INTERNATIONAL JOURNAL OF ADVANCE RESEARCH AND DEVELOPMENT

(Volume2, Issue9)
Available online at www.ijarnd.com

Effect of ARQ MAKO and Sharbat Kasni in Waram Al Rahim (Pelvic Inflammatory Disease): An Observational Clinical Trial

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ABSTRACT

Background: *Waram al rahim (Pelvic Inflammatory Disease) is a polymicrobial infection and one of the most common causes of morbidity in young women in both the developing and developed world. About 10-20 per 1000 fertile women suffer from PID. The spectrum of disease ranges from subclinical, asymptomatic infection to severe, life-threatening illness.*
Objective: *The aim of the study was to evaluate the efficacy of arq mako and sharbat kasni in the management of stage I PID.*
Methodology: *This clinical study was carried out at NIUM Hospital, Bengaluru during the year of 2016-17. Total 30 patients between 18-45 years were included and arq mako 60 ml and sharbat kasni 10 ml was administered orally twice daily for 21 days. Follow up done weekly during the trial and every 15 days for one month after trial. Primary and secondary outcome measures were assessed before and after the trial.*
Result: *Statistical analysis were done by using Fisher exact, Mc Nemar and paired T test to assess improvement in sign, symptoms of PID. Results were categorized into three groups. Out of 30 (100%) patients, 70% were cured on 3rd week of trial, 23.33% were relieved and only 6.67% had no response. Both primary and secondary outcome measures were statistically strongly significant.*
Interpretation and conclusion: *From the present study it can be concluded that Arq mako and sharbat kasni was effective in stage I PID and can be used in daily practice. It also observed that there were no adverse effects of the drugs during the trial.*

Keywords: Waram al Rahim, Pelvic Inflammatory Disease, Arq Mako, Sharbat Kasni, Mccormack Pain Scale.

INTRODUCTION

The term PID indicates an inflammatory process of infectious etiology involving at least the endometrium and fallopian tubes. [1] *Waram al rahim* (Pelvic Inflammatory Disease) is the disease of sexually active women [2] and same as *awram* (inflammations) of all other organs. [3,4] Prevalence of PID is 9-27 per 1000 fertile women, in addition, it has been estimated that large proportions of PID cases go unrecognized. [5]

Rahim is usually affected by *Warami harr* or *Warami sulab saudavi* but occasionally can also be afflicted by *Warami balghami* . [2,3,6] *Waram al rahim* is further subdivided into *waram al rahim harr* (acute PID), *waram al rahim balghami* and *waram al rahim saudavi.*[2,6,7] It is caused by either *asbabe badia* or *sabiqa* which compromise *quwa* of an organ resulting in accumulation of blood and eventually leading to swelling, warmth, redness, and pain in the effected organ. [6, 7] The etiologic agent often is never identified, but common causal agents are *C. trachomatis* and *N. gonorrhoea* and aerobic and anaerobic vaginal flora. [8]

The diagnosis of PID is imprecise due to a wide spectrum of clinical presentation. [9] The apparently mild or subclinical PID also has the potential for damage the reproductive health of women. [1, 9] A low threshold for diagnosis of PID is recommended in order to cover milder forms of PID. [8,10]

In the Unani classical text, it is mentioned that due to anatomical proximity of uterus *warami rahim harr* manifests specific as well as associated symptoms.[2,6] If *warami rahim harr* is not treated adequately, it becomes *warami rahim sulb* which is difficult to treat. [6.7]

There are marked variations in the antimicrobial regimens used in the treatment of PID, reflecting uncertainty in the optimal treatment schedule, in addition, they incur substantial health care cost and have their own side effects. [1]

Arq mako and *sharbat kasni* are a compound formulation which is having *muhallile warm* property [13,14] and also beneficial in the inflammation of visceras. [13] It also possesses *munzij*, *radae*, *qabiz*, *musaffi khoon*, *dafia'e humma*, and *musakkin hararat* properties. [6,12] The ingredients of the formulation are pharmacologically proven to possess anti-inflammatory, anti-microbial, antioxidant, analgesic, gastro-protective and hepato-protective properties. [15,16]

