

Role of Ursodeoxycholic Acid in Prophylaxis Against Development of Gall Stones Post-Bariatric Surgery

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Abstract

Background: The formation of cholesterol gallstones is linked to rapid weight loss. As a result, symptomatic gallstone disease is common in patients with morbid obesity who undergo bariatric surgery.

Aim of Study: Assessment of the efficacy of ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery.

Patients and Methods: During this study, 60 obese patients were enrolled, after consenting each of them and divided into two groups; group A received 250mg of ursodeoxycholic acid (Ursofalk®, 250mg, Hard Capsules, Mina Pharm, Egypt) twice a day (total dosage of 500mg/d) within 3 days after surgery and continuing for 6 months or until gallstone development and group B received placebo of ursodeoxycholic acid twice a day for 6 months within 3 days after surgery and continuing for 6 months or until gallstone development.

Results: Number of cases who developed gall stones were statistically significant lower 3 (10.0%) in study compared with control group 27 (90.0%) with no significant differences between both groups as regard presenting symptoms which indicates that ursodeoxycholic acid is effective in prophylaxis against development of post-operative gall stones. There was no statistically significant relation between excess weight loss level and type of bariatric operation and increasing risk of development of gall stones.

Conclusion: Ursodeoxycholic acid is effective in prevention of postoperative symptomatic gallstone disease in obese patients undergoing bariatric surgery. There is no relation between excess weight loss level or type of bariatric operation and increasing risk of development of gall stones.

Key Words: Ursodeoxycholic acid – Gall stones – Bariatric surgery.

Introduction

OBESITY and overweight are both characterised by an unhealthy or excessive fat buildup that puts one's health at risk. Overweight is defined as a

body mass index (BMI) of over 25kg/m², and obesity as over 30kg/m² [1].

According to the global burden of illness, the problem has reached epidemic proportions, with over 4 million people per year dying as a result of being overweight or obese in 2017 [2].

In every continent, with the exception of sub-Saharan Africa and Asia, more people are obese than underweight today, which is one side of the double burden of malnutrition. Overweight and obesity, once thought to be a problem exclusively in high-income nations, are now sharply increasing in low- and middle-income nations, especially in metropolitan areas [3].

In this context, bariatric surgery continues to be the main therapeutic mode for a high rate of sustainable weight loss. However, morbid obesity, along with bariatric surgery and the subsequent weight loss, is associated with an increased risk for the development of gallstones and the risk is higher during a period of acute weight loss [4].

Ursodeoxycholic acid (UDCA) is a secondary bile acid that was associated with prevention of gallstone formation in obese patients undergoing acute weight loss. During weight loss, it is believed to decrease bile lithogenicity [5].

In fact, UDCA reduces the intestinal absorption and biliary secretion of cholesterol. The main advantages regarding administration of UDCA are its short-term duration and safety [6].

Currently, there is no consensus regarding gallstone prevention in obese patients undergoing bariatric procedures. Prophylactic cholecystectomy has been proposed as a preventive strategy given that it has not been associated with increased morbidity or mortality [7].

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Even though concomitant cholecystectomy at laparoscopic RYGB is much more challenging, it has been proven feasible and safe, especially in cases of ultrasonography-confirmed gallbladder pathology. In contrast, cholecystectomy performed after RYGB has been associated with increased incidence of adverse events [8].

However, the cost-effectiveness of this option remains debatable. Consequently, UDCA remains an attractive alternative during rapid weight loss [9].

Patients and Methods

This prospective randomized, placebo-controlled, double-blind clinical trial was conducted on 60 patients at General Surgery Department, Faculty of Medicine, Ain Shams University Maternity Hospitals from February 2022 until February 2023.

Inclusion criteria:

Patients aged 18 years with body mass index 35kg/m^2 with co-morbidity or 40kg/m^2 with nono co-morbidity and patients with an intact gallbladder and scheduled to undergo any type of bariatric surgeries as Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) or mini gastric bypass were enrolled.

