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Efficacy and Safety of Dabidulward for the Treatment of Pelvic Inflammatory Disease: A Placebo Controlled Randomised Clinical Trial

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ABSTRACT

The objective of the study was to validate and to evaluate the efficacy of Capsule Dabidulward for the treatment of Pelvic Inflammatory Disease, which is a polymicrobial infection. Excellent data support the role of Chlamydia trachomatis, Neisseria gonorrhoea and facultative gram-negative and anaerobic bacteria in causing the symptoms and signs of the infection itself as well as the damage that ensues. Patient with PID were treated with Capsule Dabidulward 500mg twice daily orally for a total of 21 days. It was a single blind placebo controlled clinical trial. In total, 40 patients were treated for PID. The patients were screened and diagnosed as per revised CDC criteria for PID. Rates of clinical success for Capsule Dabidulward were comparable to those for the comparator regimen. Capsule Dabidulward was well tolerated and no adverse/side effects were encountered. In conclusion, Capsule Dabidulward was clinically effective and safe in relieving the symptoms and signs of Pelvic Inflammatory Disease. Hence, patients with PID can safely be treated with this marketed drug of Dehlvi Naturals.

Keywords: Dabidulward; NFUM; Pelvic Inflammatory Disease; Waram-e-Rehm

INTRODUCTION

Pelvic inflammatory disease (PID) is a polymicrobial ascending infection that causes inflammation of the upper genital tract, including endometritis, salpingitis, pelvic peritonitis, and occasionally leading to tuboovarian abscess (TOA) formation[1, 3,4,5]. PID is perhaps the most important avoidable cause of female tubal factor infertility, and its association with other chronic sequelae is well documented [2]. The actual burden of disease is unknown, but data from the USA suggest that > 10.0% of women of reproductive age have a history of PID and that over 1 million new cases of symptomatic PID are seen annually[6]. A crude marker of PID in resource-poor countries can be obtained from reported hospital admission rates, where it accounts for 17% to 40% of gynecological admissions in sub-Saharan Africa, 15% to 37% in Southeast Asia, and 3% to 10% in India [7]. The majority of clinically recognized cases occur in sexually active women under the age of 25 years. The sexually transmitted micro-organisms *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and the facultative and anaerobic microorganisms have all been implicated in the pathogenesis of PID [8]. Although incidence rates may have declined, PID remains a major source of short- and long-term morbidity in women. There is no evidence to suggest that there has been any reduction in the serious reproductive complications traditionally associated with PID, which include infertility, ectopic pregnancy,

and chronic pelvic pain. Treatment goals encompass not only the amelioration of the acute inflammatory condition but also the prevention or lessening of the risk for long-term reproductive sequelae. Hence, an early and accurate diagnosis of pelvic inflammatory disease (PID) is of paramount importance for the effective management of the acute illness and for the prevention of long-term sequelae. Current modern treatment depends on the cause and generally involves use of antibiotic therapy. Despite of the claim of modern medicine with regard to the presence of anti-bacterial anti parasitic medicines that there is a definite treatment of PID, the above mentioned incidence of different organisms in causing pelvic inflammatory disease is still prevailing.

Every antibacterial drug in modern medicine produces more or less adverse effects in the human body. In present era, everyone tends to become more health conscious and seeks the safer side in respect to treatment. Natural, herbal or traditional medicine is now being seen with an eye of great interest and hope. Unani medicine is one of them; this system not only provides the drugs information in abundance but also claims that the drugs are having least adverse effects.

The clinical study reported in this article validated the efficacy and tolerability of capsule form of *Majun Dabidulward* of Dehlvi Naturals, India for the treatment of pelvic inflammatory disease. *Majoon Dabidulward* is a well known classsical unani formulation used in the management of *warm-e-rahm* (PID) since ages. All the individual herbs of *Dabidulward* possesses anti-inflammatory, emmenogogue, anti-spasmodic, astringent, antiseptic, anti-microbial as well as anti-oxidant properties which are well documented in unani and modern pharmacology. These actions of individual drugs are known for their efficacy in gynaecological ailments. Similarly the compound formulation ‘‘Majoon Dabidulward’’ has been prescribed for visceral inflammations such as metritis, hepatitis, ileitis etc, in reknowed unani pharmacopeias such as Biyaz-e-Kabir[9], Kitab-ul-Murakabat[10], NFUM[11].

