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ORIGINAL CONTRIBUTIONS

Effectiveness of Ursodeoxycholic Acid in the Prevention of Cholelithiasis After Sleeve Gastrectomy

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Abstract

Purpose The use of ursodeoxycholic acid (UDCA) to prevent gallstone formation after sleeve gastrectomy (SG) is still debated. Furthermore, no study has assessed the effectiveness of UDCA on gallstone formation after the first postoperative year. Our aim was to compare the incidence of cholelithiasis (CL) at 1 and 3 years after SG between patients treated or not treated with UDCA.

Materials and Methods From January 2008, a postoperative ultrasound monitoring was scheduled for all patients who underwent SG in our institution. Patients with a preoperative intact gallbladder who performed at least one ultrasound at 1 year after SG were included. We compared the incidence of CL between patients operated before October 2013 who did not receive UDCA and those operated from October 2013 who received UDCA 500 mg once daily for 6 months postoperatively.

Results The incidence of CL at 1 year after SG was 28% in the 46 non-treated and 3.5% in the 143 treated patients ($p < 0.001$). UDCA reduced the proportion of cholecystectomies from 11% to 1.4% ($p = 0.012$). Thus, the number of patients needed to treat to avoid a cholecystectomy was about 10. Only 2 patients (1.4%) stopped UDCA for adverse effects. No gallstone appeared at 3 postoperative years in the 61 patients who performed an ultrasound at this time.

Conclusion UDCA 500 mg once daily for 6 months postoperatively is effective and well tolerated to prevent CL at midterm after SG. We recommend UDCA treatment in all patients after SG with an intact preoperative gallbladder. However, large randomized studies are needed to establish guidelines for prevention of gallstone formation after SG.

Keywords Sleeve gastrectomy · Gallstones · Cholelithiasis · Cholecystectomy · Ursodeoxycholic acid

Introduction

Rapid weight loss in obese patients increases the risk of cholelithiasis (CL). Ursodeoxycholic acid (UDCA) is a secondary bile acid that inhibits cholesterol secretion in bile, thereby reducing cholesterol stone formation, especially in obese patients [1]. American and French recommendations advocate the use of UDCA for 6 months after Roux-en-Y gastric bypass (RYGB) to prevent gallstone formation [2, 3], but the preventive strategy after sleeve gastrectomy (SG) is not established. Indeed, the effectiveness of UDCA to reduce the incidence of CL after RYGB was demonstrated more than 20 years ago [4, 5], but few studies have explored the preventive effect of UDCA after SG with heterogeneous results [6–8]. Abdallah et al. recently showed that UDCA 600 mg per day for 6 months reduced the incidence of gallstones from 5 to 0%, 1 year after SG in a retrospective study including more than 250 Egyptian patients [8]. However, the very low incidence of postoperative CL in this cohort makes this finding difficult to transpose in other populations.

We previously reported, in a prospective study, a similar incidence of about one-third of CL after RYGB and SG in patients without preventive treatment. In addition, more than 10% of the patients with CL became symptomatic during follow-up after both procedures [9]. We thus decided to systematically prescribe UDCA after RYGB and SG and showed that 500 mg UDCA once daily for 6 months reduced the

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incidence of gallstone formation from 26% in 51 untreated patients to 2.4% in 42 treated patients after SG followed for 1 year [7]. However, these results needed to be confirmed in a larger cohort. Furthermore, to our knowledge, no study has reported the incidence of gallstone formation in treated patients more than 1 year after SG.

The aims of our study were thus (1) to compare the incidence of gallstone formation using systematic abdominal ultrasound (US) at 1 year in untreated and treated patients after SG, (2) to compare its evolution at 3 years after SG, and (3) to assess the incidence of symptomatic patients requiring cholecystectomy in untreated and treated groups.

Subjects and Methods

Subjects and Surgical Procedure

This observational study was based on our prospective database including all obese patients referred for bariatric surgery in our institution from 2004 [10]. This cohort was approved by our institution and local ethics committee; informed consent was required and obtained from all patients before any investigations. Baseline characteristics were recorded for all patients, as previously described [11]. Weight loss (WL) was expressed as absolute WL, % total weight loss (%TWL), and % excess weight loss (%EWL). Laparoscopic SG was performed using the same technique between 2008 and 2017, as previously described [11].

Investigations

A preoperative abdominal US, including the examination of the gallbladder, was performed in all patients to rule out the presence of gallstones or sludge. Cholecystectomy was performed concomitantly only in case of symptomatic CL before SG.

