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ORIGINAL ARTICLE

Role of ursodeoxycholic acid in the prevention of gallstone formation after laparoscopic sleeve gastrectomy

Emad Abdallah[1] · Sameh Hany Emile[1] · Hossam Elfeki[1] · Mohamed Fikry[1] · Mahmoud Abdelshafy[1] · Ayman Elshobaky[1] · Hesham Elgendy[1] · Waleed Thabet[1] · Mohamed Youssef[1] · Hosam Elghadban[1] · Ahmed Lotfy[1]

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Abstract
Purpose Postoperative cholelithiasis (CL) is a latent complication of bariatric surgery. The aim of this study was to evaluate the role of ursodeoxycholic acid (UDCA) in the prevention of CL after laparoscopic sleeve gastrectomy (LSG).
Methods This was a retrospective analysis of the prospectively collected data of patients with morbid obesity who underwent LSG. Patients were subdivided into two groups: Group I, which did not receive prophylactic treatment with UCDA after LSG; and Group II, which received UCDA therapy for 6 months after LSG. Patients' characteristics, operation duration, weight loss data, and incidence of CL at 6 and 12 months postoperatively were collected.
Results A total of 406 patients (124 males, 282 females) with a mean age of 32.1 ± 9.4 years were included. The mean baseline body mass index (BMI) was 50.1 ± 8.3 kg/m^2. 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 12 months after LSG. Eight patients (5%) developed CL in Group I, whereas no patients in Group II did ($P = 0.0005$). Preoperative dyslipidemia and rapid loss of excess weight within the first 3 months after LSG were the risk factors that significantly predicted CL postoperatively.
Conclusion The use of UCDA effectively reduced the incidence of CL after LSG in patients with morbid obesity. Dyslipidemia and rapid EWL in the first 3 months after LSG significantly predisposed patients to postoperative CL.

Keywords Gallstones formation · Cholelithiasis · Sleeve gastrectomy · Morbid obesity · UCDA · Ursodeoxycholic acid

Introduction

Morbid obesity is known to be associated with several co-morbid conditions, such as type 2 diabetes mellitus

✉ Sameh Hany Emile
Sameh200@hotmail.com

Emad Abdallah
Emad1976@gmail.com

Hossam Elfeki
hossamelfeki@gmail.com

Mohamed Fikry
Drmfikry@hotmail.com

Mahmoud Abdelshafy
abdelshafymahmoud@ymail.com

Ayman Elshobaky
elshobakyayman@yahoo.com

Hesham Elgendy
heshammelgendy@yahoo.com

Waleed Thabet
Thabet1510@yahoo.com

Mohamed Youssef
M_elkhir@yahoo.com

Hosam Elghadban
Dr.elghadban@gmail.com

Ahmed Lotfy
dr_lotfy9@hotmail.com

[1] General Surgery Department, Mansoura Faculty of Medicine, Mansoura University Hospitals, Elgomhuoria Street, Mansoura, Egypt

(T2DM), hypertension, dyslipidemia, sleep apnea, joint pain, and cholelithiasis (CL) [1–3]. It has been estimated that up to 45% of patients with morbid obesity develop CL [4]. A recent study concluded that the elevation of the body mass index (BMI) is a causal factor for the formation of gallstones, particularly in female patients [5].

Interestingly, bariatric procedures used to treat morbid obesity can predispose patients to CL even if they have no history of gall bladder disease. Furthermore, bariatric surgery can cause asymptomatic gallstones to become symptomatic or even induce postoperative complications of gallstones [6]. It was presumed that the rapid weight loss induced by bariatric procedures within a short period of time increases the risk of cholelithiasis [7]. The mechanism of CL following bariatric surgery can be attributed to the formation of lithogenic bile that is highly saturated with cholesterol; this bile eventually precipitates, eventually forming cholesterol stones [8].

Although it was thought that the incidence of CL after roux-en-Y gastric bypass (RYGB) was higher than after sleeve gastrectomy (SG), a prospective observational study reported no significant difference ($P = 0.57$) in the incidence of postoperative gallstone formation between the procedures (34% after RYGB and 28% after SG) [9]. While CL after RYGB is somewhat predictable, due to the malabsorptive nature of the procedure, the mechanism of CL after pure restrictive procedures is not yet fully understood.

Prophylactic laparoscopic cholecystectomy (LC) has been devised as a method for preventing CL that may develop after bariatric procedures. However, performing simultaneous cholecystectomy in the setting of the primary bariatric procedure is considered challenging and technically difficult in bariatric patients. Furthermore, performing simultaneous or subsequent cholecystectomy may add further complications to the patients and prolong the operation duration and hospital stay [10].

