Gallstone Formation Prophylaxis After Gastric Restrictive Procedures for Weight Loss

A Randomized Double-Blind Placebo-Controlled Trial

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Object: To determine if a 6-month regimen of prophylactic ursodeoxycholic acid is effective in the prevention of gallstones.

Summary Background Data: Rapid weight loss after surgery for the treatment of morbid obesity is associated with a high incidence of gallstone formation.

Methods: Patients with vertical banded gastroplasty (VBG) and adjustable gastric banding (AGB) were enrolled in this study. A single-center, randomized, double-blind, prospective trial evaluated 500 mg of ursodeoxycholic acid versus placebo, beginning within 3 days after surgery and continuing for 6 months or until gallstone development, for patients with morbid obesity. Transabdominal sonography or abdominal CT scan was obtained preoperatively at 3, 6, 12, and 24 months after surgery or until gallstone formation.

Results: From March 1997 to April 2000, 262 patients were submitted to surgery. Seventy-seven patients refused to participate in the study; 43 patients with previous gallstone operation or verified gallstones preoperatively were excluded. Of 152 patients, 76 were randomized to placebo and 76 to 500 mg of ursodeoxycholic acid daily. Preoperative age, sex, weight, BMI, and postoperative weight loss were not significantly different between groups. Gallstone formation was significantly less ($P = 0.0018$, Fisher exact test) frequent with ursodeoxycholic acid than with placebo at 12 months, 3% versus 22%, and 8% versus 30% ($P = 0.0022$) at 24 months, cholecystectomy in 4.7% versus 12%, respectively ($P < 0,02$, Fisher exact test).

Conclusion: A daily dose of 500 mg of ursodeoxycholic acid for 6 months is effective prophylaxis for gallstone formation following gastric restrictive procedures.

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The development of cholesterol gallstones is associated with certain well-defined risk factors.[1–4] The risk for developing gallstones during active weight reduction is well accepted.[5–11] Between 10% and 25% of persons having lost weight through very low-calorie dieting (VLCD) develop gallstones.[12,13] In addition, 35–38% of patients with morbid obesity develop gallstones as they lose weight after bariatric surgery.[5,14,15] A routine synchronous cholecystectomy during bariatric surgery is recommended by some centers.[5,16] Concomitant cholecystectomy in bariatric surgery can be a very difficult procedure with a higher incidence of complications.[17,18] Therefore, a preventive therapy for gallstone formation is recommended in several studies. Ursodeoxycholic acid administered during VLCD seems to inhibit the development of biliary cholesterol crystals.[8] Ursodeoxycholic acid (600 mg/d) is highly effective in preventing gallstone formation in patients undergoing dietary-induced weight reduction.[19] In prospective randomized studies, the prophylactic administration of ursodeoxycholic acid has been shown to be effective in gastric bypass procedures[20–22], as well as in a small series with vertical banded gastroplasty.[23]

This randomized double-blind, prospective trial was designed to determine the safety and efficacy of 500 mg/d ursodeoxycholic acid (Ursofalk; Falk Corporation, Dortmund, Germany) versus placebo for reducing the incidence of gallstones in morbidly obese patients undergoing adjustable gastric banding and vertical banded gastroplasty surgery for morbid obesity and the effect of long-term follow-up.

MATERIALS AND METHODS

Study Design

Patients admitted to vertical banded gastroplasty (VBG) and adjustable gastric banding (AGB) for the treatment of morbid obesity were enrolled in this study. Eligible patients were over 18 years of age and had a body mass index (BMI) $\geq$ 40 kg/m^2. Patients with a BMI $\geq$ 35 kg/m^2 and comorbidities according to the guidelines of the National Institutes of Health Consensus Development Conference

Statement March 25–27, 1991, were also enrolled in the study.[24]

Exclusion criteria for the study included prior cholecystectomy, presence of gallstones, use of other investigational drugs, pregnancy or inadequate use of contraception, refusal, or inability to sign informed consent. Patients agreed to take the trial medication twice semi-daily for 6 months. They were also excluded if during the trial, they continuously used nonsteroidal antiinflammatory drugs, antihyperlipidemics such as cholestyramine or statins, or hepatotoxic drugs. Patients with no concomitant medication were claimed by the ethical committee. Transabdominal sonography or, if difficult to evaluate, abdominal CT scan was obtained preoperatively at 3, 6, 12, and 24 months after surgery or until gallstone formation. The restrictive operative procedures for morbid obesity were performed using either VBG or AGB, by 2 surgeons related to the experience in a nonrandomized fashion. The surgical technique of the procedures were published by the authors elsewhere.[25,26]

