Should we prescribe ursodeoxycholic acid after laparoscopic sleeve gastrectomy? A two-center prospective randomized controlled trial

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Background
In the recent era, laparoscopic sleeve gastrectomy (LSG) had emerged as a safe and effective bariatric procedure. Rapid weight loss is associated with deranged cholesterol metabolism in the form of gallstones.
Several studies have shown that ursodeoxycholic acid (UDCA) has a prophylactic role after gastric bypass, vertical banded gastroplasty, and adjustable gastric banding. Yet, data about its effect after LSG are scarce. In this study, we tried to unveil the prophylactic role of UDCA in the prevention of post-LSG gallstones.
Materials and methods
This two-center prospective randomized controlled trial had been conducted at Abha Private Hospital, Saudi Arabia, and Ain-Shams University hospitals, Egypt, from May 2016 to June 2017 on 89 post-LSG patients. After block randomization, patients were allocated into either group A (UDCA treatment) or group B (control). UDCA was prescribed as 250 mg twice daily for 12 months or until the development of gallstones.
Results
A total of 44 patients were included in group A and 45 patients were included in group B. There was no significant difference between both the groups regarding the baseline parameters.
At the sixth month, group A showed a significantly lower incidence of gallstones (6.8 vs. 22.2% in group B; P=0.028). This pattern was maintained till the 12th month (5.8 vs. 14.7%; P=0.031). The overall percentage of gallstones was 23.5% (20/85); it was significantly higher in the first 6 months than in the second 6 months (14.6 vs. 9.7%; P=0.043).
Conclusion
UDCA is a safe prophylactic measure against gallstones formation and should be integrated into the post-LSG prescription.

Keywords:
cholelithiasis, gallstone prevention, laparoscopic sleeve gastrectomy, postlaparoscopic sleeve complications, ursodeoxycholic acid

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Introduction

In the recent era, laparoscopic sleeve gastrectomy (LSG) had emerged as a safe and effective bariatric procedure in terms of adequate weight loss and low complication rate [1–3]. Nevertheless, the rapid significant weight loss can disturb biliary cholesterol homeostasis and may lead to gallstone formation [4–7]. Cholelithiasis is one of the commonest complications after LSG; it accounts for 15–47.9% [7–9].

Laparoscopic cholecystectomy after LSG may be technically challenging, and serious complications have been reported in 2–3% of cases [5,10,11]. Hence, the prevention of stones is of utmost importance.

The prevention of post-LSG gallstone is a highly controversial issue; to date, no consensus exists about its prevention. Several preventive approaches had been proposed like preventive, concomitant, and postoperative cholecystectomy [10–12] and prostaglandin inhibitors (such as Ibuprofen) [5], but they were either controversial or unsuccessful [13].

Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic secondary bile acid [14] extracted from the Chinese dark bear [14,15]. It was approved by the US Food and Drug Administration and is used successfully in the treatment of several hepatobiliary diseases [15]. It increases biliary acids, favors the formation of biliary micelles and vesicles [5,6,16], reduces intestinal

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absorption and biliary secretion of cholesterol and mucin, and decreases cholesterol saturation index to be less than one, hence decreasing the bile lithogenicity [6,17,18].

Several studies have settled that UDCA has a prophylactic role against gallstone formation after Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VBG), and adjustable gastric banding (AGB) [7,13,19,20]. Yet, there is a paucity of data regarding its effect after LSG. In this study, we tried to unveil the prophylactic role of UDCA in the prevention of post-LSG gallstones.

Materials and methods

Study design

This two-center, parallel-group, superiority, prospective randomized controlled trial had been conducted from May 2016 to June 2017 upon separate approval of the Institutional Review Board of each center. The first center was Ain-Shams University hospitals, Cairo, Egypt, and the second center was Abha Private Hospital, located in Abha, Saudi Arabia.