To avoid the unnecessary morbidities associated with prophylactic cholecystectomy performed in patients with no gall bladder disease, the postoperative use of ursodeoxycholic acid (UDCA) was advocated, as it helped prevent gallstone formation after bariatric surgery, particularly gastric bypass [11]. Other medications, such as ezetimibe, have been reported to be associated with markedly reduced rates of gallstone formation after SG [12].

This study aimed to evaluate the incidence of and risk factors for developing CL after laparoscopic sleeve gastrectomy (LSG) in a large cohort of patients with morbid obesity and to assess the role of UCDA as a prophylactic agent against CL after LSG.

Patients and methods

Study design and setting

This is a retrospective analysis of the prospectively collected data of patients with morbid obesity who underwent LSG from January 2010 to May 2015. The patients underwent surgery at the Department of General Surgery in Mansoura University Hospital and in three private hospitals in Mansoura City, Egypt (Mogamaa El-Eman, Aljazeera International Hospital, and Mansoura Military Hospital). Ethical approval was obtained from the institutional review board (IRB) of the Mansoura Faculty of Medicine. The study has been registered on researchregistery.com with the unique identifying number of *researchregistry1545.*

Inclusion/exclusion criteria

We included patients either with BMI > 40 kg/m^2 or with BMI > 35 kg/m^2 with at least 1 associated comorbidity who underwent LSG. Patients above 60 or below 18 years of age, patients with preoperative biliary disease (whether symptomatic or not), and patients who had previously undergone cholecystectomy or bariatric surgery were excluded from the study. In addition, after reviewing the patients' records, we also excluded the patients with missing demographic or follow-up data and those who did not complete 6 months of UCDA therapy postoperatively (Fig. 1).

Patient groups

All patients who met the inclusion criteria were included in the study and subdivided into two matched groups based on their surgery timeline: the first group (Group I) included 159 patients who underwent LSG between January 2010 and March 2012 and did not receive UCDA therapy, and Group II included 247 patients who underwent LSG between April 2012 and May 2015 and received 600 mg of UCDA per day for 6 months after surgery as prophylactic therapy.

Procedure

A single surgeon (the first author) performed LSG for all patients in a uniform fashion using a 38-Fr bougie. The stomach was divided along the greater curvature using the Echelon Flex™ Linear Cutter, 60 mm, and loaded with the ECR60 cartridges (Ethicon Endo-Surgery, Inc. Somerville, New Jersey, USA). The first stapler firing was 2 cm

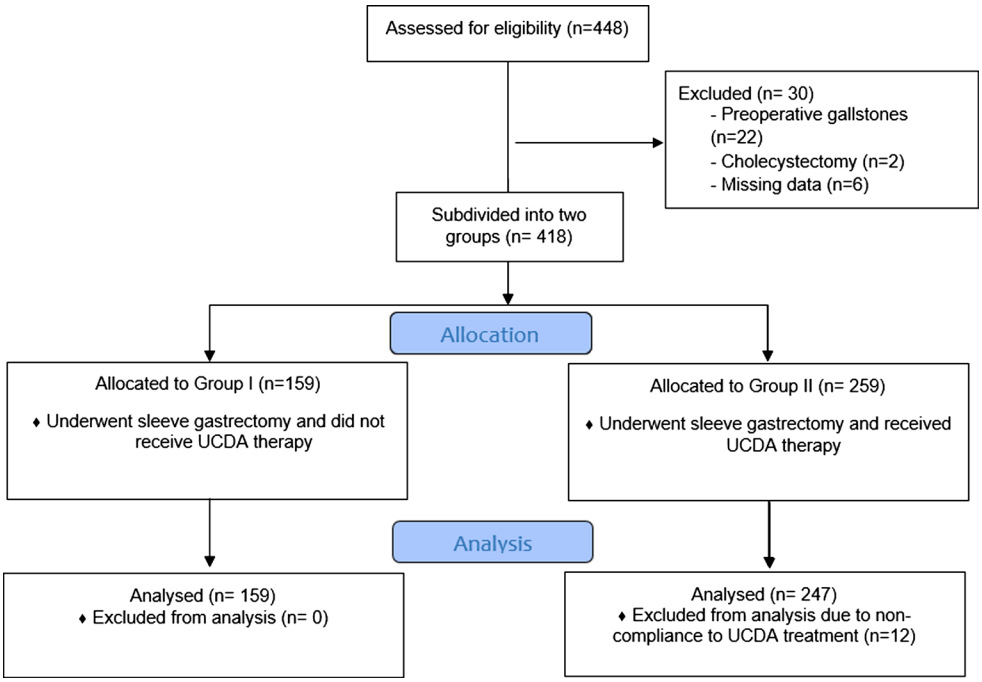

Fig. 1 Flow diagram illustrating the patient selection process

proximal to the pylorus. If concomitant hiatal hernia was present, repair of the hiatus was performed in the same operative setting.