Study Protocol

The study was approved by the ethical committee of the Landesregierung Salzburg, Austria, a government institution. Informed consent was obtained from each patient before the procedure and before initiation of the study. No financial support, grant, or donation was submitted by the Falk Corporation. Investigation site was blinded from Falk Corporation, FRG to the drug codes, except in case of emergency. A single-center, randomized, double-blind, prospective trial evaluated 250 mg of ursodeoxycholic acid twice a day (total dosage of 500 mg/d) versus placebo, beginning within 3 days after surgery and continuing for 6 months or until gallstone development. Medication compliance was monitored at every visit. If an ultrasound scan or a CT scan revealed gallstones, the patient was taken off the study agent and removed from the study. Adverse experiences of the medication were tabulated as mild, moderate, or severe. Weight loss was recorded in all patients. Complications were classified by physicians as either not related, unlikely, possibly, probably, or highly probably related to the study agent.

Statistical Methods

With 76 patients in each treatment group, a difference in proportions of -0.2 (20%) is required to achieve a beta of 0.2 and a sigma of 0.52 on the basis of a two-sided test with a significance level of 0.05. Due to the possible role of concomitant medications, differences < 0.2 were judged to be of doubtful clinical importance. All data were further analyzed by use of a Compaq Pentium III personal computer using the software programs from IDV-Versuchsplanung und Datenanalyse, Gauting, Munich, F.R.G. In each group, median, standard deviation, standard error, range, upper and lower quartile, and total mean values were calculated. Univariate analyses were performed using the Wilcoxon-Mann-Whitney-U test for continuous variables and by using a χ^2 test on 2×2 table for binary variables (Fisher exact test). The P values are those computed for each comparison, and statistically significant variables are those at the 0.05 level (two-tailed). Odds ratios for categorical variables with respect to gallstone formation were obtained with 95% confidence interval. Odds ratios are significant at $P < 0.05$ if 95% confidence limits do not include the value of one.

RESULTS

From March 1997 to April 2000, 262 patients were submitted to surgery. In the study, 76 were randomized to placebo and 76 to 500 mg/d ursodeoxycholic acid. One hundred twenty-four patients completed follow-up gallbladder sonography and were eligible for inclusion in the intent-to-treat for efficacy group. One hundred thirty patients refused to participate in the study or did not meet the inclusion criteria. Ultrasonography investigation of the gallbladder was performed in all patients. Additionally, 5 patients in the placebo and 4 patients in the ursodeoxycholic group had CT scan due to inability of gallbladder exposure in the sonography, 8.3% versus 6.25. The demographics are shown in Table 1. There were no significant differences with respect to age, sex, preoperative weight, or BMI between those receiving medication or placebo in any of the patient groups. No patient was withdrawn from the study because of a serious adverse drug reaction. Patients in the placebo and treatment groups dropped out for same reasons at similar rates.

Compliance with the trial drug regimen was similar across the operated subsets and averaged 79% (60 of 76) for placebo and 84% (64 of 76) for ursodeoxycholic acid. No severe side effects from medication were observed. Mild and moderate side effects such as nausea and constipation were equivalent in both groups: 4 patients in the placebo (6.6%) and 6 patients in the treatment group (9.3%). Mild and moderate side effects did not lead to discontinuation of the study. In the group of protocol violators, 24 patients were unable to swallow the medication (85.7%).

Weight loss was equivalent between the placebo and the ursodeoxycholic acid group (Table 2). In the VBG group, patients showed a noticeably more rapid weight loss, but no significant incident development of gallstone formation was noticed.

The primary efficacy variable was the proportion of patients developing gallstones in the intent-to-treat for efficacy group. Out of this point of view, gallstone formation was significantly less ($P = 0.0018$, Fisher exact test) frequent with ursodeoxycholic acid than with placebo at 12 months: 3% versus 22%, respectively, and at 24 months, 8% versus 30% ($P = 0{,}0022$, Fisher exact test) (Table 3).