Exclusion criteria:

Patients with existence of symptomatic gallstone disease prior to bariatric surgery, prior bariatric surgery, prior gallbladder surgery, inflammatory bowel disease, small intestine and liver disorders which may interfere with enterohepatic circulation of bile salts and hypersensitivity to ingredients of UDCA or placebo. An intake of UDCA within the last 30 days before screening, use of other investigational drugs, pregnancy or inadequate use of contraception, continuous using of non-steroidal anti-inflammatory drugs, anti-hyperlipidemias such as cholestyramine or statins, or hepatotoxic drugs and refusal or inability to sign informed consent were excluded.

Sampling method:

A systemic random sampling was used. Patients were randomized using sequentially sealed opaque envelope method into three groups each including (30) patients, to ensure that every patient fulfilling the inclusion criteria had the same chance of participating in this study, randomization was guided by a table of random members by a computer-based program (using www.randomization.com).

Ethical considerations:

Patient information and informed consent: Before being enrolled into the study, the patient consented to participate after the nature, scope and possible consequences of the clinical study had been explained in a form understandable to them.

Confidentiality:

Only the patient initials were recorded in the case report form, and when the patient's name appeared on any other document, it was kept in a secure place by the investigators. The investigators maintained a personal patient identification list (Patient initials with the corresponding patient names) to enable record to be identified.

Protocol approval:

Before the beginning of the study and any accordance with the local regulation followed, the protocol and all the corresponding documents were declared for ethical and research approval by the council of general surgery department, Ain Shams University.

Concerning safety and efficacy:

No evidence of harmful effects of ursodeoxycholic acid.

Study procedures:

All patients were subjected to complete history taking, clinical examination and laboratory investigations as complete blood picture, liver and kidney function tests, coagulation profile, thyroid profile, hepatic viral markers, total and direct bilirubin, alkaline phosphatase enzyme, gamma-glutamyl transferase and ECG.

Radiological investigations as pelvi-abdominal ultrasound, chest X-ray and abdominal erect X-ray.

Patients were randomly assigned in a 1: 1 ratio to either; group A "study group" received 250mg of ursodeoxycholic acid (Ursofalk®, 250mg, Hard Capsules, Mina Pharm, Egypt) twice a day (total dosage of 500mg/d) within 3 days after surgery and continuing for 6 months or until gallstone development and group B "control group" received placebo of ursodeoxycholic acid twice a day for 6 months within 3 days after surgery and continuing for 6 months or until gallstone development.

Randomization was done prior to surgery with a computer software program (ALEA AMC, Amsterdam, the Netherlands, and version 2.2) and implemented into a web-based application.

Randomization was stratified for the presence of gallstones (yes versus no) and type of surgery and performed by using random block.

Allocation and concealment was done by using of sealed opaque envelopes that were given to a third party (nurse) who assigned the patients to study groups. Each patient was invited to pull out an envelope. According to the number inside the envelope, patient was allocated to either group 1 or group 2 according to a computer-generated random list.

Blinding: The tablets were enclosed in an opaque packages labeled according to a computer-generated random list. Each patient was invited to pull out a package. The tablets were administered anonymously with coding by a nurse with no knowledge of the codes. Final assessment was performed by another colleague who had no information about the groups. Patients and assessor were blinded to the groups.

Data was collected and pelvi-abdominal ultrasound was done before discharge and follow-up visits were scheduled every 4 weeks for 6 months.

Medication compliance was monitored at every visit. When 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 and weight loss was recorded in all patients.

Primary outcome of current study was symptomatic gallstone disease within 6 months after bariatric surgery, defined as admission or hospital visit for symptomatic gallstone disease.

Secondary outcomes were the development of gallstones/sludge on ultrasound at 6 months in the gallstone-negative group at baseline, presence of gallstones/sludge on ultrasound at 6 months, number of cholecystectomies, side effects of UDCA, therapy compliance, patient satisfaction and costs.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean ± standard deviation. Also qualitative variables were presented as number and percentages.



Fig. (1): Female patient, 28 years old, no medical or surgical history, BMI 47kg/m², laparoscopic sleeve gastrectomy, postoperative from day 3, take ursodeoxycholic acid, follow-up by ultrasound discovered no gall bladder stone.