Variable collection

The following data were extracted from the patients' records: patients' characteristics and demographic data, including age, gender, preoperative weight, and BMI; operation duration; and data on weight loss. All patients in both groups had undergone abdominal ultrasonography before the procedure and at 6 and 12 months after LSG, and the results of their sonographic examinations were retrieved from the records and reviewed to determine the incidence of gallstone formation in each group at 6 and 12 months postoperatively.

Statistical analyses

Analyses of the collected data were performed using the Scientific Package for Social Sciences (SPSS) software program, version 23, under Microsoft Windows (SPSS, Chicago, IL, USA). Categorical variables were reported as numbers and percentages. Continuous variables were described as mean ± standard deviation [standard deviation (SD)]. The Chi-squared test or Fisher's exact test was used to compare categorical variables, and Student's *t* test was used to detect differences between continuous variables. *P* values less than 0.05 were considered to indicate statistical significance. A multivariate analysis of the risk factors for CL was conducted using the binary (binomial) logistic regression test. A post hoc analysis of the primary endpoint of the study (incidence of gallstone formation in both groups at 12 months after LSG) revealed a study power of 90% when the alpha was set at 0.05.

Results

Patients' characteristics

Of the 448 patients who underwent LSG in the study period, 406 met the inclusion criteria and were included. Forty-two patients were excluded: twenty two had gallstones preoperatively, two had undergone previous cholecystectomy, six had incomplete records, and twelve did not complete 6 months of UCDA therapy after LSG, due to either intolerance of the adverse effects or a lack of compliance. Abdominal ultrasonography was performed in all included patients both preoperatively and at 6 and 12 months after LSG.

Our population included 124 (30.5%) males and 282 (69.5%) females with a mean age of 32.1 ± 9.4 (18–65) years. The mean preoperative weight for the patients was 141.7 ± 27 (102–249) kg, and the mean baseline BMI was 50.1 ± 8.3 kg/m^2. Forty-two (10.3%) patients had T2DM, and 37 (9.1%) had dyslipidemia.

The patients were subdivided into 2 groups: Group I ($n = 159$) did not receive postoperative UDCA therapy and Group II ($n = 247$) received UDCA treatment for 6 months after LSG. No significant differences between the groups were noted regarding the baseline characteristics (Table 1).

Weight loss data

Overall, for the 406 patients studied, the BMI dropped significantly to 32.7 ± 6.7 kg/m^2 at 12 months postoperatively, and the percentage of excess weight loss (%EWL) was 71.5 ± 20.4 at 1 year postoperatively. The two groups showed comparable %EWL and decreases in BMI at 6 and 12 months after LSG (Table 2).

Table 1 Baseline characteristics of the patients in the two groups

Characteristic	Group I ($n = 159$)	Group II ($n = 247$)	P value
Male/female	46/113	78/169	0.57
Age in years (mean ± SD)	30.7 ± 9.5	32.4 ± 8.6	0.06
BMI (mean ± SD)	49.7 ± 7.7	51.2 ± 9.2	0.08
Patients with T2DM	18 (11.3%)	24 (9.7%)	0.72
Patients with dyslipidemia	17 (10.7%)	20 (8.1%)	0.47

T2DM type 2 diabetes mellitus, *BMI* body mass index, *SD* standard deviation

Table 2 Weight loss data of the two groups

Characteristic	Group I ($n = 159$)	Group II ($n = 247$)	P value
BMI at 6 months	36.9 ± 8.1	37.6 ± 6.8	0.34
BMI at 12 months	32.7 ± 7.6	32.5 ± 5.6	0.69
% EWL at 6 months	56.4 ± 22.5	53.7 ± 15.5	0.15
% EWL at 12 months	71.4 ± 24.6	71.7 ± 18.08	0.88

BMI body mass index, *EWL* excess weight loss

Incidence and risk factors for CL

Gallbladder stones were detected in 7 (1.7%) of 406 patients at 6 months, and CL was detected in another 1 patient at 12 months of follow-up; therefore, 8 (2%) patients were ultimately diagnosed with CL by the end of the study. All cases were asymptomatic and were detected by abdominal ultrasonography. All patients who developed CL were in Group I (8/159; 5%); no Group II patients developed CL. There was a statistically significant difference ($P = 0.0005$) between the two groups in the incidence of CL at 12 months after LSG (Table 3).