MATERIAL AND METHODS

Study Drug: The study drug was capsule Dabidulward of Dehlvi Naturals, India. The ingredients of capsule Dabidulward are given in Table-1. Both Dabidulward and placebo capsules were supplied by Dehlvi Naturals.

Table-1: Composition of Dabidulward Capsule

Each 500 mg capsule contains dried aqueous extract of:	
Nardostachys jatamansi (Jatamansi)- 13 mg	Rubia cordifolia (Majith)- 13 mg
Pistacia lentiscus (Mastagi))- 13 mg	Coccus lacca (Lakh)- 13 mg
Crocus sativus (Kesar)- 13 mg	Cichorium intybus (Kasni Beej)- 13 mg
Bambusa arundinacea (Tabasheer)- 13 mg	Apium graveolens (Ajmod Beej)- 13 mg
Cinnamomum zeylanicum (Dalchini)- 13 mg	Aquilaria agallocha (Agar)- 13 mg
Cymbopogon jwarancusa (Lamjak)- 13 mg	Aristolachia longa (Zarawind)- 13 mg
Valeriana wallichii (Tagar)- 13 mg	Commiphora opobalsamum (Balsan)- 13 mg

Saussurea lappa (Metha Kut)- 13 mg	Myrtus caryophyllus (Laung)- 13 mg
Gentiana olivieri (Ghafis Phool)- 13 mg	Elettaria cardamomum (Elaichi Choti)- 13 mg
Cuscuta reflexa (Kasoos)- 13 mg	Rosa damascena (Gulab Patti)- 253 mg

Study Design

The study was designed as Randomized, Single-Blind and Placebo Controlled Clinical trial; randomization was done by lottery method.

Patient Selection

The parameters for screening of subjects were lower abdominal pain, abnormal vaginal discharge, and elevated body temperature with chills associated with nausea & vomiting, irregular bleeding, Urinary symptoms such as dysuria, burning micturition etc. and dyspareunia. Patients presenting with any of the one above mentioned symptoms were screened for the clinical evidence of pelvic inflammatory disease. All the subjects fulfilling the screening criteria were then subjected to inclusion and exclusion criteria. All the screened subjects with confirmed clinical diagnosis as per Revised CDC criteria, as per inclusion/exclusion criteria were included in the study.

Treatment of Patients

The eligible patients as per the inclusion/exclusion criteria were randomly assigned to receive either Dabidulward or placebo capsule (weight of each Dabidulward/Placebo capsule =500 mg) in the dose of 2 capsules twice daily with plain water starting on 5^{th} day of mensis for a period of 21 days.

During the study period patients were asked to avoid sexual intercourse and were advised to maintain personal and local hygiene.

Inclusion criteria:

- Married women aged 20 - 40 years.
- Medical diagnosis of uncomplicated pelvic inflammatory disease (sub-acute PID with mild to moderate signs and symptoms).
- Positive clinical findings confirming the diagnosis of mild to moderate pelvic inflammatory disease as per CDC Criteria.
- Only women with first episode of PID were included.
- Patients willing to comply with various demands of study executives.
- Patients willing to sign informed consent form to participate in the study.

Exclusion criteria:

- Complicated cases of PID i.e Presence of TO abscess etc confirmed by clinical examination and by ultrasonography.
- Women with recurrent PID or chronic PID excluded history taking.
- Patients seropositive for syphillis excluded on the basis of VDRL test.

- Tubercular peritonitis excluded with the help of Mantoux test and chest radiograph in suspected cases on clinical examination.
- Malignancy was ruled out and excluded on the basis of PAP smear examination in suspected cases with bad cervical erosions and hypertrophy and presence of multiple nabothian follicles.
- Pregnant and lactating women.
- Concomitant disease that may affect the evaluation of response to protocol therapy (such as inflammatory bowel disease or significant renal or hepatic disease).
- Diabetes mellitus excluded by careful history taking and blood sugar random examination.
- Liver diseases and Chronic Renal Failure.

Clinical evaluation of patients

The effects of Dabidulward and placebo were assessed on subjective and objective parameters. Subjective parameters included pain in lower abdomen, vaginal discharge, odour of vaginal discharge, painful coitus and fever; while, assessment of objective parameters included fornical tenderness, cervical redness, cervical discharge and bacteriological examination. As these parameters differ in severity from patient to patient, an arbitrary grading of subjective and objective parameters was adopted for appropriate assessment and statistical evaluation to assess the efficacy. The patients were followed up on 7th, 14th and 21st day. At every visit, the patients were clinically examined and asked about the improvement or worsening in their symptoms. Concomitant treatment was not allowed during the protocol period.