From January 2008, we decided to systematically detect gallstone formation by US after bariatric surgery in order to study the incidence of CL. An abdominal US, including the examination of the gallbladder, was scheduled at 6 months, 1 year, and 3 years in all patients who underwent bariatric surgery in our institution. In patients with a preoperative intact gallbladder, we started to systematically prescribe UDCA 500 mg once daily for 6 months after SG in October 2013. The prescription of UDCA was driven by clinical considerations according to the high incidence of CL after both surgeries [7]. We chose 500 mg once daily, just under the recommended 600 mg per day after RYGB, because this corresponds to the most common conditioning available in France and in order to increase the compliance, which has been reported as being low in this population [12–15].

Thus, all patients with a preoperative intact gallbladder who performed at least one US at one postoperative year (± 3 months) or who were operated for cholecystectomy in the first postoperative year were included. In these subjects, evolution of CL incidence from 6 months to 3 years (< 3.5 years) was studied. Patients with early postoperative complications or who did not take UDCA for the entire period of 6 months were excluded. The incidence of gallstones and sludge was compared between untreated subjects (from January 2008 to September 2013) and treated subjects (from October 2013) after SG.

Statistical Analyses

Data are expressed as means ± SDs for continuous variables and as numbers or percentages for categorical variables. Comparisons between groups were performed using Student's unpaired t tests or Mann–Whitney rank sum tests, as appropriate, for continuous variables, and chi-squared tests or Fisher's exact tests, as appropriate, for categorical variables. A p value < 0.05 was considered statistically significant. Multiple linear regression analysis with presence or absence of CL as a dependent variable was performed including the patient's characteristics exposed in Table 2 that have been shown to be associated with CL in the literature. Statistical analyses were performed with SigmaPlot 12.5 (Systat Software, San Jose, CA).

Results

Characteristics of the Patients

Figure 1 depicts a flow diagram of the study population. Between January 2008 and August 2017, 305 SG were performed and followed in our institution. Eighty-two (27%) patients who underwent SG were excluded because of preoperative gallbladder disease or previous cholecystectomy. Thus, 223 patients had an intact gallbladder after SG and 32 patients were secondarily excluded for various reasons, including 22 (9.9%) who did not perform any US at 1 year and 12 who did not take UDCA for 6 months (6 with severe postoperative complications, 2 with adverse effects, 4 by omission). Finally, 189 patients were included in the analysis: 46 untreated and 143 treated with UDCA (Fig. 1).

The characteristics of the subjects prior to SG are shown in Table 1. No difference was found between baseline characteristics of the treated and untreated groups. In contrast, WL at 6 months after SG, when expressed as %TWL or %EWL, was significantly higher in patients treated with UDCA than those without treatment (Table 1).

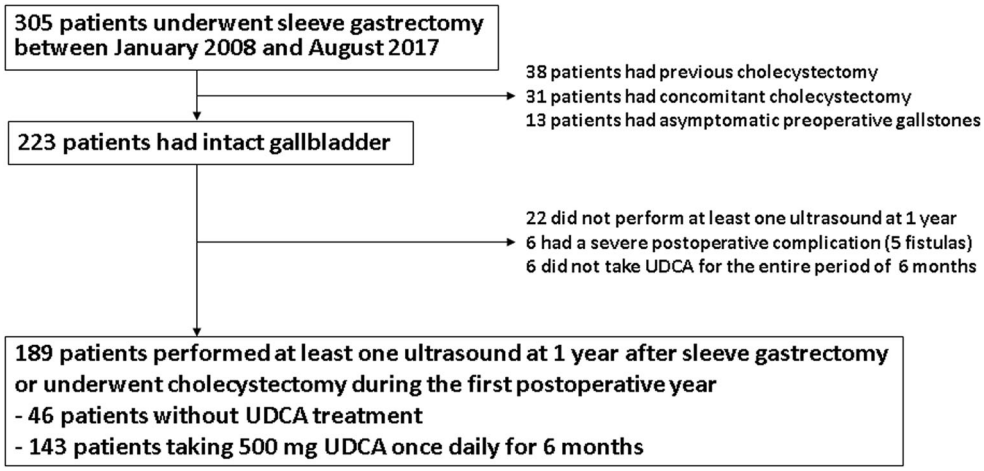

Fig. 1 Flow diagram of the study population. UDCA ursodeoxycholic acid

Comparison of the Incidence of CL After SG Between Treated and Untreated Groups

Among the 189 patients who performed an US at 1 year, 170 performed an US at 6 months and 61 at 3 years. The proportion of patients followed at 3 years was not significantly different in the treated group (63%; 42 of 67 patients operated for 3 years or more) than in the untreated group (41%; 19/46 patients, $p = 0.18$). As shown in Fig. 2, postoperative incidence of gallstones was significantly reduced from 28 to 3.5% by UDCA at 1 year after SG. About 60% of gallstones present at 1 year were already present at 6 months. No gallstone appeared at 3 years in the 61 subjects who performed an US at 1 and 3 years (Fig. 2).

