Original Research Article

Effectiveness of using ursodeoxycholic acid in reducing incidence of gallstone formation after sleeve gastrectomy

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ABSTRACT

Background: Obese persons are at risk for cholesterol gallstones because of high saturation of cholesterol in their bile. About 75% of gallstones are of cholesterol type. To reduce the risk for gallstone formation, policies of prophylactic cholecystectomy are proposed. However, this is not widely accepted. A routine cholecystectomy during bariatric surgery is recommended by some centers. Ursodeoxycholic acid enhances the conversion of cholesterol to bile acids. It also enhances cholesterol transport as liquid crystals. Furthermore, it has an inhibitory action on the prostaglandins and biliary glycoprotein, which is the possible explanation for its action on decreasing the saturation index. The objective was the effectiveness of using Ursodeoxycholic Acid (UDCA) in reducing incidence of gallstone formation after sleeve gastrectomy.

Methods: 50 morbid obese patients divided into 2 groups. Group A: 30 patients who received UDCA post-operative. (5 male and 25 female) with mean age 34.8year. Patients had a body mass index (BMI) with mean BMI 46.9kg/m². Group B: 20 patients without receiving UDCA post-operative. (2 male and 18 female) with mean age 32.9year. Patients had a mean of BMI 47.3kg/m².

Results: Using UDCA has significant role in prophylaxis against development of gall stone formation. Patients who received UDCA developed gall stones by a percentage 0% (0/30) while patients who hadn't received UDCA developed gall stones by a percentage 4.7% (3/20).

Conclusions: The use of UCDA effectively reduced the incidence of gall stone formation after laparoscopic sleeve gastrectomy (LSG) in patient with morbid obesity.

Keywords: Gallstone formation, Morbid obesity, Sleeve gastrectomy, Ursodeoxycholic acid

INTRODUCTION

Obesity is now epidemic in the United States affecting more than 60million people, and the problem will worsen in coming years as the incidence of childhood and adolescent obesity rises.¹ In the general population the risk of cholelithiasis is 10-20%, compared with post-bariatric patients where it is increased to 30-53% the overall prevalence of cholecystectomy in the general population is 1-5%, which is slightly increased after

bariatric surgery up to 6-8%.² Obese persons are at risk for cholesterol gallstones because of high saturation of cholesterol in their bile. About 75% of gallstones are of cholesterol type. The risk increases during rapid weight loss using low-calorie diets and after bariatric surgery. The mechanism for gallstone formation during rapid weight loss is not completely understood, several mechanisms have been suggested including increased bile cholesterol saturation and gall bladder stasis, increased secretion of mucin and calcium, and increased

prostaglandins.³ Multiple approaches have been proposed and studied to prevent gall-stones after weight loss surgery including concomitant cholecystectomy and prophylactic ursodeoxycholic acid (UDCA) treatment following surgery.⁴ The aim of this study is to define effectiveness of the using of the ursodeoxycholic acid in reducing incidence of gallstone formation after sleeve gastrectomy operation.

METHODS

This prospective study had been conducted to patients admitted at General Surgery Department in Menoufia University Hospital. All patients admitted for Sleeve Gastrectomy Operation at General Surgery Department. Eligible patients were between 20 and 60 years of age and had a BMI of at least 40 kg/m² or BMI of at least 35 kg/m² with Co-Morbidity were included and the patients with history of cholecystectomy, presence of gallstones or pregnancy were excluded.

Informed consent was obtained from each patient before initiation of the study and hospital ethical committee approval was obtained for the protocol of the study. All patients were subjected to

- History taking: personal history, complain, history of present illness, past history, family history.
- Full clinical evaluation
- Investigations.

Clinical evaluation: aimed at assessment of degree of obesity, preoperative clinical evaluation and detection of different complications of morbid obesity (like hypertension, skeletal problems, diabetes, joint disease, obstructive sleep apnea and restrictive lung disease).

Investigations

- Laboratory investigations: CBC, FBS, renal functions, liver functions, coagulation profile and HbA1C for diabetic patients.
- Abdomino-pelvic ultrasonography.
- Pulmonary evaluation: including chest X-ray and pulmonary functions tests.
- Cardiac assessment: ECG and echocardiography.

Author divided patients randomly into two groups which was group 1 includes 30 morbid obese patients underwent (LSG) laparoscopic sleeve gastrectomy with postoperative prophylaxis using Ursodeoxycholic Acid (UDCA) and group 2 includes 20 morbid obese patients underwent LSG without postoperative prophylaxis using Ursodeoxycholic Acid (UDCA).

Treatments initiated 15 days after surgery and continued for 6 months or until gallstone development. Patients agreed to take the trial medication for 6 months or until gallstones developed. Medication compliance was monitored at every visit.