In the 24-month follow-up period, 15 cholecystectomies were performed (mean 14.9 ± 4.3 months after bariatric

TABLE 1. Demographics of the Intent-to-Treat for Efficacy Group

Characteristics	Patient Excluded From Final Analysis (Protocol Violators)	Patients Receiving Placebo	Patients Receiving Ursodesoxycholic Acid (500 mg/d)
Patients (n)	28	60	64
Sex (M/F)	5/23	9/51	12/52
Age			
Mean	33.2	36.3	34.1
Range	17–48	18–52	21–64
SD	6.3	7.2	6.3
Weight (kg)			
Mean	134	136	137
Range	89–245	91–232	94–220
SD	18.4	14.2	13.2
BMI (kg/m^2)			
Mean	45.1	44.3	43.7
Range	37–69	39–68	38–65
SD	6.2	4.3	5.7
VBG (78)	20	28	30
AGB (74)	8	32	34

BMI, body mass index; SD, standard deviation; VBG, vertical banded gastroplasty; AGB, adjustable gastric banding.

TABLE 2. Weight Loss of the Intent-to-Treat for Efficacy Group

	Placebo		Ursodesoxycholic Acid	
	VBG	AGB	VBG	AGB
Initial weight (mean ± SD)	136 ± 18	135 ± 17	134 ± 16	137 ± 17
Weight at (mean ± SD)				
3 months	110 ± 14	124 ± 17	108 ± 13	126 ± 12
6 months	81 ± 12	108 ± 11	80 ± 9	109 ± 10
12 months	78 ± 10	88 ± 12	77 ± 14	91 ± 11
24 months	85 ± 9	84 ± 13	86 ± 14	86 ± 13

surgery) in patients with symptomatic cholelithiasis: 3 patients in the ursodeoxycholic group and 12 patients in the placebo group, 12% versus 4.7%, respectively ($P < 0,02$, Fisher exact test).

DISCUSSION

Cholelithiasis is the primary expression of obesity in the hepatobiliary system. In obese subjects, the risk of developing gallstones is increased due to a higher cholesterol saturation of gallbladder bile.[8] During weight reduction with VLCD, the incidence of gallstones increases,[7] but the mechanism for gallstone formation is not completely understood, and several pathogenetic mechanisms have been suggested: increased saturation of bile, increased gall-bladder secretion of mucin and calcium, and increased presence of prostaglandins and arachidonic acid.[8,27,28] Gallstone formation is a well-recognized complication of rapid weight loss.[1–4] Therefore, a preventive therapy for gallstone formation in bariatric surgery should be the logical consequence. Synchronous cholecystectomy, medical concomitant therapy, or relatively high-fat diet could be the options. Festi et al[8,29] reported that patients with low-fat diet develop asymptomatic gallstones in 54%, and a relatively high-fat intake could prevent gallstone formation, probably by maintaining an adequate gallbladder emptying, which could counterbalance lithogenic mechanisms acting during weight loss. Gallstones (asymptomatic) developed in 6 of 11 (54.5%) ($P < 0.01$) subjects following the lower-fat diet, but in none with the higher-fat regimen. Similar findings were reported by Erlinger[6] and Gebhard et al.[30] However, patients with morbid obesity should have an excessive weight loss of 50% minimum for having a significant benefit from the operation, which is one of the criteria

TABLE 3. Gallstone Formation of the Intent-to-Treat for Efficacy Group

Characteristics	Gallstone Formation	No Gallstone Formation	Odds Ratio	95% (CI)	*P* Value (Fisher exact)
Patient excluded from final analysis (protocol violators); Patients receiving placebo (n = 16)	4/25%	12/75%		0.0727–0.5238	0.673
Patient excluded from final analysis (protocol violators); Patients receiving ursodeoxycholic acid (n = 12)	2/17%	10/83%	0.6	0.0209–0.4841	
VBG (n = 78)	11/14%	67/86%	0.9517	0.0726–0.2383	1.0
AGB (n = 74)	10/14%	64/86		0.0668–0.2345	
All patients receiving placebo (12 months)	13/22%	47/78%		0.8916–0.9962	0.0018
All patients receiving ursodeoxycholic acid (12 months)	2/3 %	62/97%	0.116	0.6580–0.8793	
All patients receiving placebo (24 months, final analysis)	18/30%	42/70%		0.1885–0.4321	0.0022
All patients receiving ursodeoxycholic acid (24 months, final analysis)	5/8 %	59/92	0.1977	0.0259–0.173	

