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Ursodeoxycholic acid for prevention of gallstone disease after laparoscopic sleeve gastrectomy: an Atlantic Canada perspective

Intekhab Hossain[1] · Jane Brodie[1] · Erin O'Brien[1] · Katherine Tedman-Aucoin[2] · Diana Lawlor[2] · Raleen Murphy[1] · Laurie Twells[3] · David Pace[1] · Bradley Evans[1] · James Ellsmere[2]

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Abstract

Background Prophylactic ursodeoxycholic acid (UDCA) may be beneficial in reducing gallstone disease after bariatric surgery. The American Society for Metabolic and Bariatric Surgery (ASMBS) 2019 guidelines recommend a 6-month course of UDCA for patients undergoing laparoscopic sleeve gastrectomy (LSG). This has not been adopted broadly. This study intends to assess the effect of routine UDCA administration following LSG on symptomatic gallstone disease.

Methods We performed a retrospective chart review of patients who underwent LSG, between 2009 and 2019, at two tertiary care centers in Atlantic Canada. At one center, UDCA 250 mg oral twice daily was routinely prescribed following LSG for 6 months to patients with an intact gallbladder. At the other center, UDCA was not prescribed. Primary and secondary outcomes were cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) rates. Compliance with and side effects of UDCA therapy were analyzed.

Results A total of 751 patients were included in the study. Patients who had prior cholecystectomy or were lost to follow up were excluded. After exclusion criteria were applied, 461 patients were included for analysis: 303 in the UDCA group and 158 in the group who did not receive UDCA. Cholecystectomy rate was not significantly associated with UDCA administration, however there was a trend towards less cholecystectomy in patients who received UDCA (8.3% vs. 13.9%, $p=0.056$). ERCP rate was significantly lower in patients who received UDCA (0.3% vs 2.5%, $p=0.031$). Rate of gallstone disease requiring intervention, either cholecystectomy or ERCP, was significantly decreased in patients who received UDCA (8.9% vs 15.8%, $p=0.022$). The most common barriers to compliance with UDCA were cost (45.4%) and nausea (18.1%).

Conclusion This is the first study to demonstrate lower rates of ERCP in patients receiving routine UDCA following LSG. Our findings support the ASMBS 2019 guidelines for administering UDCA after LSG for preventing gallstone disease.

Keywords Laparoscopic sleeve gastrectomy · Ursodeoxycholic acid · Gallstones

Obesity and rapid weight loss, factors common in the bariatric surgery population, are well-known risk factors for gallstone formation and associated complications including biliary colic, cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis. UDCA is a secondary bile acid that decreases bile saturation and increases gallbladder emptying. Post-operative UDCA administration has been demonstrated to reduce incidence of gallstone disease in bariatric surgery patients. Most studies to date assessed the benefits of UDCA for Roux-en-Y gastric bypass (RYGB) patients, showing a lower incidence of gallstone formation [1]. Despite multiple studies evaluating the effects of UDCA on gallstone disease in LSG patients, equipoise remains [2–4]. Additionally, clinical endpoints regarding gallstone disease are inconsistent with some studies using imaging evidence of gallstone development and others using symptomatic gallstone disease [3, 5].

The 2019 ASMBS guidelines recommend UDCA 500 mg once daily for 6 months in patients with an intact gallbladder

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✉ Bradley Evans
b.evans@mun.ca

[1] Department of Surgery, Memorial University, 300 Prince Phillip Drive, St. John's, NL A1B 3V6, Canada

[2] Department of Surgery, Dalhousie University, Halifax, NS, Canada

[3] Faculty of Medicine, Memorial University, St. John's, NL, Canada

and no documented presence of gallstones or sludge undergoing LSG. This recommendation is based upon a prospective 1-year study in which most of the benefit was seen in patients undergoing RYGB. Thus, it is not widely adopted in the LSG group.

The purpose of this study was to assess the effect of routine UDCA administration following LSG on incidence of symptomatic gallstone disease requiring intervention; specifically, cholecystectomy and ERCP rates. Compliance rates of UDCA were also assessed.