Methods

- Clinical evaluation
- Investigation
- Pre-operative preparation
- Pelvis-Abdominal Ultrasound pre-operative to exclude existing gall stone or removed gall bladder.

Patients preparation

All patients fasted for at least 8 hours before performing abdominal ultra sound examination for regular checkup unless they develop symptoms like nausea, vomiting and abdominal pain. Then, all data were statistically analyzed.

RESULTS

This study had been conducted on 50 morbidly obese patients and divided into 2 groups:

- Group A includes 30 morbid obese patients who received Ursodeoxycholic Acid (UDCA) post-operative for 6 months.
- Group B includes 20 morbid obese patients without receiving Ursodeoxycholic Acid (UDCA) post-operative.

Then patients were grouped according to age, sex, body mass index, initial body weight, percentage of weight loss, presentation of gall stones. All procedures were performed laparoscopically without conversions and no mortalities.

In this study the mean age of group A was 34.8 years with $\pm$ SD 12.3 years, minimum 20 years and maximum 59 years and the mean age of group B was 32.9 years with $\pm$ SD 10.8 years, minimum 20 years and maximum 58 years. The P value of age was 0.594 which was insignificant and indicates that age has no role in gall stones formation after sleeve Gastrectomy.

Table 1: The age distribution of group A and group B.

Age	Group A (n-30) (case group)	Group B (n-20) (control group)	T-test	P-value
Mean	34.8 years	32.9 years	0.545	0.594(NS)
SD	12.3 years	10.8 years		
Min	20 years	20 years		
Max	59 years	58 years		

In this study, the sex of group A (n-30) 5 (16.66%) male patient and 25 (83.33%) female patient and group B (n-20) 2 (10%) male patient and 18 (90%) female patient. The P value of sex was 0.51 which was insignificant and indicates that gender has no role in increasing risk of development of gall stones. In this study, the mean BMI of group A was 46.9 kg/m² with $\pm$ SD 4.3 kg/m², minimum

38kg/m² and maximum 57kg/m² and the mean BMI of group A was 47.3kg/m² with $\pm$ SD 3.6kg/m², minimum 37 kg/m² and maximum 59kg/m².

Table 2: The sex distribution of group A and group B.

Sex	Group A	Group B	Chi	P-value
Male	5	2	0.44	0.51 (NS)
Female	25	18		

The p value of BMI was 0.732 which was insignificant and indicates that BMI has no role in increasing risk of development of gall stones. In this study, the mean weight of group A was 134.9kg with $\pm$ SD 14.4kg, minimum 103.5kg and maximum 171kg and the mean weight of group B was 131kg with $\pm$ SD 13.1kg, minimum 112.5kg and maximum 171kg. The p value of weight was 0.26 which was insignificant and indicates that initial weight has no role in increasing risk of development of gall stones.

Table 3: The BMI distribution of group A and group B.

BMI	Group A	Group B	T-test	P-value
Mean	46.9kg/m ²	47.3 kg/m ²	0.361	0.732(NS)
SD	4.3 kg/m ²	3.6 kg/m ²		
Min	38 kg/m ²	37 kg/m ²		
Max	57 kg/m ²	59 kg/m ²		

In this study, the mean height of group A was 170.9cm with $\pm$ SD 10.4cm, minimum 150cm and maximum 190cm and the mean height of group B was 167cm with SD. 9.8cm, minimum 150cm and maximum 185cm. The p value of height was 0.194 which was insignificant and indicates that the height has no role increasing risk of development of gall stones. In this study the mean excess body weight of group A was 66.7kg with $\pm$ SD 10.7kg, minimum 45kg and maximum 86kg and the mean excess body weight of group B was 65.4kg with $\pm$ SD 11.3kg, minimum 46kg and maximum 86kg. The p value of excess body weight was 0.69 which was insignificant and indicates that excess body weight has no role in increasing risk of development of gall stone.

Table 4: The weight of group A and group B.

Weight	Group A	Group B	T-test	P-value
Mean	134.9kg	131kg	1.17	0.26(NS)
SD	14.4kg	13.1kg		
Min	103.5kg	112.5kg		
Max	171kg	171kg		

In this study, diabetes in group A (n-30) 7 diabetic patient and 23 patients free and in group B (n-20) 6 diabetic patient and 14 patients free. 6 patients hypertensive in group A (n-30) and 24 patients free and 7 patient hypertensives in group B (n-20) and 13 patients free. 8 patients have joint disease in group A (n-30) and 22

patients free and 8 patients have joint disease in group B (n-20) and 12 patients free. 4 patients have obstructive sleep apnea in group A (n-30) and 26 patients free and 3 patients have obstructive sleep apnea in group B (n-20) and 17 patients free. 5 patients have restrictive lung disease in group A (n-30) and 25 patients free and 4 patients have restrictive lung disease in group B (n-20) and 16 patients free.