Post-LSG patients aged 18–65 years, of both sexes irrespective of ethnicity, were recruited to participate in the study. All our patients had a routine preoperative transabdominal ultrasound (US) surveillance to exclude the presence of gallstones or sludge. Exclusion criteria included preoperative cholelithiasis and/or sludge, gallbladder polyp(s), known allergy to UDCA, previous cholecystectomy, dilated common bile duct, deranged liver function tests, bleeding disorders, and those unfit for general anesthesia.

Eligible patients have been enrolled in the trial after submitting an informed written consent. They were randomized using the permuted block randomization method with an allocation ratio of 1 : 1. Such method ensures balancing of the number of the patients to both arms of the trial every ten recruits, and then they were allocated to either UDCA treatment (group A) or control group (group B). For group A patients, UDCA (Ursofalk; Dr. Falk Pharma, Freiburg, Germany) was prescribed as one tablet 250 mg twice daily starting within 3 days postoperatively and continuing for 12 months or until gallstone development. At discharge, all patients had full verbal and written instructions regarding the post-LSG complications and the symptoms of gallstones and were instructed to report it and to follow-up immediately.

The follow-up visits were scheduled for 3, 6, 9, and 12 months postoperatively. In each follow-up visit, the patients were clinically assessed, some weight loss parameters were calculated as BMI and percentage excess weight loss (%EWL), with the assessment of the compliance to treatment and detection of any UDCA-related adverse effects. US study was requested routinely at the sixth and 12th month follow-up visit only. Primary outcome measures included the formation of gallstones or UCDA-related adverse effects, whereas secondary outcome measures were the development of complications related to the gallstones and/or laparoscopic cholecystectomy.

Demographic data such as age, sex, and anthropometric data such as height, weight, BMI, and %EWL, and percentage of gallstones in each group were documented. Dropout patients and those who developed adverse effects related to UDCA administration were excluded from the study at the time of detection. We stopped US scanning once obtaining the positive US of gallstones, and their results were excluded from the next analysis at the 12th month (Flowchart 1). All relevant data were documented in a special Excel sheet for Windows (Microsoft Corporation, Redmond, Washington, USA) and were verified to check its statistical significance.

Statistical analyses

The standard descriptive statistics were used to summarize the demographic, anthropometric, and clinical data. The quantitative continuous variables with a normal distribution were expressed as the mean±SD, and qualitative data with categorical variables were expressed as frequencies and proportions.

The categorical variables were analyzed by the Fisher's exact test or χ^2-test. Univariate analyses for the continuous variables were performed by the Wilcoxon–Mann–Whitney test (also called Wilcoxon's rank-sum test), which is an accurate nonparametric test applied for data with non-normal distributions of two independent groups. The statistical analysis was performed using the statistical package for the social sciences version 22 software package (SPSS Inc., Chicago, Illinois, USA). P value of less than 0.05 is considered statistically significant.

Results

During the period of study, 123 patients underwent LSG in the two institutions. Overall, 24 patients were excluded owing to either previous laparoscopic cholecystectomy or positive preoperative gallstones. In all, 99 patients met our inclusion criteria and accepted to participate in this trial. After

randomization, patients were enrolled in one arm of the study either as a treatment group (group A) or control group (group B), and 10 patients were excluded as illustrated in Flowchart 1.

The remaining 89 patients were allocated as 44 patients in group A, and 45 patients in group B. The studied patients were 55 (65.1%) females and 34 (38.2%) males, and the mean age is 38.1±4.9 years (19.6–59.4 years). The baseline characteristics are illustrated in Table 1. There was no statistically significant difference in the age, sex, and preoperative BMI of the patients of both groups. Weight loss parameter changes were expressed in Table 2, with no statistically significant difference between both the groups.

At the sixth month follow-up, we noticed that 3/44 (6.8%) patients in group A (UDCA treatment) and 10/45 (22.2%) patients in group B (control) developed gallstones, of them only two were symptomatic and had laparoscopic cholecystectomy. Other patients were followed up till the end of the study without any intervention. We found a statistically significant difference between both the groups (P=0.028).

