OBES SURG
DOI 10.1007/s11695-015-1858-5

ORIGINAL CONTRIBUTIONS

Randomized, Prospective Comparison of Ursodeoxycholic Acid for the Prevention of Gallstones after Sleeve Gastrectomy

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Abstract
Background Several studies have examined the role of ursodeoxycholic acid (UDCA) for the prevention of cholelithiasis (gallstones) following rapid weight loss from restrictive diets, vertical band gastroplasty, and Roux-en-Y gastric bypass. However, to date, there have been no prospective, controlled studies examining the role of UDCA for the prevention of gallstones following sleeve gastrectomy (SG). This study was conducted to identify the effectiveness of UDCA for prevention of gallstones after SG.
Methods Following SG, eligible patients were randomized to a control group who did not receive UDCA treatment or to a group who were prescribed 300 mg UDCA twice daily for 6 months. Gallbladder ultrasounds were performed preoperatively and at 6 and 12 months postoperatively. Patients with positive findings preoperatively were excluded from the study. Compliance with UDCA was assessed.
Results Between December 2011 and April 2013, 37 patients were randomized to the UDCA treatment arm and 38 patients were randomized to no treatment. At baseline, the two groups were similar. At 6 months, the UDCA group had a statistically significant lower incidence of gallstones (p=0.032). Analysis revealed no significant difference in gallstones between the two groups at 1 year (p=0.553 and p=0.962, respectively). The overall gallstone formation rate was 29.8 %.
Conclusions The incidence of gallstones is higher than previously estimated in SG patients. UDCA significantly lowers the gallstone formation rate at 6 months postoperatively.

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

Introduction

Within the last decade, sleeve gastrectomy (SG) has emerged as a safe procedure that induces successful weight loss [1]. Rates of SG have increased, and there has been a corresponding decrease in rates of Roux-en-Y gastric bypass (RYGB), gastric banding, and vertical band gastroplasty (VBG) [2]. SG has been shown to have a lower risk of complications compared with other bariatric procedures such as RYGB and biliopancreatic diversion (BPD) [3–5]. As clinicians make recommendations for patients to undergo bariatric surgery, minimizing risks and complications is of utmost importance [4].

One common complication seen following bariatric surgery is the formation of gallstones [6–8]. Contributing factors to gallstone formation include supersaturation of bile due to rapid weight loss and mobilization of cholesterol [7]. Multiple approaches have been proposed and studied to prevent gallstones after weight loss surgery including concomitant

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Published online: 05 September 2015

cholecystectomy and prophylactic ursodeoxycholic acid (UDCA) treatment following surgery [9–14]. Studies regarding the use of UDCA for prevention of gallstones following RYGB, VBG and gastric banding have shown a decrease in the development of gallstones [11–14]. To date, the authors know of no prospective, controlled, randomized study examining the efficacy of UDCA for the prevention of gallstones following SG. Herein, we report our findings following investigation of the incidence of gallstones following SG as well as the effectiveness of UDCA for prevention.

Materials and Methods

This study was designed using a prospective, randomized, non-blinded control design. Institutional review board approval was obtained, and the study was registered with the University Hospital Medical Information Network Center Clinical Trial Registry (R000017419). The sample size for this study was calculated to be 36 patients per study arm (n=72). This was calculated using an overall significance level of 0.05 to assure an 80 % power to detect a difference between an estimated 30 % incidence for gallstone formation in the control group and a 5 % incidence in the ursodeoxycholic acid treatment group. The intent was to collect data for 1 year with an aim to have a sample size of approximately 40 patients for both groups to account for potential patient drop-out, which has been reported as high in this patient population [15]. Although this is a relatively small sample size given the high drop-out rate, it was necessary to acquire the data within a specified period of time to manage expenditures of both time and money as we received no outside funding support. For these reasons, we also elected not to use a placebo for those patients randomized to no treatment.

Patients undergoing SG beginning December 1, 2011 were recruited to participate in the study. Eligible patients were entered into the study after informed consent was obtained. All subjects underwent SG by one surgeon at three hospitals within two South Texas cities. Inclusion criteria included qualification for bariatric surgery according to the National Institutes of Health (1991) which is a body mass index (BMI) >35 kg/m^2 with two comorbidities or BMI >40 kg/m^2 with no comorbidities. All patients were required to present with no identifiable gallbladder disease and normal liver enzymes (bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase). Exclusion criteria included the presence of cholelithiasis, cholecystitis and sludge, previous cholecystectomy, history of ileostomy or ileoectomy, and/or the presence of contraindications for UDCA administration.