Regarding these 8 patients, CL developed in 7 females and 1 male with a mean age of 29.8 ± 7.3 years and mean BMI of 51.2 ± 8.6 gg/m^2. A univariate analysis of the risk factors associated with the formation of gallstones revealed that preoperative dyslipidemia, a rapid loss of excess weight within the first 3 months after LSG, and not using UCDA postoperatively were the risk factors that significantly predicted CL postoperatively (Table 4).

A subsequent multivariate analysis (Table 4) of these significant risk factors for CL revealed that the most significant predisposing factor for postoperative CL was dyslipidemia [odds ratio (OR) 6.42; 95% confidence interval (CI) 1.47–28.04, $P = 0.013$], whereas the use of prophylactic UCDA therapy significantly reduced the probability of developing

Table 3 Incidence of postoperative cholelithiasis in the two compared groups

Variable	Group I ($n = 159$)	Group II ($n = 247$)	P value
Incidence of cholelithiasis at 6 months	7 (4.4%)	0	0.001
Incidence of cholelithiasis at 12 months	8 (5%)	0	0.0005

Table 4 Univariate and multivariate analyses of the risk factors for gallstone formation

Variable	Patients with CL ($n = 8$)	Patients without CL ($n = 398$)	Univariate analysis	Multivariate analysis		
			P value	Odds ratio	95% CI	P value
Age (mean ± SD)	29.8 ± 7.3	31.2 ± 9.4	0.67	–	–	–
Female gender	7 (87.5%)	275 (69%)	0.44	–	–	–
Preoperative BMI (mean ± SD)	51.2 ± 8.6	50.7 ± 8.2	0.86	–	–	–
%EWL in the first 3 months	21.3 ± 3.2	18.6 ± 2.7	**0.013**	1.11	0.96–1.28	0.147
Dyslipidaemia	3 (37.5%)	34 (8.5%)	**0.028**	6.42	1.47–28.04	**0.01**
Diabetes Mellitus	1 (12.5%)	41 (10.3)	0.58	–	–	–
Use of UCDA therapy	0 (0%)	247 (62)	**0.001**	0.03	0.002–0.18	**<0.0001**

Significant bold values represent $P < 0.05$

CL cholelithiasis, *CI* confidence interval, *BMI* body mass index, *EWL* excess weight loss, *SD* standard deviation, *UCDA* ursodeoxycholic acid

postoperative CL (OR 0.03; 95% CI 0.001–0.18, $P < 0.0001$). The overall area under the curve (AUC) for the entire model was 0.882 (95% CI 0.793–0.971) with a standard error (SE) of 0.045, indicating good discriminative capacity of the test. The significance according to the Hosmer and Lemeshow test was 0.982, indicating good fit of the data to the model.

Discussion

The rapid weight loss induced by bariatric procedures is sometimes associated with certain shortcomings, one of which is the possibility of gallbladder stone formation. A recent prospective study [13] on 1398 patients with morbid obesity found that around 8% of patients developed CL and required cholecystectomy during the first 6 months after the primary bariatric procedure. Based on the findings of several reports implying the formation of gallstones after different bariatric procedures, the guidelines for Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient (AACE/TOS/ASMBS) now recommend an ultrasound examination within the first six months as a routine examination after bariatric surgery for the detection of gallstones [14].

An estimated 10–25% of patients who lose weight through very-low-calorie dieting develop CL [15]. In malabsorptive 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 gallstones [16]. However, since LSG is a purely restrictive procedure with an intact bowel transit and entero-endocrine system, the details of the 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 the haptic branch of the left vagus nerve, which controls the gallbladder motility [17, 18]; motility dysfunction can thus supervene, resulting in stasis of bile and subsequently CL.

Gallstones that form after LSG can remain asymptomatic and become detected only during abdominal ultrasonography, or they can present clinically with the classic symptoms of CL, or even with complications as obstructive jaundice or pancreatitis. Li et al. [19] reported that LSG and RYGB had comparable incidences of symptomatic and complicated gallstone disease.