All patients who developed gallstones at 6 months were excluded from the study while assessing the 12 months results to unveil the real percentage of gallstone formation in between 6 and 12 months postoperatively. By US scanning of the remaining patients at the 12th month follow-up, we found 2/38 (5.26%) patients in group A and 5/34 (14.7%) patients had the positive US findings of gallstones. These results (at 12th month) were checked statistically using the nonparametric Mann–Whitney U–test, revealing a statistically significant difference (P=0.031).

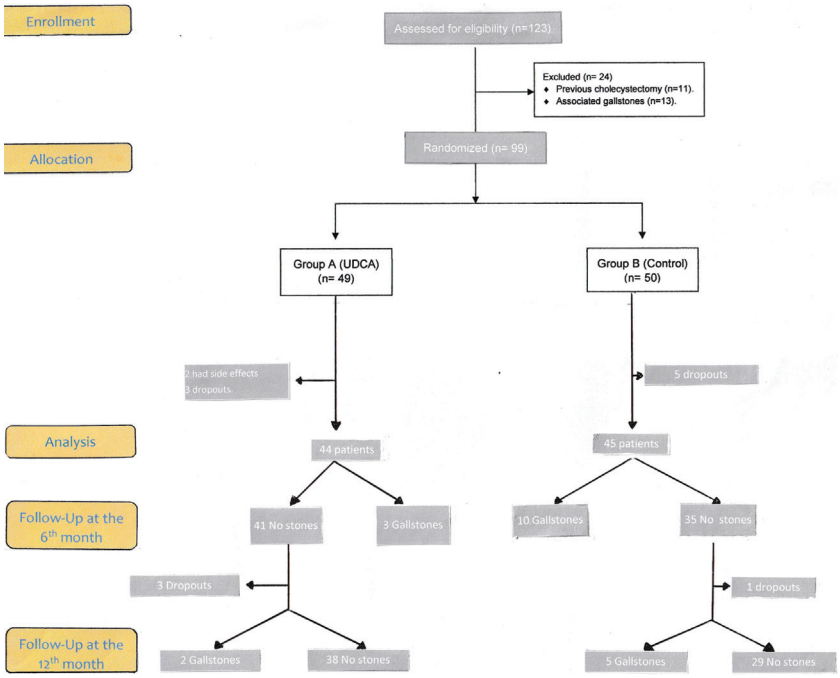
Analysis revealed that the overall percentage of gallstones was 23.5% (20/85); it is higher in the first 6 months (14.6%) than in the second 6 months (9.7%) (P=0.043; Table 3). No mortality cases were reported in this study.

Discussion

In the recent era, LSG had emerged as a safe effective bariatric procedure in terms of adequate weight loss and low complication rate. It was observed that approximately 30% of postbariatric surgery patients had gallstones, which are more common during the rapid weight loss phase [16]. Some authors [21,22] speculated that the risk of gallstone formation rises markedly if the weight loss exceeds 1.5–1.7 kg/week, or 24% of the initial body weight.

Postbariatric surgery gallstone is considered a controversial topic. It was extensively studied from some aspects as pathophysiology and risk factors. Yet, some other aspects of the natural history and prevention are still vague. Conley *et al.* [12] observed that gallstones

Flowchart 1



Study flowchart illustrating all its phases.

Table 1 Baseline demographic and anthropometric data

Variables	Group A	Group B	*P* value
Age	37.8±3.9	38.7±5.1	0.31
Sex [*n*/*N* (%)]			
Male	17/44 (38.6)	19/45 (42.2)	0.19
Female	27/44 (61.3)	26/45 (57.7)	
Weight	127.8±18.3	128.3±18.7	0.23
Height	167.5±8.6	166.9±9.4	0.36
BMI	47.3±2.2	46.7±3.1	0.26

Table 2 Changes in weight loss parameters

Variables	Group A	Group B	*P* value
BMI (preoperative)	47.3±2.2	46.7±3.1	0.26
BMI (at 6 months)	35.4±4.8	34.8±5.6	0.29
BMI (at 12 months)	31.5±5.9	30.6±6.4	0.24
EWL% (at 6 months)	54.9±12.7	55.3±13.2	0.61
EWL % (at 12 months)	68.6±18.3	68.4±19.1	0.63

EWL%, percentage excess weight loss.