Preoperatively, all patients underwent serum testing of liver function and trans-abdominal ultrasounds. Gallstones were defined as the presence of strong intraluminal echoes that were gravity-dependent and with attenuated ultrasound transmission [10]. Sludge was defined as diffuse, low-amplitude, non-shadowing echoes forming a fluid-fluid level [10]. If elevated liver enzymes, stones, and/or sludge were identified preoperatively, the patient was counseled regarding the risks and benefits of concomitant cholecystectomy and excluded from the study.

At a follow-up appointment 2 weeks postoperatively, eligible patients were randomized using simple random assignment (1:1) into a control group who did not receive UDCA treatment or a group who were prescribed 300 mg UDCA twice daily for 6 months following SG.

Demographic data including age, gender, and ethnicity were obtained from the patient chart preoperatively. Height and weight were measured preoperatively and at 2 weeks, 6 weeks, 3 months, 6 months and 1 year. A Tanita^{TM} scale was used to determine percent of body fat. Percent excess weight loss (%EWL), BMI, and percent excess BMI loss (%EBMIL) were calculated by the primary investigator at each visit. Percent EWL was calculated using an ideal body weight equivalent to a BMI of 25 kg/m^2.

Gallbladder complaints included but were not limited to epigastric pain, nausea, chest pain beneath the sternum, fever, and abdominal fullness. Repeat ultrasounds of the gallbladder were ordered on all patients at the 6-month and 1-year follow-up appointments. Ultrasounds were reviewed by an independent radiologist. UDCA compliance was self-reported at the 6-month follow-up appointment and included three levels: poor (0–2 times per week), moderate (3–5 times per week), and good (6–7 times per week).

Statistical Analysis

Demographic data such as age, gender, and ethnicity were summarized as mean and standard deviation unless otherwise stated. Gallbladder formation following the UDCA regimen was assessed using the using a non-parametric Mann-Whitney U test, which has been shown to have greater efficiency for analysis of data with non-normal distributions. The Kruskal-Wallis one-way analysis of variance (ANOVA) testing was used to evaluate cases of gallstone or sludge formation based on three levels of UDCA compliance. Kruskal-Wallis one-way ANOVA testing is used for accuracy when comparing two or more samples that are independent and that may have different sample sizes. A p value of 0.05 was used to determine statistical significance. All statistics were calculated using mean the Statistical Package for Social Sciences (version 22.0, SPSS, Chicago, IL, USA).

Results

Seventy-five patients who underwent SG between December 2011 and April 2013, met the inclusion criteria, agreed to

participate in the study, and signed informed consent forms. The treatment group, prescribed 300 mg of UDCA twice daily, included 37 patients. The control group who received no medication consisted of 38 patients. A total of 57 patients underwent ultrasound evaluations postoperatively at 6 months and/or 1 year. Demographic data for these patients is reported in Table 1.

At a mean of 6.94 months, 25 patients from the control group and 19 patients from the treatment group underwent follow-up ultrasounds of the gallbladder (Fig. 1). Some patients also stopped attending follow-up appointments. Ten patients (10/25=40 %) in the control group developed gallstones, and in the treatment group, only two patients (2/19 or 11 %) developed gallstones. Patients randomized to the UDCA treatment group had a statistically significant (p=.032) reduction in the formation of gallstones. No cases of gallstones were diagnosed prior to the scheduled ultrasound based on reported symptoms.

Ultrasounds at the 1-year visit were not ordered for patients who had positive findings for gallstones at the 6-month ultrasound but were ordered for all remaining patients (see Fig. 1). At the 1-year visit, 14 patients from the control group and 22 patients from the treatment group underwent ultrasound evaluation. Three patients (3/14=21.4 %) from the control group and two patients from the treatment group (2/22=9.1 %) had developed gallstones between 6 and 12 months following SG. Data from the 1-year ultrasounds was analyzed using a Mann-Whitney U test to examine the difference in development of gallstones between the two groups. Despite the difference in percentage rates, results at 1 year did not meet the criteria for statistical significance (p=0.553).