As shown in Fig. 2, the percentage of patients who underwent cholecystectomy during follow-up was significantly reduced by UDCA from 11 to 1.4% ($p = 0.012$). Thus, in non-treated subjects, near 40% of patients with gallstones became symptomatic and required cholecystectomy during follow-up. The 7 cholecystectomies (5 in non-treated subjects and 2 in treated subjects) were performed for symptoms: 4 for biliary colic, 1 for acute cholecystitis, and 2 for symptomatic gallstone migration.

Predictive Factors for CL After SG in the Whole Cohort

As shown in Table 2, the only preoperative variable significantly different between subjects without or with postoperative CL was body mass index (BMI) > 50 kg/m^2 that was more frequent in subjects with CL. WL at 6 months was not significantly different between patients without or with postoperative CL, but the number of subjects taking

Table 1 Subjects' characteristics

	Without UDCA ($n = 46$)	With UDCA ($n = 143$)	p value
Men/women	6/40	24/119	0.71
Age (years)	43.2 ± 10.6	40.9 ± 11.2	0.18
Preoperative weight (kg)	122.2 ± 22.8	118.5 ± 21.2	0.39
Preoperative body mass index (kg/m^2)	45.0 ± 8.4	43.3 ± 6.1	0.18
Mean weight loss at 6 months (kg)	25.6 ± 8.1	27.6 ± 7.9	0.17
Mean % total weight loss at 6 months (%)	20.8 ± 5.9	23.3 ± 5.5	0.02
Mean % excess weight loss at 6 months (%)	51.0 ± 19.1	57.9 ± 18.0	0.04
Baseline treatment for			
Diabetes	7 (15)	15 (10)	0.55
Hypertension	13 (28)	35 (24)	0.75
Dyslipidemia	6 (13)	15 (10)	0.83
Sleep apnea syndrome	17 (37)	39 (27)	0.29

Values are means ± SDs or number of subjects (percentages). Data from subjects treated or not treated with UDCA were compared using Student's unpaired t test for continuous variables and the chi-squared test for categorical variables

UDCA ursodeoxycholic acid

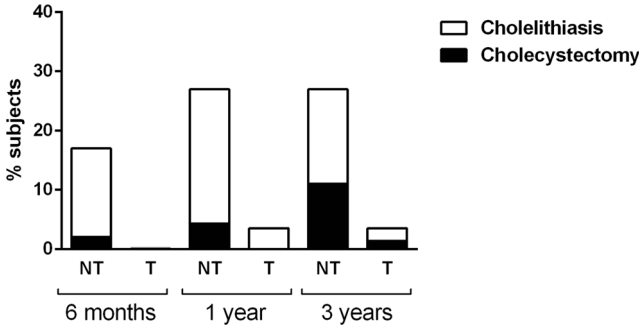

Fig. 2 Proportion of patients with cholelithiasis and cholecystectomy at 6 months, 1 year, and 3 years after sleeve gastrectomy according to treatment with ursodeoxycholic acid. NT non-treated subjects, T treated subjects

UDCA treatment was significantly lower in subjects with CL. In multivariate analysis, only absence of UDCA treatment ($p < 0.001$) was independently associated with gallstone formation after SG.

Discussion

We confirm in the present study that 500 mg UDCA once daily for 6 months is very effective to prevent gallstone formation at 1 year but also at 3 years after SG.

In our knowledge, our study is the first to assess gallstone formation in treated and untreated subjects more than 1 year after SG. In addition to our previous study [7], two studies reported incidence of CL in treated patients up to 1 year after SG. The first was an American randomized study showing a significant decrease in proportion of CL at 6 months (9% vs. 40%) in patients treated with UDCA 300 mg twice daily for 6 months, as compared with non-treated patients. However, this finding was not significant at 1 year because of numerous loss of follow-up [6]. The second study was a large Egyptian retrospective study showing a reduction of gallstone formation from 5 to 0% at 1 year with UDCA 600 mg per day for 6 months after SG [8]. In the present study, UDCA 500 mg once daily for 6 months reduced gallstone formation from 28 to 3.5% at 1 year after SG. Another important finding is that no gallstone appeared between 1 and 3 years.

