The role of Ursodeoxycholic acid in prevention of gallstone formation following laparoscopic sleeve gastrectomy

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Abstract

Background

Bariatric surgery is considered a successful modality for long-term maintaining weight loss, Rapid weight loss following these procedures is associated with an increased incidence of postoperative Cholelithiasis (CL). Postoperative use of ursodeoxycholic acid (UDCA) was advocated to prevent gallstone formation during the postoperative period and to avoid the unnecessary morbidities that occur with routine prophylactic cholecystectomy performed in bariatric surgery patients even in absence of gallstones.

Objective

This study evaluates the role of daily administration of ursodeoxycholic acid (UDCA) for 6 months in the prevention of CL after laparoscopic sleeve gastrectomy.

Methods

This prospective randomized control trial of 80 morbidly obese patients who underwent laparoscopic sleeve gastrectomy (LSG) after preoperative ultrasonographic exclusion of gallstones at Cairo university hospitals. Patients were subdivided into two groups: the control group (No UDCA group) who did not receive prophylactic treatment with UDCA, and the UDCA group, who received 500mg of UDCA therapy for 6 months postoperatively. Patient characteristics, weight loss data, any detectable complications, and incidence of CL at 6,12, and 18 months postoperatively were collected.

Results

In the UDCA group, only 5% developed cholelithiasis in comparison to 32.5% in the control group (P=0.002). Age, gender, initial body mass index, and %EBWL at 6 months did not significantly affect cholelithiasis.

Conclusion

Administration of UDCA for 6 months after LSG is effective in the prevention of cholelithiasis. It is safe and well tolerated by patients with few side effects.

Keywords: Gallstones, sleeve gastrectomy, Cholelithiasis, UDCA, Ursodeoxycholic acid

INTRODUCTION

The prevalence of obesity as a non-communicable disease has increased. It is associated with many health risks affecting different body systems secondary to the excess body weight and the altered pathophysiology in these types of patients (1)

Different modalities such as lifestyle modification, exercise, and dietary regimens have failed to maintain weight reduction, however, bariatric surgery with its restrictive and malabsorptive characteristics has

proved to be very effective in maintaining long-term weight reduction and improving comorbidities associated with obesity (2,3). Secondary to the lower complication rates in comparison to laparoscopic roux en y gastric bypass (LRYGB) and biliopancreatic diversion (BPD), the rates of sleeve gastrectomy have increased (4). Unfortunately, bariatric surgery causes rapid weight loss and has been associated with an increased incidence of cholelithiasis (5). This is caused by multiple physiological factors, including hyper saturation of bile with cholesterol, decreased gall bladder motility, increased mucin production, and stasis of bile (4,6).

Although it is theoretically expected to have lower rates of gallstones following laparoscopic sleeve gastrectomy (LSG) due to the unaltered nutrient pathway, some studies have shown comparable rates with LRYGB (4,7). It was shown that the risk of gall stones formation increases during the phase of rapid weight loss, which is more pronounced during the first 6 months following surgery (8)

Symptomatic cholelithiasis presenting either with biliary colic or by one of its complications as obstructive jaundice, pancreatitis, or cholangitis is considered the main indication for cholecystectomy (9,10). Abdominal ultrasonography is used to assess the development of cholelithiasis after weight loss procedures however there is no consensus on the timing and intervals of surveillance (11). Ursodeoxycholic acid (UDCA) has been recommended as a safe method for prophylaxis against the development of gallstones following laparoscopic sleeve gastrectomy (8,12)

Methods:

This randomized control clinical study included 80 patients at Cairo university hospital during the period between January 2020 and November 2021 who underwent laparoscopic sleeve gastrectomy after ultrasonographic exclusion of cholelithiasis.

This was done after approval from the institutional review board and obtaining informed consent from all patients including approval of the protocol of treatment.

The inclusion criteria were morbidly obese patients (BMI ≥35 kg/m2 associated with at least 1 comorbidity or BMI ≥40 kg/m2 with or without comorbidities) with no evidence of cholelithiasis by abdominal ultrasound.

The exclusion criteria were as follow:

• Morbidly obese patients with preoperative ultrasound showing cholelithiasis, cholecystitis or sludge.

• Morbidly obese patients with surgically removed gall bladder.

• Vulnerable groups: pregnant females, old age >60 years, age < 18 years

• Contraindication to UDCA administration (complete biliary obstruction, hypersensitivity to drug)

The participants were allocated into two groups, 40 patients in the control group who didn't receive UDCA and 40 patients in the UDCA group who received 500 mg of UDCA for 6 months postoperatively.