Methods

We performed a retrospective cohort study including 751 patients that underwent LSG at two Atlantic Canadian tertiary referral centres in different health authorities, between June 1, 2009 and August 31, 2019. Patients were identified through the bariatric registry at each health authority. At both centres, LSG is the most common primary bariatric operation. At one centre UDCA 250 mg oral twice daily is routinely prescribed for six months following LSG. At the other centre UDCA is not prescribed following LSG.

Patients who underwent LSG at either center during the defined time-period were initially included. Past surgical history was recorded and patients who underwent cholecystectomy prior to LSG were removed from the study group. Patients lost to follow up (4.55%) were removed from the study group.

Using the electronic medical record at each institution, data collection included patient characteristics, laboratory investigations and abdominal ultrasound (US) and/ or computed tomography (CT) imaging reports, cholecystectomy and ERCP reports, UDCA prescription compliance, and bariatric surgery clinic notes including patient Body Mass Index (BMI). Compliance was defined as UDCA prescription being filled in the prescription monitoring system. Abdominal imaging for gallstones were not routinely performed preoperatively or postoperatively.

Primary outcome was cholecystectomy rate following LSG during the study period. Secondary outcomes included ERCP rate following LSG and overall rate of gallstone disease requiring intervention following LSG.

Approval was obtained from the provincial Health Research Ethics boards.

Statistical analysis

Data were entered into SPSS version 28 for analysis. Student's t-test and analysis of variance were used for continuous variables. Chi-square or Fisher's exact test were performed for nominal variables, as appropriate. Univariate analysis was performed to identify factors associated with outcomes of interest. Logistic regression was utilized to identify factors independently associated with outcomes of interest, using a significance level of 0.05.

Results

Data were available for a total of 751 patients who underwent LSG at the two sites during the study period. This included 550 patients at the site routinely administering UDCA and 201 patients at the site not administering UDCA. At the site not administering UDCA routine data collection for bariatric patients stopped in 2014. Once exclusion criteria were applied, a total of 461 patients were included in the study, 303 in the group routinely receiving UDCA and 158 in the group not receiving UDCA (Fig. 1). Baseline patient characteristics, with respect to gender and BMI prior to LSG, were similar between the two groups. Mean age was significantly different between the groups (45.8 vs 43.0, $p=0.002$) (Table 1).

Cholecystectomy rate was not significantly associated with UDCA administration using univariate or multivariate analysis. A trend towards less cholecystectomy in the UDCA group was observed (8.3% vs. 13.9%, $p=0.056$) in univariate analysis (Table 2).

UDCA therapy was associated with lower ERCP rates (0.3% vs 2.5%, $p=0.031$) in univariate analysis (Table 3). In multivariate analysis, patients with increased age and higher preoperative BMI were more likely to undergo ERCP. Patients taking UDCA after LSG had reduced rates of ERCP (Table 4). All ERCPs were performed for complications of gallstones. No patients with cholecystectomy prior to LSG underwent ERCP following LSG in either group.

Overall event rate of gallstone disease requiring intervention, as either cholecystectomy or ERCP, was associated with UDCA administration (8.6% vs 15.8%, $p=0.022$). Number needed to treat was 14.

Of the patients offered UDCA, 3.6% were not compliant (11/303). The most cited reason for non-compliance was cost associated with lack of insurance coverage (45.4%). The remainder did not comply due to no reason stated (36.4%) or nausea (18.1%).

Discussion

This study demonstrates a reduction in symptomatic gallstone disease with routine UDCA administration for six months following LSG. A trend towards less cholecystectomy in the UDCA group was noted but this was not statistically significant (8.3% vs. 13.9%, $p=0.056$). A significant decrease in ERCP rate was noted (0.3% vs 2.5%, $p=0.031$) in patients taking UDCA after LSG, previously unreported

