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SYSTEMATIC REVIEW

Ursodeoxycholic acid for the prevention of gallstone and subsequent cholecystectomy following gastric surgery: A systematic review and meta-analysis

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Abstract

Background/Purpose: Patients who undergo gastric surgery are prone to form postsurgical gallstones. Debates still exist about the need for prevention and the selection of preventive methods. No studies had been reported comparing the efficacy of prophylactic ursodeoxycholic acid (UDCA) and prophylactic cholecystectomy (PC) for lowering postsurgical gallstone formation and subsequent cholecystectomy (SC) in patients who have undergone gastric surgery.

Methods: We did a systematic review to identify studies from PUBMED, EMBASE, and the Cochrane database through 30 June 2020. We conducted direct and indirect comparisons of each prophylaxis using conventional and network meta-analysis. Studies with patients who have no history of cholecystectomy and who have not had preoperative gallstone were included.

Results: The excellent preventive effects of PC and UDCA were demonstrated for gallstone formation (odds ratio [OR] 0.05, [95% CI 0.01, 0.22] and 0.20, [95% CI 0.16, 0.24], respectively) and the need for SC (OR 0.10, [95% CI 0.02, 0.57] and OR 0.22, [95% CI 0.14, 0.35], respectively) than control group. The UDCA group showed a tendency to generate more gallstones (OR 3.74, [95% CI 0.88, 15.82]) and a greater need for SC (OR 2.19, [95% CI 0.47-10.14]) than did the PC group without statistical significance.

Conclusions: Prophylaxis for gallstone formation may be needed for patients who undergo gastric surgery to reduce troublesome morbidities. Prophylactic UDCA seems to be a reasonable preventive method for postsurgical gallstone formation to ensure clinical benefit while reducing the burden of subsequent cholecystectomy for the patient as compared to a PC.

KEYWORDS
bariatric surgery, cholecystectomy, gastrectomy, gastric cancer, ursodeoxycholic acid

1 | INTRODUCTION

Patients who had received gastric surgery were prone to form gallstone afterwards, with a reported incidence that varied from 5.0% to 63.1%.[1] Cholelithiasis is known to occur mainly because of the rapid weight loss that follows bariatric surgery, as well as gallbladder hypomotility secondary to vagal nerve resection during gastrectomy, decreased cholecystokinin secretion, and nonphysiological gastrointestinal reconstruction following gastrectomy for gastric cancer.[2-8] Three percent to 8.2% of these patients suffered from symptomatic biliary problems,[9,10] and most needed subsequent invasive management, including cholecystectomy.

One of the available prophylactic methods for gallstone formation following gastric surgery is prophylactic cholecystectomy (PC). Researchers are still debating the rationale for a PC. The major advantages of a PC are that it serves as the most obvious solution to problems originating in the gallbladder, and the surgeon may be able to avoid the technical difficulties of performing a subsequent cholecystectomy (SC) in postgastric surgical patients.[11,12] However, the cost-effectiveness does not seem to be reasonable because the incidence of cases that needed SC is very rare, and a standard laparoscopic cholecystectomy is often feasible regardless of other concerns, given the improvements in surgical skills and technical equipment.[11,13-15] Therefore, there appears to be a clear demand for a clinically persuasive, less-invasive prophylaxis, other than a PC, for patients needing gastric surgery.

Various studies have reported on the prophylactic effectiveness of UDCA to reduce gallstone formation following gastric surgery in obese patients.[16-19] Recently, a randomized controlled study (RCT) reported that the results of UDCA administration significantly reduced the incidence of gallstones following gastrectomy for gastric cancer.[20] UDCA is not burdensome to use for prophylactic purpose because it is a well-known, long-term use drug with few severe adverse events. But the significant reduction of SC by using of prophylactic UDCA as the definite clinical benefit has not been sufficiently proven to date.

In this meta-analysis study, we evaluate the efficacy of the prophylactic use of UDCA for lowering gallstone formation and SC in patients who had undergone gastric surgery by comparing them to patients who had undergone a PC, as well as to patients without any prophylaxis.