Subjective parameters

1 Lower abdominal pain

The lower abdominal pain was assessed on Visual Analogue Scale (VAS)[12].

2 Vaginal discharge

Vaginal discharge was assessed on 3 pointer scale from 1– 3 [13], 1= No discharge; 2 = Scanty discharge; 3 = Excessive discharge.

3 Odour of vaginal discharge

Odour of the vaginal discharge was assessed on 3 pointer scale ranging from 1-3[13],1= No odour; 2 = Minimal foul odour; 3 = Excessive foul odour.

4 Painful coitus

Degree of pain or discomfort on coitus was assessed on 6 pointer scale [13], 0= Not at all; 1= Mild; 2 = Moderate; 3 = Severe; 4 = Very severe; 5 = Did not like to have intercourse due to pain

5 Fever:

Fever (temp> 38 C) was assessed as present (+) or absent(-).

Objective parameters

1 Fornical tenderness:

Fornical tenderness was assessed on 4 pointer scale [14], 1= If patient says the site is tender' 2 = If patient winces; 3 = If patient winces and moves away; 4 = If patient did not allow P/V examination

2 Cervical redness:

Cervical redness was assessed on 3 pointer scale [14], 1 = Mild; 2 = Moderate; 3 = Severe

3 Cervical discharge:

Cervical discharge was assessed on 3 pointer scale from 1– 3 [13], 1= No discharge; 2 = Scanty discharge; 3 = Excessive discharge

4 Cervical movements:

Cervical movement was assessed as painful (+) or non painful (-).

Bacteriological Assessment Of Patients

Samples for microbiological assessment were obtained from the urethra, endocervix, intrauterine-contraceptive device (if removed) and endometrium before treatment (day 1). All specimens were Gramstained. Bacteriological response to treatment was based on isolation of bacteria and reduction in number of PMN`s in gram stain specimen.

Safety Assessment

The safety was assessed by monitoring adverse events either volunteered by the patients or elicited by the investigator by clinical as well as laboratory investigations at baseline, after one week and at the termination of the study. The laboratory tests included Kidney Function Test (Blood Urea, S.Creatinine) , Liver Function Test (S. Bilirubin, SGOT, SGPT, Alk.Phosphatase) and Haemogram (Hb%, TLC, DLC, ESR)

Statistical Analysis

The pre-treatment and post-treatment values in each group separately (within group differences) were statistically analyzed by using Mann-Whitney Test for Intra-Group and Kruskal-Wallis Test with Post Dunn`s Multiple Comparisons Test for Inter-Groups comparisons.

RESULTS

In total 70 subjects with sign and symptoms of sub-acute PID as per screening criteria were enrolled for the study, however only 40 completed the study. The baseline characteristics/demographic data of patients in the two groups are summarized in Table-2

Table-2: Baseline Characteristics/Demographic Data

Characteristics	**Treatment Group**	**Drug**	**Control**
	Total No. of Patients	24	16
	Mean Age (Years)	27.7	26.4
Educational Status	Illiterate	11(45.83%)	3(18.75%)
	Primary	6 (25%)	5 (31.25%)
	Hr. Secondary	5 (20.83%)	5 (31.25%)
	Sr. Secondary	1(4.16%)	3 (18.75%)

	Graduate	1(4.16%)	0
Socio-economic Status	Higher	0	1(6.25%)
	Middle	15(62.5%)	8 (50%)
	Lower	9 (37.5%)	7 (43.75%)
Sexual Behaviour	Heterosexual	24(100%)	16 (100%)
	Homosexual	0	0
	Bisexual	0	0
Religion	Hindu	15(62.5%)	9 (56.25%)
	Muslim	9 (37.5%)	7 (43.75%)
	Christian	0	0
Parity	Nullipara	3(12.5%)	3(18.75%)
	Primipara	2(8.3%)	3(18.75%)
	Multipara	19 (79.16%)	10 (62.50%)
Contraceptives	Oral Pill	1(4.16%)	1(6.25%)
	IUD	2 (8.3%)	3(18.75%)
	Barrier	10 (41.66%)	7 (43.75%)
	Tubal Ligation	1(4.16%)	1(6.25%)
	None	10 (41.66%)	4 (25%))
Presenting Signs & Symptoms	Lower abdominal pain	22 (100%)	16 (100%)
	Vaginal discharge	22 (100%)	16 (100%)
	Foul smell of discharge	20 (90.9%)	15(93.75%)
	Painful coitus	12 (54.5%)	13(81.25%)
	Fever	0	0
	Fornical tenderness	22 (100%)	16 (100%)
	Cervical discharge	22 (100%)	16 (100%)
	Cervical redness	22 (100%)	16(100%)
	Painful cervical movements	13(81.25%)	13(81.25%)