Interview with patients was done with an explanation of the procedure and intervention and the possible side effects and consent was obtained. Data including age, gender, weight, height, BMI, and comorbidities were collected preoperatively.

All patients had serum testing of liver enzymes (bilirubin, alkaline phosphatase, aspartate transaminase, and alanine transaminase), serum lipid profile (LDL, HDL, triglycerides, and VLDL), routine preoperative labs as well as functional assessment as well as preoperative ultrasound assessment for the presence of fatty liver and exclusion of cholelithiasis or sludge.

Laparoscopic sleeve gastrectomy was done with standardization of technique in both groups including reinforcement of staple line by secondary sutures.

Patients were randomized into the UDCA-treated group who received 500 mg of UDCA orally once daily for 6 months and the control group who didn't receive UDCA treatment using computerized random numbers.

Patients were evaluated at 1 month, 6 months, 12 months, and 18 months regarding manifestations of cholelithiasis or development of complications such as acute cholecystitis or pancreatitis as well as % EWL at 6 months.

All patients had abdominal ultrasonography at 6 months, 12 months, and 18 months postoperatively for detection of the development of cholelithiasis, furthermore additional ultrasound was done in case of the presence of symptoms suggestive of cholelithiasis that includes recurrent episodes of right-upper-quadrant or epigastric pain, suggesting biliary colic and Boas' sign, fever, tender right upper quadrant with or without Murphy's sign.

Compliance to UDCA intake was reported at 6-month follow-up appointments and include poor (0-2 times per week), moderate (3-5 times per week), and good (6-7 times per week).

The Primary outcome was the occurrence of cholelithiasis after operation at 6, 12, and 18 months among the 2 groups. The secondary outcomes were % EWL [(baseline weight - actual weight)/ (baseline weight - ideal body weight)] × 100. (*The ideal body weight = Height in meters squared (m2) × 25). the relationship between cholelithiasis and possible risk factors of the patients as well as patients' compliance to UDCA intake.

Statistical methods

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired T-test. For comparing categorical data, Chi-square ($\chi 2$) test was performed. An exact test was used instead when the expected frequency is less than 5). P-values less than 0.05 were considered as statistically significant.

Results

This study included 72 females (90%) and 8 males (10%) with ages ranging from 18 to 59 with a mean age of 34.4±9.63 years. The preoperative body weight of candidates ranged from 90 kgs to 196 kgs and preoperative BMI ranged from 36.79 to 67.58 kg/m2 There was no significant difference between the 2 groups regarding age, sex, initial BMI, and percentage of excess weight loss (%EBWL) at 6 months. The initial clinical characteristics of the patients are illustrated in Table 1.

Table (1) Demographic and clinical data among the study groups:

	UDCA group	Control group	P value
Gender (male/female)	5/35	3/37	0.712
Age (years) mean±SD	33.38±9.98	35.50±9.48	0.332
Preoperative weight (kg) mean	127.78 ±18.05	126.23 ±22.46	0.735
Preoperative BMI (kg/m2) mean	47.99 ±7.15	47.79±6.24	0.897
Mean %EBWL At 6 months	51.51 ±12.13	50.32± 14.42	0.691

Among the 80 patients included, 64 patients (80%) had no comorbidities, and only 14 patients (20%) had different comorbidities shown in figure (1)