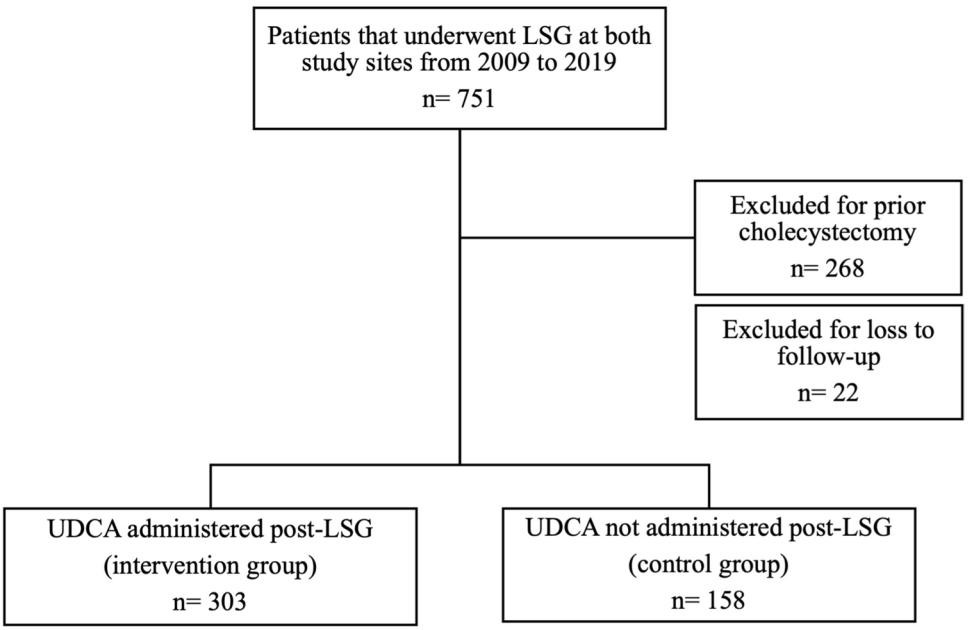

Fig. 1 Study population flow diagram

Table 1 Patient characteristics

	UDCA group, n = 303	No UDCA group, n = 158	*p* value
Age, mean (± SD)	45.8 (8.8)	43.0 (9.9)	0.002
Gender, n (%)			0.282
Male	81 (26.7)	36 (22.6)	
Female	222 (73.3)	123 (77.4)	
Pre-op BMI, mean (± SD)	47.9 (7.5)	49.2 (6.7)	0.082

in literature. The overall rate of gallstone disease requiring intervention, cholecystectomy or ERCP, was significantly lower in the UDCA group (8.6% vs 15.8%, p = 0.022). Recently published literature supports our findings and has also shown reduced cholecystectomy rates with UDCA therapy [1, 6]. Reports have shown 1.9–2.5% incidence of complicated gallstone disease, such as common bile duct stones or pancreatitis after bariatric surgery without UDCA, which is also in keeping with our findings [7, 8]. An increased risk of complicated gallstone disease has been demonstrated in patients who have undergone LSG, which is a rate that is 50 times that of the general population [5, 9]. Our demonstration of decreased ERCP rates with UDCA administration after LSG is an important finding given the costs and possible complications of ERCP including post-ERCP pancreatitis, biliary sepsis, and perforation.

The 2019 ASMBS guidelines recommend the use of UDCA 500 mg once daily for six months after LSG in patients who have an asymptomatic gallbladder [10]. This is based on a one-year study which demonstrated that 25.5% of patients undergoing LSG formed gallstones and this decreased to 5.7% with UDCA therapy ($p = 0.005$) [11]. While the incidence of gallstones was reduced, follow up was limited and the number of patients enrolled was low. A subgroup analysis in a meta-analysis of 8 studies assessing UDCA treated versus non-treated patients after LSG supported a benefit to UDCA 500 mg once daily in reducing gallstone formation ($p = 0.0002$). There is evidence that UDCA 250 mg twice a day is superior to 500 mg once a day at preventing gallstone disease 1-year post RYGB

Table 2 Univariate analysis of potential confounding variables associated with laparoscopic cholecystectomy following LSG

	Laparoscopic cholecystectomy, n = 47	No laparoscopic cholecystectomy, n = 414	*p* value
Age, mean (± SD)	42.6 (10.1)	45.1 (9.1)	0.070
Female gender—n (%)	40 (85.1)	368 (88.9)	0.102
Pre-op BMI, mean (± SD)	48.1 (6.8)	48.4 (7.3)	0.785
UDCA—n (%)			0.056
Yes	25 (8.3)	278 (91.7)	
No	22 (13.9)	136 (86.1)	

Table 3 Univariate analysis of potential confounding variables associated with ERCP following LSG