for success of the operation.[31,32] A higher-fat regimen could lead to failure of the surgical procedure with inadequate weight loss.[34,35] In addition, it is necessary to properly study dietary and other environmental factors that may affect the gallstone formation risk. Controversy exists if the gallbladder should be removed when performing gastric restrictive procedures such as VBG and AGB. In 1985, Ameral and Thompson[59] recommended in one of the earliest papers a routine cholecystectomy at the time of bariatric surgery. In contrast to the opinions favoring routine cholecystectomy, other surgeons only recommend the removal of the gallbladder in the presence of gallstones or intraoperative evidence of disease, such as *cholesterolosis* or chronic inflammation.[14,37,38] Nevertheless, they mentioned the potential complications of cholecystectomy: intraoperative difficulties in massively obese patients, prolonged operative time, and the relatively low incidence of symptomatic gallstones. Using another approach, Deitel et al[39] favored laparoscopic cholecystectomy for cholelithiasis after VBG. Synchronous cholecystectomy in bariatric surgery can be a very difficult procedure with a higher incidence of complications, especially in the field of laparoscopic surgery.[17,18] Angrisani et al reported that laparoscopic cholecystectomy in obese patients was technically more difficult, and required a significantly longer operating time.[18]

Ursodeoxycholic acid administered during VLCD and weight loss after bariatric surgery is effective in preventing gallstone formation[19–23]

The optimum dose for gallstone prophylaxis appears to be 600 mg/d, or 4 to 5 mg/kg.[19,21] This is approximately one half of the dose used for the dissolution of cholesterol gallstones.[40,41,42] The results of the present study show an effective prophylaxis with a dosage of 500 mg/d.

Deitel and Petrov reported 13% of patients requiring cholecystectomy after VBG, but the reminder of the subjects were not screened.[14] At that time, it was believed that pure gastric restriction procedures had a lesser risk of gallstone formation than malabsorptive procedures.

Ursodeoxycholic acid has been proven to be effective in reducing the risk for gallstones after restrictive bariatric surgery, namely in vertical banded gastroplasty. A small Canadian double-blind study on 29 patients reported that 6 (43%) of the 14 subjects on placebo developed stones 3 months after the operation.[23]

The question remains of how long ursodeoxycholic acid should be taken and how effective this drug is in long-term weight loss. Randomized studies ranged from 2 months to 6 months.[9,10,11,19,21] Sugerman et al could report in their study the results of 12 months, so far the study with the longest follow-up.[21] This period may be also insufficient, because in the investigation of Deitel and Petrov, the peak incidence of symptomatic gallstones was at 16 months after surgery. This finding is strikingly similar to the peak frequency at 16 months reported by Amaral et al after gastric bypass. [5,14,]. In our study, cholecystectomy was performed in symptomatic gallstone disease an average of 14.9 ± 4.3 months after bariatric surgery.

It is generally accepted that gallstone formation is correlated with weight loss. Shiffman et al could show that bile cholesterol normalized when the weight stabilized[27] 24 months after gastric bypass. The authors of the present study could demonstrate in another prospective study on more than

1000 restrictive procedures that a weight stabilization phase is reached not before 24 months.[43] Our data from this study show a significantly reduced gallstone formation rate of 8% after 24 months compared with 30% in the placebo group.

Summarizing the available data on gallstone prevention at the time of rapid weight loss, it is clear that UDCA is effective and has few adverse drug reactions, but its use has not been very common yet.

Some authors believe that the large size of the capsules may cause problems in the small outlet of VBGs and AGBs.[14] It could be possible that the size of the capsules is one of the reasons for the high drop out rate of 28 patients (18%) in our study. However, among patients with restrictive procedures, those in the VBG group had markedly lower compliance (20 patients, 26%) than those in the AGB Group (8 patients, 10%). Since 2001, the ursodeoxycholic acid suspension is available; therefore, the problem with the drug and the small outlet should be solved.

Due to increasing frequency of extreme obesity in western countries, the demand for bariatric surgery is emphasized.[44] Morbid obesity has a high incidence of gallstone formation, and it should be routinely ruled out preoperatively with ultrasonography. Postoperatively, the gallstone formation is correlated with rapid weight loss in a high incidence.

In conclusion, a daily dose of 500 mg of ursodeoxycholic acid in divided doses semi-daily for 6 months is an effective prophylaxis for gallstone formation after gastric restrictive procedures and avoids simultaneous cholecystectomy in morbid obese patients.

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