

Research Article

A Prospective Open Label Randomized Clinical Trial to Evaluate Safety and Efficacy of Olive Oil in Cases of Gall Stone

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ABSTRACT:

In the diseases of Gall bladder, Gall stones are the commonest biliary pathology which is characterized by right hypochondriac region pain and heaviness, dyspepsia, nausea and vomiting. Usually they are multiple and small in size but some time it may be single and bigger in size. Most of the times gall stones remains asymptomatic for many years, Gall stone are classified according to their chemical composition into cholesterol stones, mixed stones, and pigmented stones. Incidence of gall stones-A Fat, Fertile, Flatulent Female of Fourty is the classical sufferer from symptomatic gallstones. Useful as is this clinical memorendum, it should be tempered with knowledge that gallstones occurs in both sexes quite often at a much earlier age-even in childhood-and is more common in middle and old age. The concept of *Hisat-e-Mararah* is since "Greco Arab periods" . Unani physicians *Razi* , *Avicenna*, *RabbanTabriand Hakim Kabiruddin*has mentioned formation of *Hisat-e-Mararah*. According to them there are so many factors responsible for it like *Farbahi*(Obesity) also called *Saman-e-Mufrit*, *Ziabitus-e-Shakri* (Diabetes Mellitus) ,*Mani-e-Hamal advia*(Contraceptive pills) reduces level of *Hamiz-e-safra*(Bile acid) and it helps in the deposition and formation of *Hisat-e-Mararah*.

Roghan-e-Zaitoon(Olive oil) is effective in dissolution of gall stones andhas been used in the management of gall stone since long time. *Roghan-e-Zaitoon*is an extracted oil of fruit *Zaitoon* (*Oleaeuropaealinn*) ,the trees of *Zaitoon* found in Asia, Turkey, Unan, Portugal, Spain, Italy, South Africa, North America, Philippine, Balochistan. According to The *Holy Quran*, *Zaitoon* tree is an oldest tree in the history of *Islam* and it is sign of piece also. Research shows that *Roghan-e-Zaitoon* has two constituent one is *lunin* and other is *palmetin* and they works same as *Ursodeoxicholicacid* which dissolved gall stones. The drug needs scientific evaluation to prove its efficacy and safety in the management of *Hisat-e-Mararah*.

Key Words: Gall stones(*Hisat-e-Mararah*), *Roghan-e-Zaitoon*, *Unani system of medicine*,

INTRODUCTION:

In the diseases of Gall bladder, Gall stone is the commonest biliary pathology which is characterized by right hypochondriac region

pain, heaviness, dyspepsia, nausea and vomiting. Usually they are multiple and small in size but some time it may be single and bigger in size.

Most of the times Gall stone remains asymptomatic for many years. Gall stone is classified according to their chemical composition into cholesterol stones, mixed stones, and pigmented stones^{1,2}.

Gall stone occurs in both sexes quite often at a much earlier age even in childhood and is more common in middle and old age^{3,5}. Gall stone is a significant international health problem and it is basically a disease of affluent. In Europe 30% of female of age group 60yrs have Gall stone however 2/3rd are asymptomatic. Gall stone are quite prevalent in western countries. In the United state autopsy series have shown *gall stone* in 20% in female and 8% in males over the age of 40yrs. It is estimated that 20-60 million person have Gall stone and approximately one million new cases of Gall stone develops each year in India. The prevalence increased in American Indians. Considerable evidence is available that man in various areas of world has suffered from biliary tract calculus disease. Even before the era when history was first recorded^{2,3}. Gall stone is a disease of hepatobiliary system and has been described as early as 1500 B.C. in Eber's papyrus. The formation of the cholesterol *Hisat-e-Mararah* (Gall stone) depends on the production of the bile in while cholesterol cannot be maintained in solution. This might be related to increase secretion of cholesterol or perhaps a reduction in total bile acid pool. There are nucleation promoting and inhibitory factors in bile and imbalance between these appears to generate an environment favoring cholesterol crystallization and stone formation. The gallbladder acts reservoir allowing growth of the stone. Change in motor and other functions of the gallbladder increase the risk of stone formation^{1,3,4}.