METHODOLOGY

An open observational study on "Efficacy of *arq mako* and *sharbat kasni* in pelvic inflammatory disease" was carried out in the Department of Ilmul Qabalat was Amraze Niswan (OBG), National Institute of Unani Medicine, Bengaluru, Karnataka during the year of 2016-17. Ethical clearance was taken before starting the trial and written consent of each patient was taken after explaining the objective of the study. Institutional ethical committee of National Institute of Unani Medicine, Bengaluru under IEC No: NIUM/IEC/2014-15/014/ANQ/06 approved the study protocol.

Study participants

The study comprised of total 30 patients, age between 18-45 years. Initially, 97 patients of PID were screened for eligibility, among which 15 patients IUCD had inserted, 9 patients were on OCPs, 5 patients were lactating. Remaining 68 patients were included for investigations as they were fulfilling the inclusion criteria. Among which 15 patients were refused to participate in the study after investigations and 17 patients were excluded for not meeting the inclusion criteria. 36 patients who fulfilled the inclusion criteria were included in the study. Out of 36 eligible patients, 6 were drop out from the study in which 4 patients drop out after 2 weeks of treatment due to personal reasons and 2 patients became pregnant after 3 weeks of treatment.

Selection criteria

All married women between 18-45 years with stage I PID (CDC major diagnostic criteria i.e. pelvic or lower abdominal pain and uterine/adnexal or cervical motion tenderness and ≥1 of its minor criteria i.e. fever (>101^0F), abnormal cervical or vaginal mucopurulent discharge, abundant number of WBC on wet mount test of vaginal fluid, elevated ESR or CRP, positive test for cervical infection with *N. gonorrhoea* or *C. trachomatis*) were included in the study [9] and women who were with systemic illnesses and malignancies, complicated PID, tubo-ovarian abscess, haemorrhagic ovarian cyst, uterine fibroid, adenomyosis, appendicitis and pelvic peritonitis, history of using antibiotic therapy, delivery, abortion or gynaecological surgery within the last 30 days and also who were on OCPs and IUCD and who were pregnant and lactating women were excluded. [17]

Patient evaluation

All the married patients between 18-45 years of age with the complaint of lower abdominal pain, abnormal vaginal discharge with or without a low backache were evaluated for the presence of stage I PID and recorded in case record form designed for the study.

A detailed clinical history including the socioeconomic status of the patient, which was assessed by Kuppuswamy's Socioeconomic Scale, contraceptive history or history of vaginal douching and previous history of similar complaints were enquired. Associated symptoms such as dysuria, frequency, dyspareunia and pruritus vulvae were also enquired and recorded in case record form designed for the study. Assessment of *mizaj* of every patient was done according to parameters mentioned in unani classical literature. Complete physical and systemic examination was done to rule out any systemic diseases. Local examination of external genitalia for excoriation, erethema, and edema was done. Abdominal palpation was carried out to assess the direct and rebound tenderness.

During speculum examination colour, quantity, consistency, the odour of vaginal discharge was noted and under all aseptic precaution, the specimen was obtained for wet mount test and endocervical swab for culture. The bimanual vaginal examination was done for the assessment of uterine size, position, mobility, the severity of tenderness of uterus/ cervical motion/ adnexa and adnexal condition to rule out any mass.

Each patient was subjected to biochemical (SGOT, SGPT, Alkaline phosphatise, Blood urea, Serum creatinine) for safety of the patients as well as specific investigations (Complete blood count, ESR, CRP, Cervical swab culture before and after trial and Wet mount test at every visit) to assess the efficacy of test drug. Investigations include CUE, RBS, VDRL, HIV and Pap's smear was done to exclude UTI, diabetes mellitus, syphilis, HIV and genital malignancy respectively and also abdomino-pelvic scan to exclude abdomino-pelvic pathology.