The p value of this study of diabetes was 0.59 which was insignificant. The p value of this study of hypertension was 0.236 which was insignificant. The p value of this study of joint disease was 0.201 which was insignificant. The p value of this study of obstructive sleep apnea was 0.868 which was insignificant. The p value of this study of restrictive lung disease was 0.764 which was insignificant.

Table 5: The height of group A and group B.

Height	Group A	Group B	T-test	P-value
Mean	170.9cm	167cm	1.36	0.194
SD	10.4cm	9.8cm		
MIN	150cm	150cm		
MAX	190cm	185cm		

Table 6: The excess body weight distribution of group A and group B.

Excess body weight	Group A	Group B	T-test	P-value
Mean	66.7kg	65.4kg	0.39	0.69(NS)
SD	10.7kg	11.3kg		
MIN	45kg	46kg		
MAX	86kg	86kg		

Table 7: The comorbidity distribution of group A and group B.

Comorbidity	Group A		Group B		chi	P-value
	Yes	No	Yes	No		
Diabetes	7	23	6	14	0.277	0.59 (NS)
Hypertension	6	24	7	13	1.403	0.236 (NS)
Joint disease	8	22	8	12	1.638	0.201 (NS)
Obstructive sleep apnoea	4	26	3	17	0.028	0.868 (NS)
Restrictive lung disease	5	25	4	16	0.090	0.764 (NS)

The results had been found insignificant according to diabetes, hypertension, joint disease, obstructive sleep apnea and restrictive lung disease in this study and indicate that diabetes, hypertension, joint disease, obstructive sleep apnea and restrictive lung disease have no role in increasing risk of gall stones formation after sleeve gastrectomy. In this study, the mean of the excess body weight loss after one year of group A was 75.7% with $\pm$ SD 9.8%, minimum 50% and maximum 90%.

Table 8: The comorbidity distribution of group A and group B.

Weight loss after 1 year as % of excess body weight	Group A	Group B	T-test	P-value
Mean	75.7%	73.3%	1.51	0.15(NS)
SD	9.8%	7.8%		
Min	50%	55%		
Max	90%	95%		

Table 9: The using of UDCA for 6months and the incidence of gall stone formation for one year follow up.

Gall stone	Group A with using UDCA (n-30)	Group B without using UDCA (n-20)	Chi	P-value
+ve Gall stone formation	0	3	4.787	0.029 (S)
-ve Gall stone Formation	30	17		

Table 10: The incidence of symptomatic gall stone distribution of group A and group B.

Symptomatic gall stone	Group A	Group B	Chi	P-value
Yes	0	1	1.531	0.216 (NS)
No	30	19		

The mean of the excess body weight loss after one year of group B was 73.3% with $\pm$ SD 7.8%, minimum 55% and maximum 95%. The p value of the excess body weight loss after one year was 0.15 which was insignificant and indicates that the excess body weight loss after one year has no role in increasing risk of development of gall stones. In this study, the using of UDCA and the incidence of gall stone formation for one year follow up of group A (n-30) no patient has positive gall stone formation. Group B (n-20) 3 (15%) have positive gall stone formation and 17 (85%) patient have negative gall stone formation.

The p value of the using of UDCA and the incidence of gall stone formation for one year follow up was 0.029 which was significant and indicate that UDCA has role in prophylaxis against development of gall stones formation after sleeve gastrectomy. In this study, the incidence of symptomatic gall stone formation for one year follow up of group A (n-30) no patient has develop symptoms like nausea, vomiting and abdominal pain. Group B (n-20) 1 (5%) have develop symptoms like nausea, vomiting and abdominal pain and 19 (95%) patient have negative symptomatic gall stone formation. The p value of this study of the incidence of symptomatic gall stone

distribution of group A and group B were 0.216 which was insignificant and indicates that the incidence of symptomatic gall stone distribution of group A and group B has no role in increasing risk of development of gall stones formation after sleeve gastrectomy.

