 0.43*	0.82 ± 0.46	$p < 0.0362$
	Week 4	1.63 ± 0.65*	1.17 ± 0.62	$p < 0.0097$
Pain in Vulva and Vagina [#]	Week 2	0.43 ± 0.56*	0.11 ± 0.32	$p < 0.0322$
	Week 4	0.46 ± 0.61*	0.11 ± 0.32	$p < 0.0303$
Painful Coitus	Day 1	0.00 ± 0.00	0.06 ± 0.24	NS
	Week 2	0.00 ± 0.00	0.06 ± 0.24	NS
	Week 4	0.00 ± 0.00	0.00 ± 0.00	NS
Backache	Day 1	0.77 ± 0.77	0.71 ± 0.86	NS
	Week 2	0.23 ± 0.55	0.29 ± 0.46	NS
	Week 4	0.14 ± 0.49	0.14 ± 0.36	NS
Loss of Appetite	Day 1	0.71 ± 0.79*	1.17 ± 0.75	$p < 0.022$
	Week 2	0.20 ± 0.41	0.26 ± 0.44	NS
	Week 4	0.06 ± 0.24	0.09 ± 0.28	NS
Constipation	Day 1	0.57 ± 0.70	0.46 ± 0.78	NS
	Week 2	0.06 ± 0.24	0.17 ± 0.38	NS
	Week 4	0.00 ± 0.00	0.17 ± 0.38	NS
Weakness	Day 1	0.94 ± 1.06	0.77 ± 0.97	NS
	Week 2	0.20 ± 0.41	0.17 ± 0.51	NS
	Week 4	0.00 ± 0.00	0.17 ± 0.51	NS
Abdominal pain	Day 1	0.14 ± 0.36	0.31 ± 0.58	NS
	Week 2	0.00 ± 0.00	0.00 ± 0.00	NS
	Week 4	0.00 ± 0.00	0.14 ± 0.36	NS
Vaginal discharge	Day 1	0.71 ± 1.18	1.14 ± 1.33	NS
	Week 2	0.54 ± 0.95	0.63 ± 0.88	NS
	Week 4	0.20 ± 0.41	0.46 ± 0.70	NS

Statistical test: Mann Whitney test
 NS: Not significant

Note: [#] For itching for vulva and vagina and pain in vulva and vagina the change in the values from baseline to each follow up is considered as there was a statistical significance at baseline (Day 1) for Lukol Syrup Vs Placebo.

Table 3: Effect of treatment on microbiological examination (Number of cases)

	Treatment	Before treatment	After treatment	Significance
<i>Candida albicans</i>	Lukol Syrup	15	8	NS
	Placebo	12	10	
<i>Trichomonas vaginalis</i>	Lukol Syrup	12	5*	$p < 0.0224$
	Placebo	13	9	

Table 4: Overall impression

Lukol Syrup	Patient		By investigator	
	In no.s	Percentage response	In no.s	Percentage response
Overall response by				
Cured = 1	3	8.57	5	14.29
Marked improvement = 2	16	45.71	16	45.71
Moderate improvement = 3	11	31.43	12	34.29
Slight improvement = 4	5	14.29	2	5.71
No change = 5	0	0.00	0	0.00
Symptoms became worse = 6	0	0.00	0	0.00
Total	35	100	35	100
Placebo	Patient		By investigator	
Overall response by	In no.s	Percentage response	In no.s	Percentage response
Cured = 1	0	0.00	0	0.00
Marked improvement = 2	1	2.86	2	5.71
Moderate improvement = 3	12	34.29	12	34.29
Slight improvement = 4	4	11.43	5	14.29
No change = 5	12	34.29	12	34.29
Symptoms became worse = 6	6	17.14	4	11.43

7. Discussion

Leucorrhoea is one of the most common complaints encountered in gynaecological practice. The term "leucorrhoea" is applied to cases of abnormal vaginal discharge, non-haemorrhagic in nature, which is not caused by neoplasm or other serious organic disease. It is considered that changes in the vaginal epithelium; changes in the normal bacterial flora and pH of the vaginal secretion predispose to leucorrhoea. Chronic illness, fatigue, malnutrition, emotional disturbances, chronic retroverted uterus, congestive cardiac failure, gonococcal and monilial infections, vulvovaginitis, lesions of the vaginal wall and uterine cervix have all been associated with leucorrhoea. An increase in normal vaginal secretion occurs physiologically at puberty, during pregnancy and in some women during the premenstrual phase. Non-pathological leucorrhoea can be classified into (a) cervical and (b) vaginal. In cervical leucorrhoea cervical discharge is mucoïd in nature and can arise due to chronic cervicitis, cervical erosion, mucous polyp etc. Vaginal leucorrhoea is very common and is seen when the discharge originates in the vagina. Most probably it is due to disturbances of oestrogenic function caused by ovarian insufficiency.