Effects of Dabidulward and Placebo on Subjective Parameters:

As shown in Table-2 and Figures 1&2, the median score of pain before starting treatment was 6.4 and on termination of Dabidulward treatment, it was 1.95, the percentage of improvement was 69.76% ($p<.0001$ [Mann-Whitney Test]). The median percent change in placebo group was 1.3%, which was found statistically insignificant. The inter-group comparison by applying Kruskal-Wallis Test showed highly significant difference between the two groups ($p<.001$).

In test group vaginal discharge and foul smell of discharge were improved by 33.33% and 66.66% respectively (both $p<.001$- Mann Whitney Test). In control group no any improvement was detected in

vaginal discharge, however the foul smell of discharge was reduced by 33.33% (p<.0001- on comparison between the two groups by Kruskal-Wallis Test).

Fifty percent improvement in painful coitus was ascertained in test group (p<.001- Mann Whitney), no any improvement was detected in control group (p<.0001- on comparison between the two groups by Kruskal-Wallis Test).

Effects of Dabidulward and Placebo on Objective Parameters:

The percentage of improvement in fornical tenderness was found 33.33% after completion of treatment in test group (p<.001- Mann Whitney Test), no improvement detected in placebo group (p<.0001- on comparison between the two groups by Kruskal-Wallis Test). The mean score of cervical discharge was reduced from 3 to 2 after completion of treatment with *Dabidulward* and the percentage of improvement was 33.33% (p<.001- Mann Whitney), whereas no change was observed after treatment with placebo capsule (p<.0001- on comparison between the two groups by Kruskal-Wallis Test). Cervical redness was improved by 33.33% in drug group (p<.001- Mann Whitney) no improvement in cervical redness was detected in placebo group (p<.0001- on comparison between the two groups by Kruskal-Wallis Test). Painful cervical movement was noticed in total 18 cases in test group, after accomplishment of *Dabidulward* therapy, 14 patients were completely recovered from painful cervical movements. In control group painful cervical movement before treatment were encountered in 13 patients and persisted even after completion of treatment in all these cases.

All the subjects in test group and control group showed the presence of Gram +ve Bacteria on Gram`s Staining of the endocervical swab smear. However, no Gram –ve Bacteria was detected in any subject of either group. No effect of the drug/control was discovered on Gram +ve Bacteria in either group. However, a significant reduction in neutrophil count was discovered in test group after completion of therapy. No such finding was encountered in control group

Table-3:Effects of Dabidulward and Placebo on Various Parameters of PID

Group	Presenting Symptom	No. (%) Of Subjects	Median Score Before Treatment	Median Score After Treatment	Percent Change	P Value
TEST (N=24)	Lower Abdominal Pain	22 (91.66%)	6.45	1.95	-69.76	<.0001
	Vaginal Discharge	22 (91.66%)	3.00	2.00	-33.33	<.001
	Foul Smell Of Discharge	20 (83.33%)	3.00	1.00	-66.66	<.001
	Painful Coitus	12 (50%)	4.00	2.00	-50	<.001
	Fever	0	0	0	0	
CONTROL (N=16)	Lower Abdominal Pain	16 (100%)	6.55	6.4	-1.53	NS
	Vaginal Discharge	16 (100%)	3 .00	3.00	0	NS
	Foul Smell Of Discharge	15(93.75%)	3.00	2.00	-33.33	<.001
	Painful Coitus	13(81.25%)	3.00	3.00	0	NS
	Fever	0	0	0	0	NS

Group	Presenting Sign	No. Of Subject presented With %	Median Before Treatment	Median After Treatment	% Change	P Value
TEST (N=24)	Fornical Tenderness	22 (91.66%)	2 .00	1.00	-50	<.001
	Cervical Discharge	22 (91.66%)	3.00	2.00	-33.33	<.001
	Cervical Redness	22 (91.66%)	3.00	2 .00	-33.33	<.001
	Painful Cervical Movements	18(75%)	Improved In 14 Subjects			
CONTROL (N=16)	Fornical Tenderness	16 (100%)	2 .00	2.00	0	NS
	Cervical Discharge	16 (100%)	3 .00	3.00	0	NS
	Cervical Redness	16(100%)	2 .00	2.00	0	NS
	Painful Cervical Movements	13(81.25%)	Not Improved In All 13 Subjects			