All enrolled patients were instructed to maintain local hygiene, to abstain from sexual intercourse or use a barrier contraceptive during the study period and also advised her sexual partner to get treatment simultaneously.

Clinical diagnosis

Patients were diagnosed if they are having Lower abdominal pain, abnormal vaginal discharge**,** cervical motion/ uterine/ adnexal tenderness and Presence of WBCs in Wet mount test more than 10 per HPF

Intervention

Arq mako 60 ml and *Sharbat Kasni* 10 ml orally [(13)] administered twice daily for 21 days. To confirm the patient compliance at every visit 840 ml of *arq mako* and 140 ml of *sharbat kasni* were dispensed to each patient in unlabelled bottles for 7 days and was advised to return on every 8th day with empty bottles to receive the remaining of treatment.

Assessment and follow up

Patients were followed weekly once for 3 weeks during the trial and after the trial at 15 days for one month. At every visit, the patients were asked and reassessed about improvement or worsening of their sign and symptoms during the study and recorded on assessment chart.

Assessment of Outcome

The outcome was assessed by changes in subjective parameters (Visual Analogue Scale (VAS) to assess lower abdominal pain and low backache) and Changes in objective parameters (Modified Mc Cormack pain scale to assess abdomino-pelvic tenderness).

Subjective parameters i.e. Lower abdominal pain and Low backache were assessed at baseline and at every visit by Visual Analogue Scale (VAS) score which is graded as 0 to 10 from left to right and 0 means no pain, 1-2 means mild pain, 3-6 means moderate pain and 7-10 means severe pain. The abnormal vaginal discharge was assessed by speculum examination before trial and at every visit. It is graded according to the severity like No discharge, Mild: without staining or moistening under clothes, Moderate: underclothes are wet and require changing and Severe: requires the wearing of the extra absorbent pad.

Objective parameters i.e. cervical motion/ uterine/ adnexal tenderness was assessed by bimanual examination at baseline and at every visit. Abdomino pelvic tenderness was assessed by using McCormack pain scale (McPS) [13] McPS has four point tenderness scale used to assess direct and rebound tenderness of abdomen and pelvis ranging from 0 to 3 in which O = No tenderness, 1 = Tenderness referred by patient, 2 = Tenderness causing observable distress, 3 = Rebound tenderness, Total score = Sum of individual scores for 12 abdominal and pelvic region (Maximum score= 36). Presence of excess leucocytes (≥10 WBC per HPF) on Wet mount test was assessed at baseline and at every visit. A drop of vaginal discharge was placed on a glass slide with 1-2 drops of 0.9% sodium chloride solution and examined for no of WBCs per high-power field (×400). It was considered positive if WBC was ≥10/HPF in vaginal discharge. [9] Cervical swab culture was assessed before and after trial

The therapeutic outcome was assessed on the basis of symptomatic relief and changes in laboratory parameters in term of:

Cured: Absence of symptoms and Normalization of TLC, DLC, ESR values, negative CRP value, <10 WBC on wet mount test, and no organism growth/ normal flora in cervical swab culture

Relieved: Significant reduction in symptoms and Absence of two out of four objective parameters

No response: No changes in subjective and objective parameters during or after the trial.

Withdrawal criteria: Those were a failure to follow the protocol and any adverse reaction or adverse events.

Statistical analysis of results

Descriptive and inferential statistical analysis has been carried out. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). The significance is assessed at 5% level of significance. Student t test (two tailed, dependent) has been used to find the significance of study parameters on a continuous scale, Fischer exact test has been used to find the significance of study parameters on the categorical scale and Mc Nemar test also has been used to find the significance of the study.