Gall stone in Unani System of Medicine:

In classical Unani literature this disease comes under the heading of *Hisat-e-Kabid* but after the confirmation with the help of modern equipment

it has come in notice that *Hisat-e-Kabid* is nothing but *Hisat-e-Mararah* (Gall stone) or gall bladder stone. According to *Mohd.RabbanTabri*, (9th century AD) *Hisat-e-Mararah* (Gall stone), is abnormal reaction of gall bladder caused by the deposition of cholesterol and bile acid. In the view of present living status *Hisat-e-Mararah* (Gall stone) is very common in female, but males may suffer^{4,5}.

In Allopathic System of Medicine for *Hisat-e-Mararah* (Gall stones) open and laparoscopic surgeries are advised. Some people do not like invasive techniques and prefers to take herbal medicine. Unani herbal medicine like *Safoof-e-sang-e-saremahi*, *Safoof-e-Hajrul-yahood*, *Sharbat-e-Tamarhindi*, *Sharbat-e-Anarain* similarly *Roghan-e-Zaitoon* (Olive oil) are effective in dissolution of *Hisat-e-Mararah* (Gall stone) and has been used in the management of *Hisat-e-Mararah* (Gall stone) since long time. Hence a prospective open label randomized clinical trial to evaluate safety and efficacy of olive oil in cases of gall stone was carried out at the OPD of Z.V.M. Unani Medical College, and hospital, azam campus, camp, pune.

In the diseases of Gall bladder, *Hisat-e-Mararah* (Gall stone) are the commonest biliary pathology which is characterized by right hypochondriac region pain and heaviness, dyspepsia, nausea and vomiting. Usually they are multiple and small in size but some time it may be single and bigger in size, Most of the times *Hisat-e-Mararah* (Gall stone) remains asymptomatic for many years^{1,2}. *Hisat-e-Mararah* (Gallstone) is formed from constituents of the bile (viz. cholesterol, bile pigments and calcium salts) along with other organic components. Accordingly, the gallstones commonly contain cholesterol, bile pigment and calcium salts in varying proportions. They are usually formed in the gall bladder, but sometimes may develop within extrahepatic biliary passages, and rarely in the larger intrahepatic bile

duct^{1, 3}. The risk factors and the incidence of *Hisat-e-Mararah*(Gallstone) varies markedly in many geographic areas, genetic Factors, age, sex, drugs, obesity, diet, gastro intestinal diseases, Factors in pigment gallstones and various other risk factors. These factors which largely pertain to cholesterol stones can be summed up in the old saying that gallstones are common in 4F's- '*fat, female, fertile and forty*'^{(1,2, 3,5, 7, 8, 9, 12, 14, 16).}

MATERIAL & METHOD:

Before starting the project, a comprehensive protocol was checked out and put forth for ethical clearance, from the Institutional ethical committee. After ethical clearance clinical study was started by enrolling eligible patients. This study stretched from April-2011 to July-2011. The blue print of the study was conceptualized as material and methods which can be described under few headings for convenient comprehension.

Criteria for Selection of Cases:Inclusion Criteria are Patient of gall stone less than 10mm in size, Patient of both genders, Patients unfit for cholecystectomy, Age group from 20-60 years and Exclusion Criteria are The patient of Choledocholithiasis, The patient of Acute Calculus Cholecystitis, Carcinoma of gall bladder along with Cholelithiasis, Cholelithiasis with any complication such as Pyocele, Mucocele, Perforation and fistula formation, Patients having AIDS, Hypertension, Uncontrolled Diabetes Mellitus, and Pregnant women.