Negative (-) sign is indicative of improvement; NS = Not significant

Figure-1: Effects of Dabidulward and Placebo on Subjective Parameters

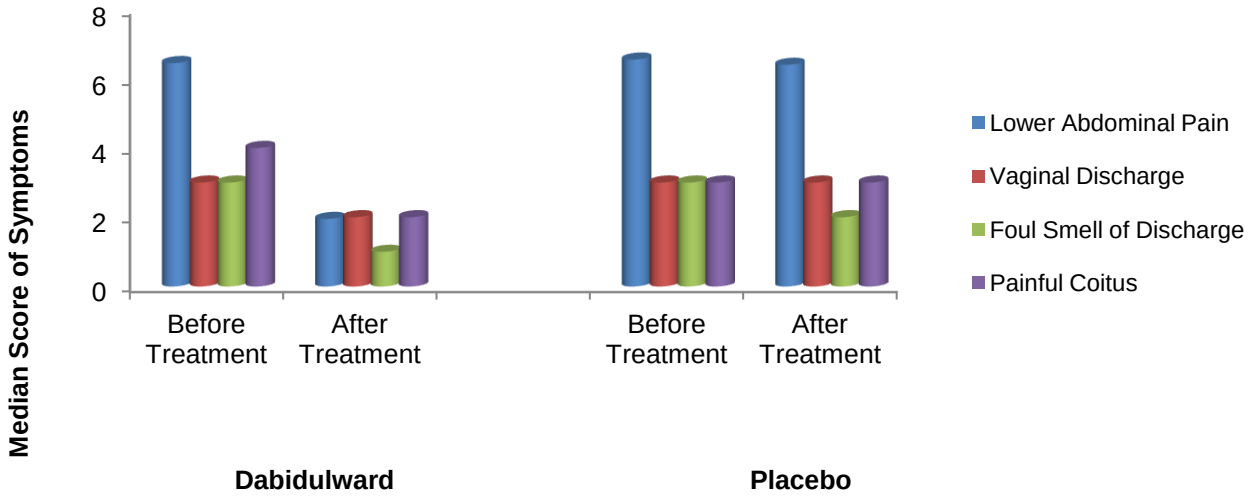
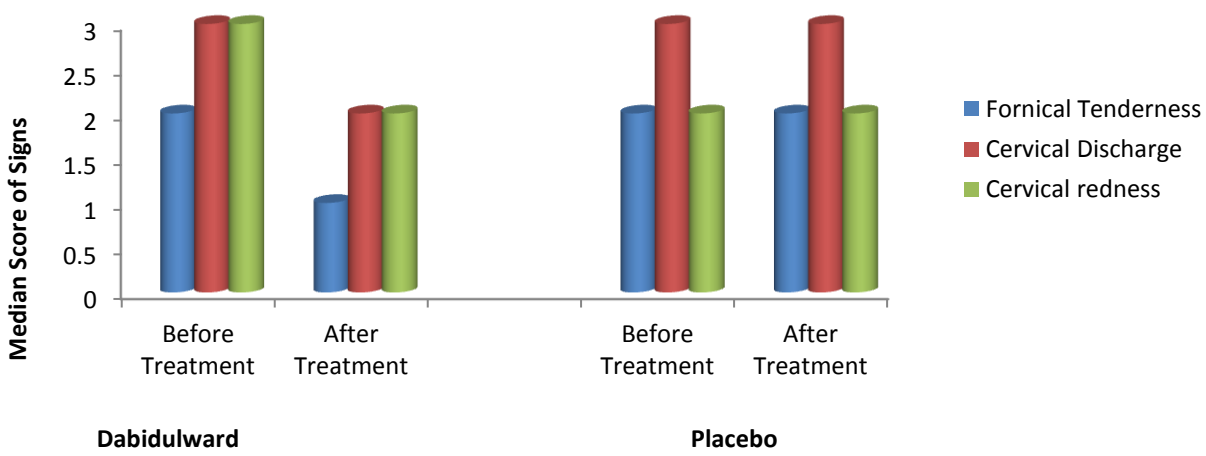


Figure-2: Effects of Dabidulward and Placebo on Objective Parameters of PID



SAFETY

During the course of the study, no adverse events were reported by the patients, no any adverse effects were detected by clinical examination and/or laboratory investigations. The formulation was well tolerated as indicated by 90% drug compliance.