2 | METHODS

2.1 | Search strategy and study selection

This systematic review and meta-analysis conforms to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA).[21] We conducted a search of PUBMED, EMBASE, and the Cochrane Library from their inception to 30 June 2020. The search terms used in this search were ursodeoxycholic acid, UDCA, ursodiol, bariatric surgery, bariatric procedures, Roux-en-Y gastric bypass, RYGB, sleeve gastrectomy, SG, gastroplasty, gastrectomy, postoperative, surgery, surgical, resection, resected, cholecystectomy, laparoscopic cholecystectomy, prophylactic cholecystectomy, postcholecystectomy, cholelithiasis, gallbladder disease, gallbladder stone, gallstone, black pigment stone, and cholesterol stone. Supplementary Table S1 shows our search strategies in each database.

We considered comparison studies that report the outcomes of prophylactic UDCA or a PC in the prevention of gallstone formation or SC following gastric surgery in adult humans. We included studies of patients who have no history of cholecystectomy and who had not had gallstones prior to surgery. Full-text articles in English were available.

2.2 | Data identification and extraction

Two independent reviewers (JHC and IRC) performed the data extraction. They gathered full-text articles of potentially relevant studies and data on study characteristics, patient features, prophylactic strategies, and the results of all included studies were independently extracted. We accounted for the number of gallstones formed and any SC subsequent to gastric surgery, according to each study's prophylactic strategies. Any discrepancies between the two investigators were resolved following discussion with the corresponding author (SHL).

2.3 | Study outcome and statistical analysis

The outcomes of interest in this study were the rate of gallstone formation and SC after gastric surgery. These outcomes were binary, and the relative treatment effects were reported as odds ratios with 95% confidence intervals (95% CI). We conducted conventional meta-analysis for outcomes of interest for prophylactic methods. We used the random-effects methods with an estimate of heterogeneity from the Mantel–Haenszel model to pool the odds ratios (ORs) from the included studies. We also planned to conduct frequentist network meta-analyses using the random effects model for outcomes of interest to evaluate the clinical implications of UDCA as compared to a PC because there are no studies that directly compare both strategies.

We performed subgroup analysis according to study design or indications for surgery to assess the robustness of the results. We used the I^2 statistic to assess the heterogeneity of the efficacy, and we used the cut-off value

of 50% to find substantial heterogeneity in the results of significant differences between the included studies. All statistical meta-analyses were performed using the "meta" and "netmeta" packages of R version 3.5.2 (R Core Team, Vienna, Austria).[22,23]

2.4 | Quality assessment and publication bias assessment

We assessed the risk of bias in the included RCTs by using the Cochrane collaboration tool for randomized trials for each outcome.[24] The Newcastle-Ottawa Quality Assessment Scale was used as an assessment tool to evaluate the non-RCTs.[25] The scale's range varies from zero to nine stars, and studies with a score equal to or higher than five stars were considered to have an adequate methodological quality to be included. The certainty of evidence assessment of each comparison was evaluated according to the guideline from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[16,26] Two reviewers (JHC, IRC) rated the studies independently and they reached the final decision of quality by consensus.

We used a funnel plot with visual inspection and the Egger regression asymmetry test to assess potential publication bias by using the "metabias" function for conventional meta-analysis and comparison-adjusted funnel plots for network meta-analysis.[27,28]

3 | RESULTS

3.1 | Study selection and patient demographics

Supplementary Figure S1 presents this study's flowchart of search results, done in accordance with the PRISMA. Our database search identified 7452 articles in PUBMED, 20 629 in EMBASE, and 1521 in the Cochrane library. After duplicate removal (n = 22 652), we further excluded those studies that are unrelated to this study topic (n = 7442), non-English articles (n = 3892) and unoriginal articles (n = 3251). Among the 8067 original articles, we further excluded studies that were not related to the prophylaxis or prevention of postgastric surgical cholelithiasis or subsequent cholecystectomy (n = 7516). Of the remaining 551 articles, we further excluded studies (n = 519) unfit for this study topic after review of the abstract and the full text. We further excluded 11 studies after meticulous and detailed review of the full text. Finally, we included 11 RCTs and 10 non-RCTs, for a total of 5365 patients, in this meta-analysis. Table 1 summarizes the detailed information of each included study.[3,17-20,29-44]