DISCUSSION

Sleeve gastrectomy operation effective in providing weight loss of large magnitude, correction of comorbidities, decreasing overall mortality and providing a marked survival advantage. Development of gall stones post sleeve gastrectomy operation became very common and many studies are done in order to discuss causes and prophylaxis against its development.⁵

Lithogenesis was modified following Laparoscopic Sleeve Gastrectomy Operation (LSG). Post bariatric modifications include cholesterol hyper-saturation of bile (through cholesterol mobilization from fatty tissues enhancing cholesterol crystallization, decreased secretion of biliary acids (caloric restriction), increased mucin production (enhancing crystallization) and last, gallbladder hypo-motility (secondary to decreased cholecystokinin secretion related to the hypo-caloric diet, or obesity related resistance to cholecystokinin, to gastroduodenal exclusion, or due to intraoperative injury to the hepatic branches of the vagus nerves.⁶

A prospective study, on 1398 patients with morbid obesity found that around 8% of patients developed cholelithiasis (CL) and required cholecystectomy during the first 6months after the primary bariatric procedure.⁷ Based on the findings of several reports implying the formation of gallstones after different bariatric procedures, the guidelines for perioperative nutritional, metabolic, nonsurgical support of the bariatric surgery patient. Now, recommended an ultrasound examination within the first 6months as a routine examination after bariatric surgery for the detection of gallstones.⁸

An estimated 10-25% of patients who lose weight through very low-calorie dieting develop CL. In mal-absorptive procedures, such as RYGB, CL develops due to changes in the composition of bile, with increases in the calcium and mucin contents leading to the formation of supersaturated or lithogenic bile that crystalizes, deposits and eventually forms cholesterol gallstone.⁹

However, since LSG is a purely restrictive procedure with an intact bowel transit and entero-endocrine system, the details of mechanism of CL development after SG remain unclear. It was assumed that the division of the lesser omentum during bariatric procedures may cause inadvertent injury to hepatic branch of the left vagus nerve, which controls the gallbladder motility.¹⁰ Motility dysfunction can thus supervene, resulting in stasis of bile and subsequently CL. Gallstone that form after LSG can remain asymptomatic and become detected only during abdominal ultrasonography or they can present clinically

with the classic symptoms of LC or even with complications as obstructive jaundice or pancreatitis.¹¹

Reported that LSG and RYGB had comparable incidences of symptomatic and complicated gallstone disease. Efforts have been made to prevent the formation of gallstone after bariatric procedures. Concomitant cholecystectomy has been proposed but the added morbidities as well as the prolongation of the operation time and hospital stay have rendered this option controversial.¹² Found that concomitant cholecystectomy prolonged the operation time of LSG and resulted in unnecessary complication such as bile leakage. Prophylactic cholecystectomy with bariatric surgery appeared to be an unnecessary procedure that should be applied only in the presence of symptomatic gallstone as advocated.¹³

The use of UDCA has been advocated as prophylactic measure against postoperative CL. The UDCA acts by inhibiting cholesterol secretion in bile, thereby preventing the super saturation of bile and cholesterol stone formation.¹⁴ Daily oral administration of UDCA for 6months was associated with a decreased rate of gallstone formation after restrictive bariatric procedures.¹⁵ Furthermore, a meta-analysis of randomized controlled trials reported that the use of UDCA reduced the incidence of gallstone formation from 27.7% in placebo group to 8.8% in the treatment group including that UDCA can effectively prevent CL after bariatric procedures.¹⁶

However, despite the encouraging results found with UDCA, it has not been widely applied as a routine prophylactic measure against CL after bariatric surgery. This was likely due to the lack of distinct criteria that define the proper indication for UDCA based on measurable risk factors and to the adverse effects of UDCA including nausea, vomiting and diarrhea that affect patient compliance.⁹

In this study, conducted on 50 patients divided into two groups after they met the inclusion criteria of this study. Group A received (UDCA) 500mg daily for 6months 15days postoperatively and Group B hadn't received (UDCA). Results were collected regarding age, sex, BMI, initial body weight, excess weight loss.

Results showed that using (UDCA) has significant role in prophylaxis against development of gall stones, patients who received (UDCA) developed gall stones by a percentage 0% (0/30) while patients who hadn't received (UDCA) developed gall stones by a percentage 4.78% (3/20). Which was concordant with Miller K et al, who reported that of 152 patients, 76 were randomized to placebo and 76 to 500mg of Ursodeoxycholic Acid daily to assess the role of (UDCA) in prophylaxis against development of gall stones after restrictive bariatric surgeries. Gall stone formation was significantly less frequent with Ursodeoxycholic Acid than with placebo at

12months, 3% versus 22%, and 8% versus 30% at 24months, cholecystectomy in 4.7% versus 12%, respectively.¹⁵ It is also concordant with Abdallah E et al, who conducted a study on a total of 406 patients (124 males, 282 females) with a mean age of 32.1±9.4years were included. The mean baseline body mass index (BMI) was 50.1±8.3kg/m².

Patients were subdivided into two groups which was group I, which did not receive prophylactic treatment with UCDA after LSG and group II, which received UCDA therapy for 6months after LSG. Group I comprised 159 patients, and group II comprised 247 patients. The two groups showed comparable demographics, % excess weight loss (EWL) and decrease in BMI at 6 and 12months after LSG. Eight patients (5%) developed CL in group I, whereas no patients in group II did (P=0.0005).¹⁷

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