In non-treated patients, rapid weight loss has been reported to be the main risk factor for gallstone formation after SG [9, 15–17]. In the present study including a majority of treated patients, only preoperative BMI > 50 kg/m^2 was associated with presence of CL, in contrast to the amount of weight loss at 6 months. Finally, in accordance with Abdallah et al. [8], we found that only absence of UDCA treatment was significantly associated with presence of CL after SG in multivariate analysis.

In addition, UDCA for 6 months reduced the number of cholecystectomies for symptoms from 11 to 1.4% after SG in our study. Thus, the number of subjects needed to treat with UDCA for 6 months after SG to avoid one cholecystectomy

Table 2 Factors associated with cholelithiasis after sleeve gastrectomy

	$n = 189$		p value
	With CL $n = 18$	Without CL $n = 171$	
Age (years)	41.2 ± 12.4	41.5 ± 11.0	0.95
Gender (men/women)	4/14	26/145	0.66
Preoperative weight (kg)	129.5 ± 29.7	118.5 ± 20.4	0.16
Preoperative body mass index (kg/m^2)	46.5 ± 11.2	43.5 ± 6.0	0.22
Preoperative body mass index > 50 kg/m^2	6 (33)	20 (12)	0.03
Baseline treatment for			
Diabetes	2 (11)	20 (12)	0.75
Hypertension	3 (17)	45 (26)	0.54
Dyslipidemia	1 (6)	20 (12)	0.69
Sleep apnea syndrome	7 (39)	48 (28)	0.49
Use of UDCA for 6 months	5 (28)	138 (81)	< 0.001
Weight loss at 6 months (kg)	29.6 ± 8.8	26.8 ± 8.3	0.19
% total weight loss at 6 months (%)	22.8 ± 4.5	22.7 ± 7.1	0.93
% excess weight loss at 6 months (%)	54.7 ± 16.1	56.5 ± 22.7	0.81

Values are means ± SDs or number of subjects (percentages)

Data from subjects with CL and without CL were compared using the Mann–Whitney rank sum test for continuous variables and the chi-squared test or Fisher's exact test, as appropriate, for categorical variables

CL cholelithiasis, *UDCA* ursodeoxycholic acid

was around 10. As in France, the cost of 6 months of UDCA 500 mg/day is about 150 euros per patient, and the cost of a cholecystectomy is currently about 2500 euros per patient; this treatment appears to be also cost-effective. Another benefit of UDCA treatment after SG is probably a reduction in the risk of acute pancreatitis since Hussan et al. recently reported a two-fold greater increase in the risk of acute pancreatitis within 6 months after SG compared with RYGB in a large American database [18].

UDCA 500 mg once daily was very well tolerated in our study: only 2 patients (1.4%) stopped treatment for side effects (allergy and nausea). The reasons for other patients who did not take UDCA were surgical complications ($n = 6$) or lack of compliance ($n = 4$). Of note, UDCA treatment is fully reimbursed by the French public healthcare system, likely favoring the high compliance observed in our study. Furthermore, patients were systematically informed on the expected risk of CL with and without treatment, which may also improve the compliance.

However, there is still a debate concerning prevention and management of CL after SG. Indeed, in previous studies, the incidence of symptomatic CL in non-treated patients after SG was heterogeneous and usually lower than in the present study: 7.5% in a large cohort including 361 patients [19], around 6% in most studies [15, 20, 21], 2% in another study [22], and near from 0% in two studies [8, 23]. As a result, most authors do not advocate prophylactic cholecystectomy, use of UDCA treatment, or routine ultrasound surveillance after SG [15, 19, 23, 24]. In our study, we found the same prevalence of about 10% of symptomatic gallstones after SG, as Altieri et al. [25] who followed 1650 patients after SG. Thus, we think as others [6, 8] that the high effectiveness and the good tolerance of low-dose UDCA after SG justify the use of UDCA treatment to prevent gallstone formation after SG.

Our study has two main limitations. First, it is not randomized and the treated and untreated groups were not followed during simultaneous time periods. However, baseline characteristics of both groups were similar and %TWL at 6 months was higher in the treated group, which enhances the effectiveness of UDCA treatment. Second, as in other studies, approximately 40% of patients were lost to follow-up at 3 years. However, the follow-up was not significantly different between treated and untreated patients and no CL occurred after the first postoperative year in subjects with US available at 3 years in our study.

In conclusion, UDCA 500 mg once daily for 6 months postoperatively is very effective in preventing CL up to 3 years after SG, is well tolerated, and appears to be cost-effective. We therefore recommend the use of UDCA in all patients with an intact preoperative gallbladder to prevent gallstone formation after SG. However, large randomized studies are needed to establish guidelines for prevention of gallstone formation after SG.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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