RESULTS

Table 1: Demographic data of the trial subjects

Characteristics		No. of patients N= 30
Age (years)	Mean ± SD	30.23±4.82
Mizaj	*Balghami*	10 (33.3 %)
	Damvi	12 (40 %)
	Safrawi	8 (26.67 %)
SES	Lower middle	13 (43.3 %)
	Upper lower	1 (3.3 %)
	Upper middle	16 (53.3 %)
History of PID	Yes	27 (90 %)
	No	3 (10 %)
Contraceptive history	No	5 (16.6 %)
	Yes	25 (83.3%)
Associated symptoms	Dyspareunea	16 (53.3 %)
	Pruritus vulvae	7 (23.3 %)

Table 2: Subjective parameters: An assessment from before treatment and after treatment

Subjective parameters	Before trial	After trial	P value (a)	Improvement (b)
	No. of patients	No. of patients		
Lower abdominal Pain	30 (100%)	5 (16.66%)	<0.001	83.3%
Abnormal Vaginal discharge	30 (100%)	19 (63.33%)	<0.001	36.7%
Low backache	24 (80%)	9 (30%)	<0.001	50.0%

Table 3: Objective parameters
An assessment from before treatment and after treatment

Objective parameters	Before trial	After trial	P value (a)	Improvement (b)
	No. of patients	No. of patients		
Uterine tenderness	16(53.33%)	2(6.66%)	<0.001	46.67
Fornices tenderness	30(100%)	1(3.33%)	<0.001	96.66
Cervical motion tenderness	6(20%)	0(0%)	0.024	20.00
Wet Mount Test	30(100%)	7(23.3%)	<0.001	76.66

Assessment of Abdomino pelvic tenderness by using McCormack Pain Scale score

Abdomin pelvic tenderness	**Total tenderness**	Mean 4.100	Mean 1.167	P value <0.0001
	Pelvic tenderness	Mean 3.600	Mean 1.067	P value <0.0001

Cervical Swab Culture	**Positive**	26 (86.66%)	19 (63.33%)	0.052
	Negative	4 (13.33%)	11 (36.66 %)	
CRP	**Positive**	0 (0 %)	0 (0 %)	
	Negative	30 (100 %)	30 (100 %)	

Table 4: Treatment outcome

Outcomes	**No. of patients**	**%**	**P value**
Cured	21	70	<0.0001
Relieved	7	23.33	
No response	2	6.67	

DISCUSSION

Demographic data was statistically similar before and after the trial. The mean age of the patients was 30.23±4.82 which is similar and in accordance with the finding of a study of Eggert *et al* [10] where they reported that more than half patients were of 30 years age. It may be because of screening for PID properly done in this age group or most likely the result of bias in selecting low-risk females.[20] 53.3% belonged to upper middle class. This finding was contradicted by the study conducted by Ness *et al* [21] in which risk of PID was more common among patients with less than high school education and low income, the reason for this apparent vulnerability in upper middle class may be because of their negligent health seeking behaviour or delayed medical care. The previous history of PID was found in 10% patients which are contradictory to the findings of Ness *et al* [22] who reported that about one-third patients had a previous diagnosis of PID. This may be because of not visiting OPDs properly and not diagnosing or due to negligent health seeking behaviour of women. 83.3% were tubectomized and they were not using any barrier methods. This finding was correlated with the finding of Arredondo J. L. *et al* [23] who reported in their study that most patients used IUCD or nothing. Pruritus vulvae were seen in 7 (23.3%) of patients, whereas Dyspareunea was seen in 16 (53.3%) which can support the diagnosis of PID.[24] Majority of the patients with PID were of *damvi mizaj* (sanguineous temperament) which conform the observation of eminent unani physician Ibn Sina who stated that *sue mizaj maddi* produces *warm* (Inflammation). [25]