DISCUSSION

Analysis of the results of 40 cases of pelvic inflammatory disease treated with capsule Dabidulward revealed some interesting facts which are discussed in the following lines.

- PID is a very common ailment of married women in India. The disease commonly affects married women of different age groups. In this study maximum number of patients was observed in age group of 25-29 years. These data are in agreement with the findings reported by L Westrom [15].
- The prevalence of PID was found to be higher among Muslims (60%) than in the other religions. No convincing data is available that demonstrates the distribution of PID among different religious communities in the society. This study, however, reflects a preponderance of Muslims among the patients of pelvic inflammatory disease. The probable reason may be the majority of Muslim patients visiting Tibbia College Hospital, as Unani Medicine is more popular among Muslim community.
- The highest incidence of PID was observed in middle class (57.5%), followed by patients in lower class (40%). This is in consonance with the unani description that malnutrition and poor sanitation which is common in low socio-economic group are the predisposing factors for warm-e-rahm [16,17,18]. Low income, minor communities have higher risk than higher income community [16].
- This study shows the highest prevalence of PID among Illiterates' group (35%). The prevalence of PID decreased with the level of education and found to be lowest with Senior Secondary level of literacy status (10%).
- Higher prevalence of PID was observed in women having multiple child birth (72.50%). According to unani literature ibtedae jimah (early age of coitus) is included in the etiology of warm-e-rahm and it is also associated with multiparity [16,17,18]. PID prevalence was higher among women who were using barrier methods as means of contraception (42.5%), followed by non users (35%) and it was observed in 12.5% of IUCD users. Contraceptives play an important role in predisposing women to acquisition of PID. Non-use of contraception is a risk factor for PID, whereas barrier methods can decrease the risk of STD acquisition and subsequent development of PID [20-24]. Although use of an intrauterine device traditionally has been believed by most clinicians to confer an elevated risk of PID, the risk seems to be primarily restricted to the first 3 months after insertion, likely because of bacterial contamination at the time of insertion [25-32]. The differences observed are supposed to be due to relatively small sample size of the study.
- During the course of the study subjects, were asked about their sexual behaviour and all of them (100%) replied with heterosexual orientation.

All the participating subjects (100%) were engaged sexually with single partner only but (17.5%) of the husbands admitted having sexual relationships with other than wives. Though, studies have shown that women with multiple sexual partners, especially in the preceding 30 days, have a fourfold elevated risk of acquisition of PID [20-33]. It can be inferred that female subjects did not give the right information about their sexual activity and the difference may due to the social & cultural shyness regarding the disclosure of personal sexual relations or may be due to the relatively small sample size.

It is evident from the results of present study that the convenient capsule form of *Majun Dabidulward* has analgesic, antispasmodic and anti-inflammatory activities as it produced remarkable improvement in various subjective/objective parameters of PID such as lower abdominal pain, painful coitus, painful cervical movement, cervical redness and tenderness etc. The significant decrease in polymorphonuclear leucocyte count also supports its anti-inflammatory activity. However, a large scale, prospective, double blind, randomized standard controlled clinical trial is warranted to support the efficacy of test formulation in the management of pelvic inflammatory disease. This test formulation can also be tried and tested in the acute cases of pelvic inflammatory disease which were not studied due to the limitation of the present trial.

Limitations Of Study

This study had certain limitations like: a small cohort size which failed to yield appropriate epidemiological data. With a larger sample size, the trial drug might have demonstrated superior efficacy in the onset of subjective and objective parameters, Lack of blinding of the patients i.e. double blinding, Lack of better and more precise efficacy assessment investigations in the institution, like culture facility which would have specifically demonstrated the antibacterial efficacy of the trial drug, We were not able to assess exactly that for how long the effects of the test formulation persisted owing to the limited time duration. In addition, the results of the study cannot be extrapolated to the patients of acute pelvic inflammatory disease, considering the severity of the disease and limitations of the trial, these cases were excluded from the study.

CONCLUSION

On the basis of above observations, it can be concluded that the test drug is clinically effective in relieving the symptoms and signs of pelvic inflammatory disease and hence can safely be prescribed to the patients for the management of PID. The test drug is cheaper, easily available and well tolerated by the patients without having any side effects.

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