Fig. (2): Male patient 40 years old, no medical or surgical history, BMI 48.9kg/m², laparoscopic gastrectomy, postoperative from day 3, take placebo (vitamins), during follow-up she had biliary colic, ultrasound discovered gall bladder stone, laparoscopic cholecystectomy was done

Results

This table shows no statistically significant difference between groups according to demographic about age and sex, with *p*-value (*p*>0.05) (Table 1).

Table (1): Comparison between study group and control group according to demographic data.

Demographic data	Study Group (n=30)	Control Group (n=30)	Test value	<i>p</i> value
Age (years):				
Mean±SD	31.60±9.84	32.80±8.99	<i>t</i> : -0.493	0.624
Range	18-52	19-49		
Age Group:				
>25-45 years	19 (63.3%)	21 (70.0%)	<i>x</i> ² : 0.386	0.825
>45 years	3 (10.0%)	3 (10.0%)		
18-25 years	8 (26.7%)	6 (20.0%)		
Sex:				
Female	21 (70.0%)	24 (80.0%)	<i>x</i> ² : 0.800	0.371
Male	9 (30.0%)	6 (20.0%)		

This table shows no statistically significant difference between groups according to anthropometric measurement about initial weight and BMI, with p -value ($p>0.05$) (Table 2).

Table (2): Comparison between study group and control group according to anthropometric measurements.

Anthropometric measurement	Study Group (n=30)	Control Group (n=30)	Test value	p -value
<i>Initial Weight (kg):</i>				
Mean \pm SD	164.03 \pm 25.10	158.20 \pm 28.21	t : 0.846	0.401
Range	77-182	79-181		
<i>BMI [wt/ (ht)²]:</i>				
Mean \pm SD	47.10 \pm 7.25	47.90 \pm 6.39	t : 0.453	0.652
Range	36-64	36-66		
<i>BMI Level:</i>				
BMI <40	3 (10.0%)	1 (3.3%)	χ^2 : 1.697	0.428
BMI >50	7 (23.3%)	5 (16.7%)		
BMI 40-50	20 (66.7%)	24 (80.0%)		

There is no statistically significant difference between groups according to excess weight loss% after 6 months, with p -value ($p>0.05$) (Table 3).

Table (3): Comparison between study group and control group according to excess weight loss% after 6 months.

	Study Group (n=30)	Control Group (n=30)	Test value	p -value
<i>Excess weight loss% after 6 months:</i>				
Mean \pm SD	54.73 \pm 13.23	54.57 \pm 12.98	t : 0.049	0.961
Range	17-66	16-69		
<i>Excess weight loss Level:</i>				
<50%	4 (13.3%)	6 (20.0%)	χ^2 : 1.518	0.468
>60%	16 (53.3%)	18 (60.0%)		
50-60%	10 (33.3%)	6 (20.0%)		

Regarding the gall stones, developed gall stones in 3 (10%) patients of study group in 12 (40%) patients of control group. There was a statistically significant difference between the two groups with p -value ($p=0.007$), this indicates that the ursodeoxycholic acid in prophylaxis against development of gall stones post-operative (Table 4).

Table (4): Comparison between study group and control group according to gall stones.

Gall Stones	Study Group (n=30)	Control Group (n=30)	Test value	p -value
Developed gall stones	3 (10.0%)	12 (40.0%)	7.200	0.007*
Hadn't developed gall stones	27 (90.0%)	18 (60.0%)		

Discussion

In agreement with us, Salman et al. [10] found that UDCA 500mg once daily for 12 months following LSG is effective in lowering gallstone development at one year. The frequency of cholecystectomies decreased from 7 to 2.3% with UDCA treatment. The independent preoperative variables substantially linked to stone development are high BMI and dyslipidemia. Data are shown for 128 patients in the Control group and 130 patients in the UDCA group. During the first year following surgery, 41 (32.0%) and 11 (8.5%) patients in the UDCA group, respectively, and the Control group, developed gall stones. Three patients (2.3%) in the UDCA group and nine (7.0%) in the control group required a cholecystectomy. On multivariate analysis, higher BMI, dyslipidemia, and lacking UDCA prophylaxis were the independent factors significantly associated with stone development. Also, stone development was associated with higher weight loss after 6 and 12 months.