The difference in the value of subjective parameters especially lower abdominal pain was found significant with 83.3% reduction and found statistically strongly significant with p value <0.001. Improvement in abnormal vaginal discharge was observed in 63.33% patients with p value <0.001 which was considered as strongly significant. The reduction in abnormal vaginal discharge may be attributed to *qabiz* (Astringent), *musaffi khoon* (blood purifier) [12] and *muhallil i waram* (Anti-inflammatory) [14] properties of drugs and effective in *sayalan al rahim* (Leucorrhoea) [12] as it is having antimicrobial activity.[15] The percentage of improvement in a low backache was 50% and the difference was strongly significant with p value <0.001. The reduction of pain may be due to properties of *Musakkin i hararat* (Anti pyretic) and *muhallil i awram harrah batini wa zahiri* (Anti-inflammatory both external and internal) [14,26] and also the analgesic activity [27] of drugs which causes prevention of sensitization or inhibition of central pain receptors and peripheral analgesic activity due to reduction in liberation of inflammatory mediators due to presence of steroidal compounds, alkaloids, flavonoids, tannins etc.

Objective parameter i.e Uterine tenderness was present more or less in 53.33% patients and this is similar to the finding of Eggert *et al* [10] who reported that almost half of the patients of PID had uterine tenderness. This difference was found statistically significant with p value of <0.001 in uterine tenderness. Fornices tenderness was relieved in 29 patients with 96.66% improvement which was found significant with p value of <0.001. The percentage of improvement in cervical motion tenderness was 20% and the difference was significant with p value 0.024. reduction of tenderness may be due to the effect of drugs in *awrame ahsha* (Inflammation of the organs) especially in *warm al rahim* (Inflammation of uterus) [26] Improvement in wet mount test was observed in 23 (76.66%) patients which were statistically significant with p value <0.001. a significant difference in between means of McPS score was present with p value <0.0001 may be due to anti-inflammatory [28] and anti-oxidant [29] activities of drugs.

In the majority of the patients i.e. 26 (86.6%) microorganisms were detected and reduced to 19 (63.33%) patients only with the p value 0.052 which was not significant. Reduction in growth of organisms may be due to *musaffi khoon* (Blood purifier) [12] and antimicrobial effect[15] of the research drugs due to the presence of the agents like phenols, phenolic acids, flavonoids, alkaloids etc.

The difference of means for safety profiles was found insignificant and was within normal range at baseline as well as after treatment. It indicates that the research drugs were found to be safe. Studies also confirm the hepatoprotective [30] and nephroprotective properties [31] of these drugs.

Results were analyzed on the basis of improvement in subjective parameters and objective parameters, which revealed that out of 30 patients 21 (70%) were cured with p value <0.0001 (Table 4) Recurrence of symptoms was not reported in any patients within one month of trial.

LIMITATIONS OF THE STUDY

The main limitation of this study was small sample size, short duration of intervention and loss of long term for efficacy and recurrence of symptoms. Follow up and specific diagnostic tests like NAAT and endometrial biopsy were not used to ascertain the microbiological and histological cure rate.

FURTHER RECOMMENDATION

Drug dose should be increment and should be given three times a day for one month to get significant results. There should be longer follow up to assess recurrence and long term reproductive outcome. These drugs can be tried in a patient with stage II PID and phase III trial should be done to generalize the results.

CONCLUSION

On the basis of above observations, it can be concluded that the Arq mako and sharbat kasni was clinically effective in relieving the symptoms and signs of stage I pelvic inflammatory disease as its ingredients possess anti-microbial, anti-inflammatory, anti-oxidant, analgesic and hepatoprotective activities due to the presence of alkaloids, tannins, flavonoids, monoterpenes, camphor, saponins, anthraquinone, and terpenoids. Therefore it can be inferred that arq mako and sharbat kasni can safely be prescribed to the patients for the management of stage I PID. The test drugs are cheaper, easily available and well tolerated by the patients without having any side effects. Hence it can be used as an alternative therapy in the management of PID.

ACKNOWLEDGEMENT

The authors are thankful to Prof. M. A. Siddiqui, Director, NIUM for providing all facilities required for the completion of research work.

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