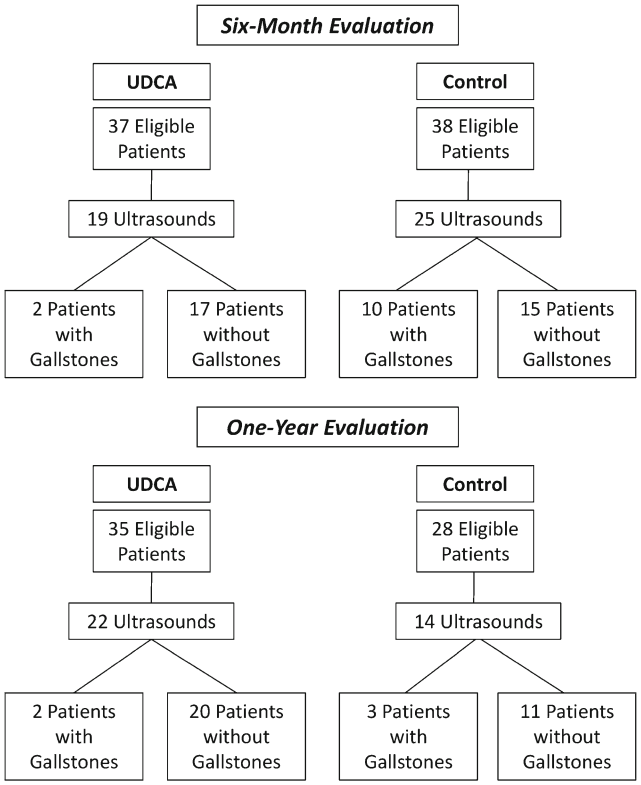

Fig. 1 Subject attrition diagrams: 6-month and 1-year ultrasound evaluations

Table 1 Demographics and preoperative height, weight, body mass index (BMI), and percent body fat of subjects

Variable	UDCA group[a]	Control group[b]	Total
	n=28	n=29	n=57
Gender			
Male	7	10	17
Female	21	19	40
Ethnicity			
Caucasian	20	26	46
African American	1	1	2
Asian	0	0	0
Native American	0	0	0
Hispanic	7	2	9
Age	43.7±11.2	46.0±12.1	44.9±11.6
Height (cm)	169.5±9.8	169.5±10.6	169.5±10.1
Weight (kg)	123.2±20.7	124.2±20.7	124.1±21.1
BMI (kg/m^2)	42.7±5.2	43.1±5.1	42.9±5.1
Percent body fat	44.1±9.5[c]	41.3±10.1[d]	42.7±9.8[e]

[a] The treatment group consisted of patients prescribed 300 mg of UDCA twice daily

[b] The control group consisted of patients who did not receive UDCA following SG

[c] n=23

[d] n=24

[e] n=47

When ultrasound data were combined, 57 patients (76 %) from our total sample (n=75) obtained either the 6-month and/or 1-year ultrasound examinations. Again, using the Mann-Whitney U test for examination of the overall results, there was a statistically significant difference in the development of gallstones between the control group (13) and the treatment group (4) (p=0.013).

Further analysis revealed no significant difference in gallstone formation in subjects who completed 6-month follow-up ultrasounds or 1-year ultrasounds based on %EWL (p= 0.614). There was also no significant difference in gallstone or sludge formation based on gender in 6-month or 1-year data (p=0.546 and p=1.00). There also was no significant difference in gallstone or sludge formation based on ethnicity, Caucasians versus non-Caucasians, among those who completed 6-month ultrasounds (p=0.932) or 1-year ultrasounds (p=0.899).

Of the 17 patients who developed gallstones, 7 patients underwent cholecystectomy. All patients were screened and continue to be screened for symptoms related to gallstones. If

they are found to have consistent symptoms, cholecystectomy is recommended. All patients were instructed that if they developed abdominal pain to call our office immediately.

A post hoc analysis was conducted to determine gallstone or sludge formation on the basis of UDCA compliance. A non-parametric Kruskal-Wallis one-way ANOVA test was conducted based on three levels of UDCA compliance: poor, moderate, or good. From those patients who completed the 6-month ultrasounds, neither gallstones nor sludge were reported in zero of 11 patients who reported good compliance. Two out of three patients who reported moderate compliance developed gallstones or sludge, and two out of five who reported poor compliance developed gallstones or sludge. A significant difference in the mean number of patients who reported gallstones or sludge was found based on level of compliance with UDCA prescription (p=0.025). Patients were not prescribed UDCA after the first 6 months.