According to Mechanick et al. [11], Roux-en-Y gastric bypass patients should take UDCA for 6 months to avoid the development of gallstones (RYGB).

Adams et al. [12] earlier randomised trial, which supported our findings, found that the overall gallstone development rate was around 30%. The authors randomly assigned 75 patients to receive either no treatment or a daily dose of 600mg of UDCA. At 6 months, UDCA decreased gallstone incidence, however after 1 year.

Another study conducted by Coupaye et al. [13] compared the effect of UDCA 500mg once daily for 6 months in patients subjected to RYGB and SG. It proved effective in both procedures after 1 year.

A retrospective Egyptian study conducted by Abdallah et al. [14] compared those who received UCDA for 6 months after LSG with those who did not. Gallstone formation was found in 5% of untreated patients and none of those under UCDA. Another study conducted by Coupaye et al. [15] reported similar conclusions.

A more recent study conducted by Sen et al. [16] found that 23% of the patients developed cholelithiasis after LSG. UDCA prophylaxis with 500 mg daily reduced the frequency to 10.5% compared to 37.5% in untreated patients.

A single prospective randomized study conducted by Nabil et al. [17] confirmed the effectiveness

of UDCA in preventing gallstone formation up to 12 months postoperatively.

Against our study Abdallah et al. [14], Tsirlina et al. [18], Li et al [19] and Melmer et al. [20] reported that rapid weight loss has been reported as the most important risk factor for gallstone formation after SG.

Machado et al. [21] agreed with us and reported that patients who did not use UDCA showed a 24.4-fold greater probability of developing cholelithiasis. A community-based clinical trial was conducted. A total of 137 patients were included in the study; 69 were treated with UDCA, starting 30 days after the surgery, at a dose of 150mg twice daily (300mg/day) over a period of 5 consecutive months (GROUP A), and 68 were control patients (GROUP B). Of the 69 patients who used UDCA, only one patient developed cholelithiasis (1 %), whereas 18 controls (26%) formed gallstones.

Lee et al. [22] evaluated the efficacy and safety of ursodeoxycholic acid (UDCA) in preventing gallstone formation after gastrectomy in patients with gastric cancer. They were in line with us and reported that administration of UDCA for 12 months significantly reduced the incidence of gallstones after gastrectomy for gastric cancer. These findings suggest that UDCA administration prevents gallstone formation after gastrectomy in patients with gastric cancer. The proportion of patients developing gallstones within 12 months after gastrectomy was 8 of 151 (5.3%) in the 300-mg group, 7 of 164 (4.3%) in the 600-mg group, and 25 of 150 (16.7%) in the placebo group. Compared with the placebo group, odds ratios for gallstone formation were 0.27 (95% CI, 0.12-0.62; $p=.002$) in the 300-mg group and 0.20 (95% CI, 0.08-0.50; $p<.001$) in the 600-mg group. No significant adverse drug reactions were detected among the enrolled patients.

Worobetz et al. [23] corresponded with us and published a double-blind study in which one group received a placebo and the other group UDCA to study the prevention of gallstone development in 29 morbidly obese patients who underwent bariatric surgery. Six of the 14 placebo-treated patients (43%) developed gallstones. None of the 10 patients treated with UDCA formed gallstones.

In clinical practice, it has been observed that during rapid weight loss the formation of gallstones begins to occur after only 4 weeks. Desbeaux et al. [24], Taylor et al. [25] and Stokes et al. [26] were in line with us and reported that prophylactic treatment with UDCA at 600mg/day in the six-

month period after bariatric surgery has been advocated by researchers in preventing gallstones or biliary sludge, factors responsible for developing severe complications such as biliary pancreatitis.

In addition to the already reported benefits, Tolman and Dalpiaz [27] and Higuera-de la Tijera and Servin-Caamano [28] reported that it has been highlighted in the literature that UDCA, a hydrophilic bile acid, may block the progression of non-hepatic fatty liver disease to non-alcoholic steatohepatitis by protecting hepatocytes through handling bile salts in mitochondrial trauma, anti-apoptotic signaling pathway, anti-inflammatory, antioxidant, immunomodulatory function, anti-fibrotic properties, and is being widely used in liver diseases.