Selection of subjects: Patients were selected on the basis of clinical diagnosis. Any patient of age group 20-60 years, giving history of dyspepsia, right hypochondric pain, and nausea was selected from *Moalajat* OPD/ IPD and evaluated for the consideration as a research subject. In the process of selection, ultrasonography of abdomen and pelvis was done. If ultrasonography shows gallstone; the patient then labelled as a case of *Hisat-e-Mararah*(Gall

stone). These diagnosed patients, if fulfilled all the terms of inclusion criteria, were selected for the study, written informed consent was taken from every patient before inclusion in the study. During the selection procedure, complete history including general physical and systemic examination was carried out and recorded on a prescribed case report proforma which was designed with the consultation of the guide. The patients were enquired about their name, age, sex, marital status, address and occupation. All the patients were interrogated about their chief complaints and duration of suffering in detail, which were noted down in chronological order in the prescribed Performa. While taking the history, emphasis was given on past history for any disease especially obstructive jaundice, hypertension, diabetes mellitus, ischaemic heart disease, gall bladder cancer, AIDS.

Investigations: Certain investigations were carried out aiming following important objectives.

a) To exclude the patients other than *Hisat-e-Mararah*(Gall stone) as part of exclusion criteria.

b) To establish the safety of the test drug LFT (Liver function test) investigations were done in every case. c) USG (Ultrasonography) of abdomen and pelvis is done to rule out size and position of the *Hisat-e-Mararah* (Gall stone).

Sample size:The sample size was fixed as 60 patients. The duration of treatment was 90 days. The *Roghan-e-Zaitoon* (*Olive oil - Oleaeuropaealinn*) 10 ml is given orally OD (Once in a day) (bed time).

Follow up during treatment: 90 days study was divided into three visits of follow up, which were made at an interval of 30 days. At every visit, the patients were asked about the improvement or worsening in their symptoms and subjected to examination to assess clinical findings. Concomitant treatment was not allowed during the protocol period. The patients, who were

taking any other medicine as a treatment of *Roghan-e-zaitoon*, were advised to observe abstinence for a week from consuming any other drug before commencing treatment with the test drug.

Efficacy assessment: The assessment of the efficacy in the test was based on two types of parameters. a. Subjective parameters & b. Objective parameters, Subjective parameters included dyspepsia, right hypochondric region pain, nausea while assessment of objective parameters included laboratory investigations, radiology (Ultrasonography of abdomen and pelvis) of the patients suffering from *Hisat-e-Mararabs* (Gall stone). As these parameters differ in severity from patient to patient, an arbitrary grading of subjective parameters was improvised for appropriate assessment and statistical evaluation of various signs and symptoms to evaluate the efficacy of the test drug.

Before starting treatment, each sign and symptom was recorded in the case report form according to their grades at the maiden visit and any worsening or improvement in any of the parameters was noted down at every visit of follow up, till the end of the treatment. After 90 days of the treatment, the pre and post treatment values of different parameters (subjective and objective) were analyzed grade wisely and subjected to comparison and statistical analysis to evaluate the efficacy of the treatment.

Parameters:

A. Subjective parameters,

1. Dyspepsia.

Grades of Dyspepsia

Grade	Severity	Duration
0	No dyspepsia	0 hour
1	Mild	For 1-8 hrs after meal
2	Moderate	For 9-16hrs after meal
3	Severe	For 17-24hrs (whole day)

2. Right hypochondriac region pain: Grades of Right hypochondriac region pain:

Grade	Severity	Symptom
0	No pain	No pain
1	Mild	Pain on deep breathing
2	Moderate	Pain on palpation
3	Severe	Pain at rest

3. Nausea: Grades of Nausea:

Grade	Severity	Duration
0	No nausea	No nausea
1	Mild	Nausea after 2-4hrs of meal
2	Moderate	Nausea immediately after meal
3	Severe	Nausea at empty stomach

B. Objective Parameters:

1. Radiological changes (Ultrasonography of abdomen and pelvis):

Grade	Size of stone
0	No stone
1	Single stone < 5mm
2	Single stone 5-10mm
3	Multiple stone < 5mm
4	Multiple stone 5-10mm

Withdrawal Criteria: 1) Loss to follow up for more than 7 days. 2) Any severe adverse effect with *Roghan-e-Zaitoon*. 3) Gallstone causes acute calculus cholecystitis. 4) If calculus larger than 10mm.