Discussion

To our knowledge, no prospective, controlled studies investigating gallstone prevention with UDCA in SG patients have been published to date. Cholelithiasis and sludge formation occur after bariatric procedures secondary to rapid weight loss and cholesterol supersaturation in bile, which increase the risk of gallstone formation [7]. After RYGB, gallbladder dysmotility due to division of the hepatic branch of the vagus nerve and absence of duodenum-induced gallbladder emptying may also increase the risk for gallstone development [7]. RYGB results in reduction of cholecystokinin levels due to food stream diversion. This may favor bile stasis, incomplete gallbladder contraction, and gallstone formation [16]. Gastric bypass is known to have major effects on the serum lipid profile, which may also alter cholesterol saturation [17, 18]. Another possible reason for gallstone development involves the effects of very low calorie and low fat diets on biliary lipid composition. Biliary lipid composition is dependent on the balance of hepatic uptake of cholesterol. Diminished dietary intake of cholesterol and changes in hepatic cholesterol synthesis and bile acid secretion may, therefore, result in gallstone formation, although this effect is not universal [19–21]. The diets that have been associated with gallstone formation in most clinical studies did not have enough fat or protein to maximally stimulate gallbladder contraction. This may create bile stasis which, as mentioned previously, favors gallstone formation [22–24].

In this study, 17 out of 57 patients (30 %) who underwent either the 6-month or 1-year follow-up ultrasounds developed gallstones, which is comparable to the rates seen in RYGB patients [7, 8, 25, 26]. Various studies have shown the rate of asymptomatic gallstone formation ranging from approximately 20 to 52.8 % in a range of 6 to 12 months after gastric bypass [7, 8, 25, 26]. The rate of gallstone formation was not expected to be as high in SG patients as lower rates have been reported [9], and lower rates may be seen in clinical experience. Many patients had asymptomatic gallstones that would not have been discovered clinically if an ultrasound had not been ordered. Contrary to previous studies which report %EWL to be the only predictor of gallstone development in bariatric patients, %EWL was not a significant predictor of gallstone/sludge formation in the current study [7, 8, 25, 26].

Unfortunately, 18 patients did not return for either of the follow-up ultrasound evaluations in the current study, and several did not return for follow-up visits. We believe the high loss to follow-up may be attributed to several factors: (1) many of the patients live outside of the area and returning for follow-up visits and/or ultrasound evaluations represents a substantial burden in terms of both time and money; (2) many of the patients were not symptomatic and were therefore not compelled to undergo the inconvenience of additional visits; (3) finally, the added costs to patients in the treatment arm for the UDCA prescriptions may have been another cause for non-compliance. Maintaining high retention rates in research studies involving bariatric patients is a documented challenge [15]. Honoraria and travel reimbursements have been shown to be effective retention strategies [15]; however, because we received no outside funding, we were unable to provide any financial support for the time, effort, and costs associated with multiple follow-up visits and prescriptions. If patients visited a specific center, they were given their ultrasound evaluations at no cost; however, if they were unable to visit that specific center (located near our offices), they had to pay for the evaluations themselves and forward us the results for evaluation. We believe some patients may have been unable or unwilling to incur these expenses.

Traditional risk factors for cholecystopathy may not be predictive of gallstone/sludge formation in patients after bariatric surgery [27, 28]. This was true in the current study; age, gender, and ethnicity did not predict gallstone formation. However, the small sample size and skewed distribution of gender and ethnicity may have affected the results. This sample was predominately female, Caucasian patients with a mean age of 43.3±11.8 years.

The greatest weaknesses of this study were the relatively small sample size and the incomplete data due to loss of patients to follow-up. Another weakness was the self-reporting of UDCA compliance by patients. Pill counts were initially planned with poor results as patients did not bring in pills or staff was not available to complete the task. There was a moderate level of self-reported UDCA non-compliance. Higher UDCA compliance was significantly related to lower rates of gallstone development. Of note, no patients in the control group developed sludge only compared to two patients in the treatment group, which may also show a protective effect of UDCA preventing full progression to gallstone development.

Following the positive results of this study, we now routinely prescribe a postoperative course of prophylactic UDCA (300 mg twice daily for 6 months) for both GS and RYGB patients who have a gallbladder.

Conclusions

UDCA was associated with significantly lower rates of gallstone development at 6 months. When 6-month and 1-year data sets were combined, UDCA was again associated with significantly lower rates of gallstone development. Compliance with UDCA prescription regimens was associated with lower rates of gallstone/sludge formation. Larger, well-designed studies are needed to establish a standard guideline for prevention of gallstones in SG patients.

Conflict of Interest The authors declare that they have no competing interests.

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

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

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article (does not apply).

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