Table 3 Gallstones formation percentage

	Group A [*n*/*N* (%)]	Group B [*n*/*N* (%)]	*P* value
At 6 months	3/44 (6.8)	10/45 (22.2)	0.028
At 12 months	2/38 (5.2)	5/34 (14.7)	0.031
Total	5/44 (11.36)	15/45 (33.3)	0.017

formed during weight loss have a higher chance to be symptomatic than those formed before LSG. In other words, they behave in a completely different way.

Surprisingly, in a retrospective study conducted in Cleveland Clinic on 796 postbariatric surgery patients, Li *et al.* [23] stated that the classic risk factors for gallstone formation in the general population (such as increasing age, female sex, BMI greater than 45 kg/m^2, diabetes mellitus, hyperlipidemia) are not the same as that in postbariatric surgery. They found that a weight loss of more than 25% of the original weight is the only postoperative risk factor for cholelithiasis after bariatric surgery.

Furthermore, Paik *et al.* [24] found that risk factors for cholelithiasis after gastrectomy for cancer included male sex, increasing age, decreased BMI of more than 4% after gastrectomy, and diabetes mellitus. These risk factors differ markedly from the risk factor after bariatric surgery.

Hence, we can find that different risk factors of cholelithiasis result in different biochemical alterations through vague pathophysiological pathways leading to cholelithiasis.

Gallstone disease may go beyond what is expected and cause significant morbidity. Hence, the prevention of this serious disease is of utmost importance for improving patients' healthcare and saving the huge cost incurred in the treatment.

Many studies have evaluated the prophylactic role of UDCA following rapid weight loss after AGB, VBG, as well as RYGB [7,13,19,20]. However, data in the literature about post-LSG gallstones are few. UDCA has been proposed as an effective preventive measure against the gallstone formation during rapid weight loss phase.

Uy *et al.* [25] reported in a meta-analysis of five RCTs including 521 patients that UDCA is an effective modality in the prevention of gallstone after bariatric surgery (8.8 vs. 27.7%). In another larger meta-analysis of thirteen RCTs including 1836 patients, Stokes *et al.* [26] found that 5% in the UDCA group versus 23% in the control group developed gallstones, and they suggested that UDCA and a high-fat diet may be considered in the primary prevention of gallstones during weight loss. These results were further confirmed by Magouliotis *et al.* [2] in another recent meta-analysis of eight studies incorporating 1355 patients.

In a landmark prospective randomized trial conducted by Miller *et al.* [20] on 152 patients after VBG and AGB, they reported a less frequent gallstone formation rate in UDCA group in comparison with the placebo group (3 vs. 22% at 1 year, and 8 vs. 30% at 2 years) and also noted a lower rate of cholecystectomy in the UDCA group (4.7 vs. 12%).

Kiewiet *et al.* [13] retrospectively assessed the prevalence and risk factors of gallstone formation after AGB in 120 Dutch patients over 9 years without UDCA. They found that the total prevalence of gallstones was 30.1% and stated that UDCA is a cost-effective preventative measure. In addition, Coupaye *et al.* [7] found that UDCA decreased the gallstones after RYGB, and they found that it was more efficient if given as 250 mg twice daily than 500-mg single dose.

In this study, analysis of the baseline criteria of the eligible patients revealed a nonsignificant difference between both groups denoting that these variables run evenly in the two study arms, and it had no effect on the final results. In general, US scanning documented that 20/85 patients had gallstones with an overall percentage of 23.5%. This is in range reported by some other studies: Coupaye *et al.* [7] found that 15% of their patients developed gallstones, Adams

et al. [8] documented that 17/57 (29.8%) patients developed gallstones, whereas Manatsathit *et al*. [9] reported a higher percentage of cholelithiasis (47.9%) in a retrospective cohort study on 96 patients.