Safety Assessment: The assessment of the safety of the treatment was done on the following parameters: a) Clinical assessment at every visit of follow up, b) LFT (Liver function test).

Statistical analysis: "Chi-squar" statistical tests were carried out to analyze the data using instant graph pad in the treatment group was considered significant at $p < 0.005$.

OBSERVATION AND RESULT:

The distribution of demographic parameters:

Table-1: Distribution of the patient according to age group

Age Group (years)	No. of Cases (n=60)	Percentage	Chi-Square value	P-value
≤30	15	25.0	1.900	0.387
31 – 40	23	38.3		
≥41	22	36.7		

Comments: While analyzing age of patients they were divided into three age groups viz. ≤30years, 31-40years, and ≥40years, as depicted from the (Table-1). It was observed that incidence of Gall stone was found maximum in female of menstruating and reproductive age of 30-45years. The distributions of age differ significantly in last two age groups (i.e. 31-40years and ≥40years). In other words, the two groups are not matched for age (P=0.387).

Table-2: Distribution of the patient according to sex

Sex	No. of Cases (n=60)	Percentage	Chi-Square value	P-value
Male	20	33.3	6.667	0.010
Female	40	66.7		

Comment: It was observed that 33.3% of male and 66.7% of female as depicted from (Table-2). It shows Gall stone is more common in female as described in literature. The distribution of sex differ significantly between male and female in other words, the two group are not matched for sex (P=0.010).

Table-3: Distribution of the patient according to Dietary habit

Dietary habit	No. of Cases (n=60)	Percentage	Chi-Square value	P-value
Veg	6	10.0	38.400	0.001

Comment: During study all patients were divided into Vegetarians and Non-Vegetarians. It was observed that 10% cases were Vegetarian and 90% of cases were Non-Vegetarians. The result

was according to the prevalence literature of Gall stone, i.e. it is more common in Non-Vegetarians. The distribution of dietary habits differ significantly between two groups (P=0.001).

Table- 4: Comparison of RHRP at each follow-up with respect to the baseline condition.

RHRP	Mean	Standard deviation	Comparison	P-value
Day 0	0.87	0.83	--	--
Day 30	0.65	0.62	Day 0 v/s Day 30	0.001
Day 60	0.45	0.42	Day 0 v/s Day 60	0.001
Day 90	0.42	0.35	Day 0 v/s Day 90	0.001

Comment: After intervention clinical symptom (Right hypochondriac pain) improved significantly in each follow up gradually, as shown in Table-4 (P=0.001).

Table-5: Comparison of Dyspepsia at each follow-up with respect to the baseline condition.

Dyspepsia	Mean	Standard deviation	Comparison	P-value
Day 0	1.47	0.68	--	--
Day 30	1.05	0.68	Day 0 v/s Day 30	0.001
Day 60	0.62	0.74	Day 0 v/s Day 60	0.001
Day 90	0.52	0.70	Day 0 v/s Day 90	0.001

Comment: After intervention clinical symptom (Dyspepsia) improved significantly in each follow up gradually, as shown in Table-5 (P=0.001).

Table-6: Comparison of Nausea at each follow-up with respect to the baseline condition.

Nausea	Mean	Standard deviation	Comparison	P-value
Day 0	0.73	0.66	--	--
Day 30	0.37	0.49	Day 0 v/s Day 30	0.001
Day 60	0.17	0.38	Day 0 v/s Day 60	0.001
Day 90	0.12	0.32	Day 0 v/s Day 90	0.001

Comment:After intervention clinical symptom (Nausea) improved significantly in each follow up gradually, as shown in Table-6 (P=0.001).

Table-7: Comparison of USG in last follow-up with respect to the baseline condition.

USG	Mean	Standard deviation	Comparison	P-value
Day 0	3.08	0.94	--	--
Day 90	1.57	0.98	Day 0 v/s Day 90	0.001

Comment:After intervention USG shows significant dissolution of Gallstone in last follow up as compare to baseline USG, as shown in Table-7 (P=0.001).