White discharge or leucorrhoea are very common complaints in clinical practice. The common causes of leucorrhoea include vaginal infection with trichomonas vaginalis, candida albicans or mixed bacteria. Very often a causative agent is not found. Another important cause is post-menopausal vaginitis, which is treated with hormone replacement or by use of vaginal creams. Vaginal infections are treated with proper antibiotics. But in most of the cases, leucorrhoea persists or recurs.

There are various medications available but are not without adverse effects. While the modern medicines tries to address the treatment, Lukol syrup in addition also is aimed to prevent the recurrence, which is a common in Leucorrhoea. The Beneficial effect of Lukol Syrup could be due to the synergistic actions of the individual ingredients in the

formulation. The efficacy could be attributed to the following activity of the herbs.

1. Antibacterial activity

Symplocos racemosa^{6,7}, *Woodfordia fruticosa*⁸, *Asparagus racemosus*⁹, *Butea frondosa*^{10,11}, and *Cuminum cyminum*¹² have potent antimicrobial action against bacteria responsible for leukorrhoea associated with bacterial vaginosis and PID.

2. Antifungal activity

*Syzygium cumuni*¹³, *Vetiveria zizanioides*¹⁴ and *Zingiber officinale*¹⁵ have potent antifungal action against commonly involved fungi in leukorrhoea associated with Candida vulvovaginitis.

3. Anti-spasmodic activity

*Zingiber officinale*¹⁶ and *Piper nigrum*¹⁷ possess antispasmodic property which is helpful in relieving spasms and cramps in leukorrhoea associated with chronic cervicitis and PID.

4. Antioxidant activity

Woodfordia fruticosa^{18,19}, *Asparagus racemosus*²⁰, *Boerhaavia diffusa*²¹, *Cuminum cyminum*^{22,23}, *Aegle marmelos*²⁴, *Triphala*^{25,26}, and *Phoenix dactylifera*^{27,28}, are potent antioxidants, which synergistically contribute to the anti-inflammatory and wound healing activities in cases of leukorrhoea associated with chronic cervicitis, atrophic vaginitis and PID.

5. Anti-inflammatory and analgesic action

Boerhaavia diffusa^{29,30}, *Adhatoda vasica*^{31,32}, *Vetiveria zizanioides*³³, *Zingiber officinale*^{34,35}, *Piper nigrum*³⁶ and *Butea frondosa*³⁷ have potent anti-inflammatory and analgesic actions which help in the symptomatic relief of leucorrhoea associated with chronic cervicitis and PID.

6. Adaptogenic action

Triphala^{38,39}, *Asparagus racemosus*⁴⁰, *Boerhaavia diffusa*^{41,42}, and *Zingiber officinale*⁴³ act as adaptogenic which increases the body's resistance to stressors such as trauma, anxiety and body fatigue.

7. Astringent action

Syzygium cumuni, *Aegle marmelos*, *Butea frondosa*, and *Symplocos racemosa* have astringent activity that may be helpful in the management of clinical symptoms of leukorrhoea.

8. Other beneficial actions

Laxative effect of Triphala may be beneficial for relieving chronic constipation which is one of the precipitating factors of leukorrhoea. *Phoenix dactylifera* is having nutritional significance which is useful in emaciated and weakness⁴⁴. The efficacy of the formulation in alleviating the symptoms of Leucorrhoea can be attributed to the synergistic activity of the herbs in Lukol syrup

8. Conclusion

The present clinical study clearly shows that significant symptomatic relief was observed with Lukol Syrup in individuals with leucorrhoea. Statistical significant

beneficial effect was observed with Lukol Syrup treatment in the parameters like itching in vulva and vagina, pain in vulva and vagina, loss of appetite. In other parameters associated with leucorrhoea like weakness, abdominal pain and vaginal discharge there was a trend towards improvement. In Microbiological examination, there was a trend towards improvement in individuals with *Candida albicans* and significant improvement in individuals with *Trichomonas vaginalis*. There were no adverse effects either observed or reported during the clinical study. Therefore, it may be concluded that, —Lukol Syrup” is effective and safe in relieving the symptoms of leucorrhoea.

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