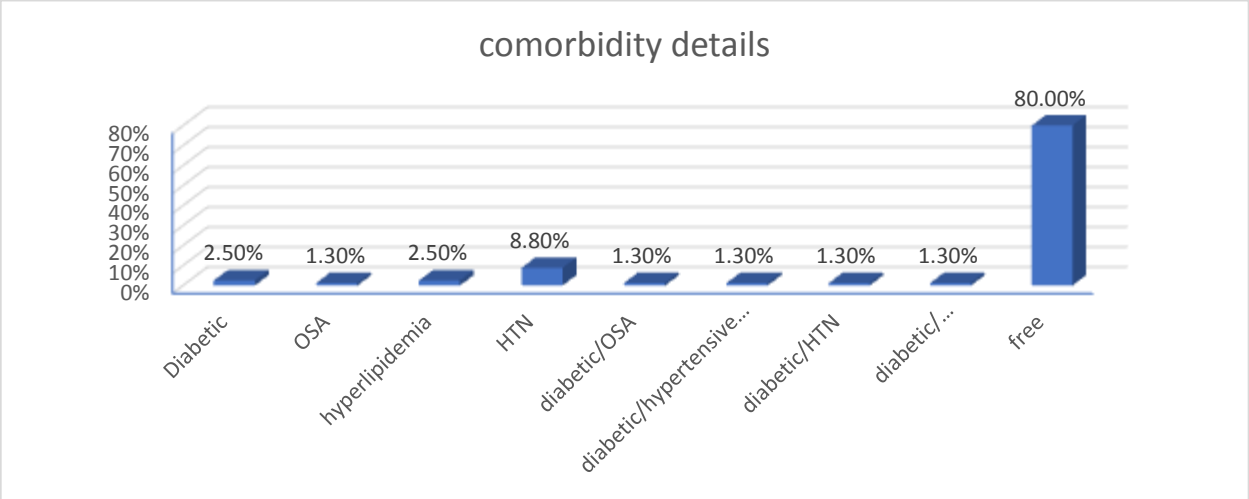

Figure (1) Associated medical comorbidities.

During follow-up, 15 patients developed gallstones representing 18.75% of the population included. 8 patients (10%) developed gallstones in the first 6 months and another 7 patients (8.75%) developed gallstones between 6 to 12 months of the postoperative period, yet no gallstone formation was reported after the first postoperative year.

In the UDCA group, only 1 patient (2.5%) developed asymptomatic cholelithiasis detected at the 6-month follow-up ultrasonography. With another patient developed symptomatic cholelithiasis 10 months postoperatively with an incidence of cholelithiasis at 12 months of 5%. No further symptomatic or asymptomatic cholelithiasis was detected beyond the first postoperative year, with the incidence of cholelithiasis at 18 months of 5%, with an overall cholecystectomy rate of 2.5%.

In the control group, 7 patients (17.5%) developed gallstones at 6 months follow-up, 2 of them were symptomatic and required cholecystectomy. Another 6 patients (15%) developed cholelithiasis between 9 to 12 months with a mean duration of 10.5 months with an incidence of cholelithiasis at 12 months of 32.5%, 3 of them were symptomatic and needed cholecystectomy. it is to be noted that no patients developed gallstones after 12 months with the incidence of cholelithiasis at 18 months of 32.5% as well, with an overall cholecystectomy rate of 12.5%.

There was no significant reduction in the incidence of cholelithiasis after 6 months in the UDCA-treated group (P=0.057). However, there was a significant reduction in the development of cholelithiasis at 12 months and 18 months with a p-value of 0.002.

Age, gender, preoperative BMI, the presence of one or more comorbidity as well as the %EBWL at 6 months weren't significant contributors to the development of postoperative cholelithiasis, with details explained in table 2.

Table (2) Relation of age, Gender, Preoperative BMI, and % EBWL at 6 months with cholelithiasis development

	Cholelithiasis development	**No cholelithiasis development**	**P value**
Mean age	36.93±10.28	33.86±9.59	0.273
Gender Male (n=8) Female (n=72)	 2 (25%) 13 (18.1%)	 6 (75%) 59 (81.9%)	 0.640
Preop BMI at: 6 months 12 months 18 months	 48.11±6.22 48.97±8.78 48.97±8.78	 47.87±6.76 47.64±6.14 47.64±6.14	 0.923 0.490 0.490
%EBWL at: 6 months	 51.11±18.93	 50.86±11.77	 0.962

Among the 40 patients who received UDCA, 92.5% showed good compliance (6-7 times per week) and only 7.5% showed moderate compliance (3-5 times per week) with no patients reporting poor compliance (0-2 times per week). Side effects appeared in 4 patients (10%), 3 patients complained of nausea and 1 patient complained of diarrhea, however, these symptoms were tolerated and didn't require discontinuation of the treatment.

Discussion:

In the current study, the overall incidence of postoperative cholelithiasis was 18.75% with a significant decrease in the incidence of gallstone formation from 32.5% in the control group to 5% in the treated group with UDCA. Also, there was a decrease in the incidence of symptomatic cholelithiasis from 12.5% in the control group to 2.5% in the treated group , this result is close to Coupaye et al, who found the incidence of cholelithiasis in 46 non treated patients with UDCA at 1 year after LSG to be 28%. (13). Our results were more or less similar to Guzman et al, who studied the development of cholelithiasis in 176 patients who underwent sleeve gastrectomy, sleeve gastrectomy with jejunal bypass and LRYGB, with incidence of cholelithiasis to be 36.9% (14).