	ERCP, n = 5	No ERCP, n = 456	*p* value
Age, mean (± SD)	51.4 (12.3)	44.8 (9.1)	0.059
Female gender—n (%)	4 (80.0)	424 (93.0)	0.549
Pre-op BMI, mean (± SD)	50.5 (6.8)	48.3 (7.3)	0.434
UDCA—n (%)			
Yes	1 (0.3)	302 (99.7)	0.031
No	4 (2.5)	154 (97.5)	

Table 4 Binary logistic regression model for ERCP following LSG

	Odds ratio	95% Confidence interval	*p* Value
Age	1.176	1.045—1.324	0.007
Pre-op BMI	1.195	1.031—1.385	0.018
Taking UDCA	0.059	0.005—0.726	0.027

[11]. As well, another study reported increased compliance in patients receiving twice a day compared to once-a-day UDCA dosing [12]. Decreased compliance was primarily due to symptoms of nausea and vomiting with the higher single dosing. Given this discordance in UDCA effect and compliance, our intervention study site adopted a 250 mg twice daily UDCA therapy post-LSG. Our data adds evidence to the literature that UDCA 250 mg twice a day for 6 months after LSG decreases incidence of ERCP and overall number of interventions for gallstone disease.

A systematic review of UDCA and adverse effects demonstrated that it is generally well tolerated with diarrhea being the most frequent side effect in up to 9% of patients [13]. Adverse events and drug toxicity are rare, and the medication has been safely used in pregnancy [14]. There is a paucity of literature on compliance with UDCA in bariatric surgery patients. One study reported only 28% of patients were compliant with UDCA while undergoing weight loss but no reasoning for poor compliance was assessed [15]. Another study on UDCA following LSG examined self-reported compliance but relied on patients bringing in medication or having staff available to count remaining medication which was problematic and compounded by attrition [3]. In the current study, compliance was very high with 96.5% of patients being compliant with UDCA prescriptions. The difference between our documented compliance rate compared to previous work may be related to non-standardized definitions of compliance. The most common barrier to compliance was cost, as the medication was not covered by provincial health care insurance.

There is inconsistency in the literature as to the relevant clinical outcome after UDCA, be it cholelithiasis or symptomatic disease [3, 5]. A randomized control study demonstrated a significant difference in gallstone development at 6 months after UDCA (40% non-treated vs 11% treatment group, $p = 0.032$), but did not detect symptomatic cholelithiasis and suffered from high attrition [3]. While our study did not allow us to assess all cases of symptomatic cholelithiasis or cases of asymptomatic gallstones, it included all cases significant enough to undergo intervention, either cholecystectomy or ERCP or both.

Limitations

This study has some limitations. Firstly, it was a retrospective cohort study, and thus was limited to the available collected data. It inherently lacks the advantages of a randomized control study such as matching of known and unknown confounding factors. Secondly, the study population did not receive routine pre- and post-operative biliary imaging and only evaluated those undergoing treatment for symptomatic disease. Data for other interventions for symptomatic gallstone disease such as percutaneous cholecystostomy tube or transhepatic cholangiogram were not captured. Lastly, the study had a relatively small sample size from two small volume bariatric centers. This may have been a factor in the study's finding of a trend towards, rather than a significant difference in UDCA therapy's effect on lower cholecystectomy rate.

Conclusion

This study demonstrates routine UDCA therapy following LSG is associated with reduced ERCP rates, previously unreported in literature. It also demonstrates UDCA administration following LSG is associated with a reduced overall rate of gallstone disease requiring intervention, as either cholecystectomy or ERCP. Our findings support the 2019 American Society for Metabolic and Bariatric Surgery (ASMBS) guidelines for administering prophylactic UDCA after LSG for preventing gallstone disease.

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Declarations

Disclosure Dr. Intekhab Hossain, Dr. Jane Brodie, Erin O'Brien, Dr. Katherine Tedman-Aucoin, Diana Lawlor, Raleen Murphy, Dr. Laurie Twells, Dr. David Pace, Dr. James Ellsmere, and Dr. Bradley Evans have no conflicts of interest or financial ties to disclose.