DISCUSSION:

Gall stone is most common diseases of biliary tract. This increase in the gall stone, appears because of easy availability of ultrasonography. In the past patients with upper gastro-intestinal symptoms and hepatobiliary symptoms were treated as acid-peptic disease, pancreatitis or gastritis, but after the invention of modern investigation techniques like ultrasonography and computerized tomography it was found that gall stone are found in gallbladder and it can cause symptoms like dyspepsia, right hypochondriac pain, right hypochondriac region heaviness and nausea. The present study was designed to evaluate safety and efficacy of *Roghan-e-Zaitoon* (Olive oil) in the cases of *Hisat-e-Mararah* (Gall stone).

Comparison Baseline characteristics: As depicted from Table 1-3 and Figure 1-3, distribution of baseline characteristics like age, sex, dietary habit differ significantly. While studying the baseline characteristics, incidence of gall stone was found maximum in females of age group 30-45years. While studying the etiology of gall stone it was found that, most of the patient had history of having fatty and non-veg food. It was similar to the reference, the most important cause of gall stone is fatty and non-veg food in

which excessive cholesterol deposits in the liver and secreted by the liver into the bile which is responsible for the gall stone formation.

Comparison of clinical sign and symptoms between before and after treatment: There was significant improvement in reduction of signs and symptoms like; Right hypochondriac pain and heaviness, dyspepsia, nausea, vomiting. It shows *Roghan-e-Zaitoon* is effective in reducing all above mentioned clinical sign and symptoms. According to unani literature the disease *Hisat-e-Mararah* develops due to *Farbahi* (Obesity) also called *Saman-e-Mufrit*, *Ziabitae-e-Shakri* (Diabetes Mellitus), *Mani-e-Hamal advia* (Contraceptive drugs) reduces level of *Hamiz-e-safra* (Bile acid). Due to excessive gall stones sometimes gallbladder becomes nonfunctional.

Comparison of cost effectiveness: While comparing the cost of the drugs, it was observed that the drug olive oil is cheap, easily available and well tolerated by patients with no side effect and acceptability is good for olive oil as compare to ursodeoxycolic acid. Patient treated with the drug reported a distinct feeling of well being. Hence on taking an overview it may be concluded that *Roghan-e-Zaitoon* is cost effective as compare to surgery which is expensive and invasive as well.

CONCLUSION:

There were no report or observed significant adverse events during the study period. In addition to relief in associated symptoms, normalization of routine daily activity also contributed to the efficacy of the *Roghan-e-Zaitoon*. Therefore, it can be concluded that the *Roghan-e-Zaitoon* (Olive oil) is effective and safe in the management of *Hisat-e-Mararah* (Gall stone).

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LIST OF ABBREVIATIONS

%	= Percentage
F	= Female
≥	= Greater than
M	= Male
≤	= Lesser than
ESWL	= Extracorporeal shockwave lithotripsy
AT	= after treatment
S.Bilirubin.T	= Serum bilirubin total
BT	= before treatment
Alk.Phos	= Alkaline phosphatase
BP	= Blood pressure
P.I.S.	= Patient information sheet
CRF	= Case record form
I.C.F.	= Informed consent form
Etc	= Etcetera
P.R.NO	= Patient reference number
Gm	= Gram
IPD	= Indoor patient department
OPD	= Out patient department
LFT	= Liver function test
R/r	= Respiratory rate
ECG	= Electrocardiogram
H.O.	= History of infection

IVC = Intravenous cholangiography
LC = Lower class
MRS = Magnetic resonance spectroscopy
UC = Upper class
Day 0 = First follow up
MC = Middle class
Dept = Department
IOC = International olive council
OCM = Oil cleaning method
Day 30 = Second follow up
PGI = Protected geographical indication
Day 60 = Third follow up
PGO = Protected geographical origin
Day 90 = Last follow up
USDA = United state department of agriculture
Saf = Safravi
FDA = Food and drug administration
Dam = Damvi
SGPT = Serum Glutamic Pyruvic Transaminase
ERCP = Endoscopic retrograde
cholangiopancreatography