Altieri et al., evaluated the large data base in New York state for more than 15000 patients who underwent different weight loss surgeries, the rate of postoperative cholecystectomy for symptomatic gallstones among LSG was 10.1% which is comparable to our study which is 12.5%. (7).

In contrast to our study, Manatsathit et al. who performed a retrospective cohort study of 96 patients who underwent LSG, the incidence of gallstone formation was 47.9% and the incidence of symptomatic gallstones of 22.9% which is higher than our study (15). On the contrary Mishra et al performed a retrospective analysis of 1397 different bariatric surgery patients and showed a much lower incidence of cholelithiasis and symptomatic cholelithiasis following LSG at 8.42 % and 1.94% respectively (16). This disparity is probably due to the variability in number of patients include, different baseline patient characteristics, variable rates of %EBWL among patients and variable follow up periods.

In this study, it was shown that both gender and age distribution didn't significantly influence gallstones formation (P= 0.640) and (P=0.273) respectively, this was consistent with De Oliveira et al that found no evidence of association between calculus formation during postoperative weight loss and sex or age (P=0.4554) and (P=1) respectively (17), the results were also supported by the studies conducted by Nabil et al, and Talha et al who found age and gender has no contribution to the development of postoperative cholelithiasis. (18,19)

In the current study the mean preoperative BMI and mean %EBWL at 6 months were homogenous

among the treated and the non-treated groups with no significant difference in the development of cholelithiasis, this finding is in concordance to Nabil et al, Moon et al, Manatsathit et al., they reported that preoperative BMI and %EBWL weren't predictive factors for postoperative cholelithiasis (15,18,20). On the other hand, D'Hondt et al. found that a loss > 50% of EBWL at 3 months doubles the risk of postoperative cholecystectomy (21). Tsirline et al. found that excess weight loss >25% within the first 3 months was the strongest predictor of postoperative cholecystectomy (P<.001) (22). Talha et al found the %EBWL could be a predictor of postoperative cholelithiasis (19).

The use of UDCA has been advocated as a prophylactic measure against postoperative cholelithiasis it acts by preventing the supersaturation of bile and cholesterol stone formation. (23). In our current study the use of a daily dose of 500 mg of UDCA for 6 months post LSG has significantly reduced the incidence of cholelithiasis at 12 and 18 months postoperatively from 32.5% in the control group to 5% in the UDCA treated group (P=0.002 and the rate of cholecystectomy from 12.5% in control group to 2.5% in UDCA treated group. Uy et al. reported that the use of UDCA reduced the incidence of gallstone formation from 27.7% in the placebo group to 8.8% in the treatment group, concluding that UDCA can effectively prevent CL after bariatric procedures (24), Abdallah et al. conducted a study on 406 morbid obese patients who underwent LSG, 159 patients were included in the control group and 247 patients received a daily dose of 600 mg of UDCA for 6 months. UDCA have shown a decrease in the incidence of gallstones from 5% in the control group to 0% in the treatment group (P=0.0005) (25). In another study by Coupaye et al, that included 189 patients who underwent LSG, 46 patients were in the control group and 143 patients received a daily dose of 500 mg UDCA for 6 months, there was a reduction of postoperative gallstone formation from 28% in the control group to 3.5% in the treated group ($p < 0.001$) with reduction of rate of cholecystectomies from 11% to 1.4% ($p = 0.012$) (13). Nabil et al, also used a daily dose of 500 mg of the drug and have shown a significant decrease in cholelithiasis rate from 40% in control group to 6% in the treatment group (P<0.001) their results are nearly similar to our study (18) Talha et al who reported a significant decrease in the incidence of gallstone formation from 22% in placebo to 6.5% in UDCA group following the use of UDCA for 6 months (p=0.001) (19) Sakran et al used UDCA at a dose of 300 mg twice daily for 6 months with a reduction in cholelithiasis from 45.7% in placebo to 23.9% in UDCA (P=0.029) (26)

In conclusion, UDCA proved to be very effective if given with a daily dose of 500mg for 6 months to guard against the development of cholelithiasis after LSG, it is well tolerated by the patients with only minor side effects including nausea, vomiting, and diarrhea that don't require omitting the drug. However, the limitation of this study is the relatively small sample size, being a single-center study and the relatively short follow-up period.

Conflict of interest:

All authors disclose that they have no conflicts of interest that are relevant to the manuscript.

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