References

1. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Chatedaki C, Sioka E, Zacharoulis D (2017) Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: an updated systematic review and meta-analysis. Obes Surg. https://doi.org/10.1007/s11695-017-2924-y
2. Sakran N, Dar R, Assalia A, Neeman Z, Farraj M, Sherf-Dagan S, Gralnek I, Hazzan R, Mokary SE, Nevo-Aboody H, Dola T, Kaplan U, Hershko D (2020) The use of ursolit for gallstone prophylaxis following bariatric surgery: a randomized-controlled trial. Updates Surg. https://doi.org/10.1007/s13304-020-00850-2
3. Adams LB, Chang C, Pope J, Kim Y, Liu P, Yates A (2016) Randomized, prospective comparison of ursodeoxycholic acid for the prevention of gallstones after sleeve gastrectomy. Obes Surg. https://doi.org/10.1007/s11695-015-1858-5
4. Talha A, Abdelbaki T, Farouk A, Hasouna E, Azzam E, Shehata G (2020) Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial. Surg Endosc. https://doi.org/10.1007/s00464-019-07323-7
5. Boerlage TC, Haal S, Maurits de Brauw L, Acherman YI, Bruin S, van de Laar AW, Moes DE, van Wagensveld BA, de Vris CE, van Veen R, Schouten R, Dijkgraff MG, Fockens P, Gerdes VE, Voermans RP (2017) Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery: study protocol for a randomized controlled trial (UPGRADE trial). BMC Gastroenterol. https://doi.org/10.1186/s12876-017-0674-x
6. Salman MA, Salman A, Mohamed US, Hussein AM, Ameen MA, Omar HS, Elewa A, Hamdy A, Elias AA, Tourky M, Helal A, Mahmoud AA, Aljarad F, Moustafa A, Shaaban HE, Nashaat A, Husseun AM, Omar T, Balamoun H (2022) Ursodeoxycholic acid for the prevention of gall stones after laparoscopic sleeve gastrectomy: a prospective controlled study. Surg Endosc. https://doi.org/10.1007/s00464-021-08980-3
7. Li VK, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P (2009) Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. Surg Endosc. https://doi.org/10.1007/s00464-008-0204-6
8. Csendes A, Csendes P, Orellana O, Cuneo N, Figueroa M, Martinez G (2019) Patients remain at high risk of gallstones development late (10 y) after sleeve gastrectomy? Surg Laparosc Endosc Percutan Tech. https://doi.org/10.1097/SLE.0000000000000700
9. Sioka E, Zacharoulis D, Zachari E, Papamargaritis D, Pinaka O, Katsogridaki G, Tzovaras G (2014) Complicated gallstones after laparoscopic sleeve gastrectomy. J Obes. https://doi.org/10.1155/2014/468203
10. Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, Kushner RF, Lindquist R, Pessah-Pollack R, Seger J, Urman RD, Adams S, Cleek JB, Correa R, Figaro MK, Flanders K, Grams J, Hurley DL, Kothari S, Seger MV, Still CD (2020) Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Surgery for Obesity and Related Diseases. https://doi.org/10.1016/j.soard.2019.10.025
11. Coupaye M, Calabrese D, Sami O, Msika S, Ledoux S (2017) Evaluation of incidence of cholelithiasis after bariatric surgery in subjects treated or not treated with ursodeoxycholic acid. Surg Obes Relat Dis. https://doi.org/10.1016/j.soard.2016.11.022
12. Sugerman H, Brewer WH, Shiffman ML, Brolin RE, Fobi MA, Linner HJ, MacDonald KG, MacGregor AM, Martin LF, Oram-Smith JC (1995) A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. Am J Surg. https://doi.org/10.1016/s0002-9610(99)80115-9
13. Hempfling W, Dilger K, Beuers U (2003) Systematic review: ursodeoxycholic acid–adverse effects and drug interactions. Aliment Pharmacol Ther. https://doi.org/10.1046/j.1365-2036.2003.01792.x
14. Paumgartner G, Beuers U (2004) Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. Clin Liver Dis. https://doi.org/10.1016/S1089-3261(03)00135-1
15. Wudel LJ, Wright JK, Debelak JP, Allos TM, Shyr Y, Chapman WC (2002) Prevention of gallstone formation in morbidly obese patients undergoing rapid weight loss: results of a randomized controlled pilot study. J Surg Res. https://doi.org/10.1006/jsre.2001.6322