Shiffman et al. [29] agreed with us and reported that ursodeoxycholic acid, 600mg/d, is highly effective in preventing gallstone formation in patients having dietary-induced weight reduction. Gallstones developed in 28% of patients receiving placebo, in 8% of patients treated with 300mg/d of ursodeoxycholic acid, in 3% of patients treated with 600mg/d of ursodeoxycholic acid, and in 2% of patients treated with 1200mg/d of ursodeoxycholic acid. The differences between patients receiving placebo and patients receiving ursodeoxycholic acid were statistically significant. The percentage of ursodeoxycholic acid in bile increased stepwise with increasing doses of ursodeoxycholic acid.

Conclusion:

Ursodeoxycholic acid is effective in prevention of postoperative symptomatic gallstone disease in obese patients undergoing bariatric surgery. There is no relation between excess weight loss level or type of bariatric operation and increasing risk of development of gall stones.

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Conflict of interest: None declared.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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دور حمض الأورسوديوكسيكوليك أسيد في الوقاية من تطور حصوات المرارة بعد جراحة السمنة

المقدمة: في الواقع، يقلل حمض أورثوديوكسيكوليك من امتصاص الأمعاء وإفراز الكوليسترول الصفراوي. المزايا الرئيسية فيما يتعلق بإعطاء حمض أورثوديوكسيكوليك هي مدته قصيرة المدى وسلامته. حالياً، لا يوجد إجماع فيما يتعلق بالوقاية من حصوات المرارة لدى مرضى السمنة الذين يخضعون لإجراءات علاج البدانة. تم اقتراح استئصال المرارة الوقائي كإستراتيجية وقائية نظراً لأنه لم يرتبط بزيادة معدلات المراضة أو الوفيات.

الهدف من الدراسة: هدفت هذه الدراسة إلى تقييم فعالية حمض أورسوديوكسيكوليك للوقاية من مرض حصوة المرارة المصحوب بأعراض بعد جراحة علاج البدانة.

طرق الدراسة: خلال هذه الدراسة، تم تسجيل ٦٠ مريضاً يعانون من السمنة المفرطة، بعد موافقة كل منهم وتم تقسيمهم إلى مجموعتين. تلقت المجموعة أ ٢٥٠ مجم من حمض أورسوديوكسيكوليك (أورسوفالك، ٢٥٠ مجم، كبسولات صلبة، يما فارم، مصر) مرتين يومياً (جرعة إجمالية ٥٠٠ مجم / د) خلال ٣ أيام بعد الجراحة وتستمر لمدة ٦ أشهر أو حتى تكون حصوة المرارة وتجمعها، تلقت المجموعة ب الدواء الوهمي من حمض أورسوديوكسيكوليك مرتين يومياً لمدة ٦ أشهر في غضون ٣ أيام بعد الجراحة واستمر لمدة ٦ أشهر أو حتى تكون حصوة المرارة.

النتائج: فيما يتعلق بحدوث حصوات المرارة، كشفت دراستنا أن عدد الحالات التي ظهرت فيما حصوات المرارة كانت ذات دلالة إحصائية أقل ٣ (١٠٠٪) في مجموعة الدراسة مقارنة مع مجموعة التحكم ٢٧ (٩٠٠٪) مع عدم وجود فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بالأعراض مثل غثيان. أو القيء أو آلام في البطن مما يشير إلى أن حمض أورسوديوكسيكوليك فعال في الوقاية من تكون حصوات المرارة بعد الجراحة.

الإستنتاج: في حالة عدم وجود موانع، ينصح باستخدام حمض أورسوديوكسيكوليك في الوقاية من تكون حصوات المرارة المصحوب بأعراض ما بعد الجراحة في المرضى الذين يعانون من السمنة المفرطة والذين يخضعون لجراحات السمنة لعلاج البدانة. يمكن للدراسة الحالية أن تثقل المعرفة وتلقى بعض الضوء على الدراسات المستقبلية بأحجام عينات أكبر، ودرجات السمنة والمتابعة الغذائية لإعادة تقييم نتائج دراستنا وتأكيد استنتاجنا.