The differential statistical analysis of the data of both groups revealed that UDCA has a protective role against gallstones formation after LSG; the rate of gallstones formation in group A is significantly lower than in group B (11.3 vs. 33.3%; *P*=0.017). Further analysis showed that this protective effect was evident 6 months postoperatively. Such effect is demonstrated through the significant reduction of gallstones formation rate (6.8 vs. 22.2%; *P*=0.028). Coupaye *et al*. [7] found that 13/51 (25.5%) cases developed gallstones in the control group versus only 1/42 (2.4%) case in the UDCA group.

By exclusion of those who developed gallstones and dropout cases, data analysis through Wilcoxon–Mann–Whitney *U*-test at the 12th month showed again a significant reduction of gallstones (5.2 vs. 14.7%; *P*=0.031). This could suggest a maintained prophylactic role of UDCA at 12 months after LSG. This is in contrary to the results reported by Adams *et al*. [8] who did not find any significant difference in cholelithiasis rate between the two groups at 1 year.

The differential data analysis unveiled also the higher rate of stone formation in the first 6 months that decreased after that till the end of the first year. These results are in accordance with another study [8] that showed the decrease of cholelithiasis rate from 11 to 9.1% in UDCA group and from 40 to 21.4% in the control group. Similarly, Elgamal and Fawzy [27] showed a similar pattern with a decreased stone rate from 4.7 to 2.04% in UDCA group and from 11.7 to 5.8% in the control group.

In this context, this dynamic pattern could be attributed to a positive correlation between rapid weight loss and rate of gallstone formation. The underlying cause of this phenomenon is not completely understood. To date, several explanations have been hypothesized based on pathophysiological or biochemical findings like gallbladder hypomotility and bile stasis, increased secretion of mucin and calcium, increased the concentration of prostaglandins and arachidonic acid, and accelerated cholesterol crystal nucleation.In contrast, only one series presented a continuously rising titer of gallstone formation rate, and it was conducted by Miller *et al*. [20] on post-VBG and AGB patients; they observed that the rate increased from 22% (at 12th months) to 30% (at 24th months) in the control group and from 3 to 8% in the UDCA group.

Of interest, the incidence of symptomatic gallstones was 3.52% (3/85), which is in accordance with other series (0.7–3.8%) [7,9,11,12,22]. These figures are much lower than that reported after RYGB (4.5–16%) [19,28,29]; this could be explained by the preserved enteric–endocrine reflex [28].

Eleven (8.9%) patients were excluded owing to prior cholecystectomy, which is much lower than reported by another series (32.7%) [28]. Another concern is related to the safety profile of the drug, as only two patients in group A developed adverse effects related to the administration of UDCA such as headache, diarrhea, dizziness, and allergic skin rash, and they discontinued the drug at the seventh and ninth month and were excluded from the data analysis at the 12th month. This small percentage (4.8%) of adverse effects further confirms that UDCA is a safe well-tolerated medication.

In addition, 12 (12.1%) dropout cases were excluded from this series. Miller *et al*. [20] had a similarly high rate of dropout cases (18%). They attributed this high figure to the large capsules size that may be difficult to be swallowed after restrictive procedures.

We herein report that this study agrees with the scarce published data about the safety and efficacy of UDCA as a pharmacoprophylactic agent against post-LSG gallstones. The limitations of this current study included the small number of patients and short-term follow-up. The lack of a standardized protocol concerning the prevention of post-LSG gallstones necessitates the design of larger-scale studies with a cost-effective background which could help to establish a consensus for the universal administration of UDCA after LSG.

Conclusion

Gallstone formation is a common complication after LSG. The incidence of gallstones is higher during the first 6 months postoperatively, which can be correlated with the higher %EWL. It seems that pharmacoprophylaxis by UDCA remains to be a safe effective line of prevention against post-LSG gallstones. Thus, it should be integrated into the post-LSG drug prescription.

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The authors made an equal contribution to this study regarding conception, design, literature review, data acquisition, collection and analyses, and writing, editing, and approving the final manuscript.

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Conflicts of interest
There are no conflicts of interest.

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