Efforts have been made to prevent the formation of gallstones 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. Raziel et al. [20] found that concomitant cholecystectomy prolonged the operation time of LSG and resulted in unnecessary complications, 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 gallstones, as Worni et al. [21] advocated.

The use of UCDA has been advocated as a prophylactic measure against postoperative CL. UDCA acts by inhibiting cholesterol secretion in bile, thereby preventing the supersaturation of bile and cholesterol stone formation [22]. Sugerman et al. [23] and Miller et al. [24] reported that daily oral administration of UCDA for 6 months was associated with a decreased rate of gallstone formation after restrictive bariatric procedures. Furthermore, a meta-analysis of randomized controlled trials [25] reported that the use of UCDA reduced the incidence of gallstone formation from 27.7% in the placebo group to 8.8% in the treatment group, concluding that UCDA can effectively prevent CL after bariatric procedures.

However, despite the encouraging results found with UCDA, it has not been widely applied as a routine prophylactic measure against CL after bariatric surgery. This is likely due to the lack of distinct criteria that define the proper indications for UCDA based on measurable risk factors and to the adverse effects of UCDA, including nausea, vomiting, and diarrhea, that affect patient compliance [16].

This study comprised 406 patients overall and was, to our knowledge, the largest series to assess the prophylactic role of UCDA after LSG. Our successful follow-up of such a large cohort of patients can be attributed to two factors: first, most of the patients included received their surgery at a private practice and were informed before the procedure that strict follow-up was mandatory to achieve the desired goal; therefore, they were highly motivated to follow the instructions of the surgeon regarding the postoperative follow-up. Second, the majority of patients were in regular contact with the operating surgeon via telephone, social media, or through clinic visits; in addition, the follow-up visits were free of charge; as such, recruiting patients for follow-up at 6 and 12 months postoperatively was not cumbersome.

We found the overall incidence of post-LSG CL to range from 2 to 5% in the group that did not receive UCDA therapy, which is close to the incidence of symptomatic gallstones after LSG (3.8 and 7.5%) reported by Li et al. [19] and Dakour Aridi et al. [8], respectively. However, our incidence was much lower than that reported by Manatsathit et al. [16], who found that symptomatic CL developed in 23% of patients after LSG, and Coupaye et al. [9], who found that 28% of patients developed gallstones after LSG. This disparity is probably due to the different baseline patient characteristics between the studies and the variable rates of EWL among patients in the first 3 months postoperatively, in addition to the different research methodologies employed, as highlighted by Manatsathit et al. [16].

At 1 year after LSG, none of the patients who received prophylactic UCDA therapy developed CL, while 5% of patients who did not receive UCDA therapy developed CL by this point. This finding strongly implies the important role of UCDA in the prevention of gallstone formation, which is in accord with the findings of other randomized controlled trials [12, 24] and a meta-analysis [25]. A recently published randomized trial [26] confirmed these data by reporting a significantly lower rate of CL after LSG in patients who received UCDA than in those who did not receive UCDA (9.1 vs. 21.4%); however, this trial was limited by a small sample size and high drop-out rates in both groups.

Almost all patients who developed gallstones in our study were females in their third decade of life with a BMI over 50 kg/m^2. Of note, a previous study found that women with a BMI exceeding 45 kg/m^2 are at a sevenfold increased risk of CL [27]. Dyslipidemia and a rapid loss of excess weight in the first 3 months were the only significant predictive factors for gallstone formation, in contrast with the findings of Li et al. [28], who reported EWL $\geq$25% as the only risk factor for postoperative gallstone formation. While the previous reports [23, 24] have suggested a blanket prescription of UCDA for 6 months after bariatric surgery to prevent CL, we think that only patients with these significant risk factors for CL (rapid EWL and dyslipidemia) should receive this 6-month therapy, as an abbreviated 3-month regimen should be sufficient for other patients without these risk factors.

This study is limited by its retrospective nature, which may impose some risk of selection bias; however, the comparable demographics of patients in both groups and the sequential grouping of patients may serve to reduce this risk. Another limitation was the lack of several important data, such as the incidence and type of adverse effects of UCDA, since its gastrointestinal side effects may be confused with the side effects of other medications prescribed to the patients.

Conclusion

The incidence of CL after LSG was not as high in this study as reported in other trials. The use of UCDA as a prophylactic agent effectively reduced the incidence of gallstone formation after LSG in morbidly obese patients. Dyslipidemia and rapid EWL in the first 3 months after LSG significantly predisposed patients to postoperative CL, which typically develops within the first 6 months after surgery.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with this study.

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