3.2 | Prophylaxis for gallstone formation and subsequent cholecystectomy after gastric surgery

3.2.1 | Efficacy of the prophylactic usage of UDCA

We observed a significant preventive effect of UDCA for gallstone formation (6.0%; 172 of 2855) in comparison to the control group (25.7%; 380 of 1481) (Figure 1A, Odds ratio 0.20 [95% CI 0.16, 0.24]) and a similar efficacy was revealed in subgroup analysis done according to the study design (for non-RCTs, OR 0.18 [95% CI 0.11, 0.28]; For RCT, OR 0.20 [95% CI 0.16, 0.26]) and subgroup analysis according to surgical indication (For gastric cancer, OR 0.25 [95% CI, 0.13-0.49]; for obesity, OR 0.19 [95% CI 0.15, 0.24]) (Supplementary Figure S2A,B).

The need for SC (3.46%, 60 of 1732 in UDCA group; 8.53%, 77 of 902 in control group) was significantly lower among patients who had been treated with UDCA (Figure 1B, OR 0.22 [0.14, 0.35]), and a similar efficacy was showed in subgroup analysis in accordance with the study design (for non-RCTs, OR 0.23 [95% CI 0.13, 0.40]; for RCT, OR 0.19 [95% CI 0.07, 0.49]), as well as a subgroup analysis according to surgical indication (for gastric cancer, OR 0.05 [95% CI, 0.00-0.96]; for obesity, OR 0.23 [95% CI 0.15, 0.36]) (Supplementary Figure S3A,B).

3.2.2 | Efficacy of prophylactic cholecystectomy

We observed a significant preventive effect of a PC (0%; 0 of 244) for gallstone formation in comparison to the control group (17.6%; 82 of 466) (Figure 1A, Odds ratio (OR) 0.05 [95% CI 0.01, 0.22]), and similar efficacy was revealed in subgroup analysis, according to surgical indication (for gastric cancer, OR 0.08 [95% CI, 0.02-0.42]; for obesity, OR 0.02 [95% CI 0.00, 0.22]) (Supplementary Figure S2D). A subgroup analysis of non-RCTs showed consistent OR results (OR 0.04 [95% CI 0.01, 0.22]), but subgroup analysis of RCTs that include only one RCT showed no statistically significant OR results (OR 0.10 [95% CI 0.01, 1.98]) (Supplementary Figure S2C).

The need for SC (0%, 0 of 244 in PC group; 11.2%, 52 of 466 in control group) was significantly lower among patients who had been treated with a PC (Figure 1B, OR 0.10 [0.02, 0.57]), and similar efficacy was shown in subgroup analysis, according to the surgical indication (for gastric cancer, OR 0.05 [95% CI, 0.00-0.96]; for obesity, OR 0.23 [95% CI 0.15, 0.36]) (Supplementary Figure S3D). Subgroup analysis of non-RCTs showed consistent OR results (OR 0.08 [95% CI 0.01, 0.59]), but subgroup analysis of RCTs that only included

TABLE 1 Characteristics of the studies that were finally included in the systematic review and meta-analysis

Study, year	Country	Type of study	Surgery	Indication	Intervention	Patients, n		Female, n		Mean age, years		Gallstone formation, n		Biliary problem, n		Symptomatic biliary problem, n		Subsequent cholecystectomy, n	
						E	C	E	C	E	C	E	C	E	C	E	C	E	C
Lee,[20] 2020	Republic of Korea	RCT	Gastrectomy	Malignancy	UDCA 600 mg or 300 mg for 1 y	315	150	106	48	56	56	15	25	15	25	0	4	0	4
Pizza,[39] 2020	Italy	RCT	Gastric bypass surgery	Obesity	UDCA 600 mg for 6 mo	95	95	62	59	35.2	34.2	4	24	1	24	4	7	1	2
Talha,[44] 2020	Egypt	RCT	Gastric bypass surgery, sleeve gastrectomy, or greater curve plication	Obesity	UDCA 500 mg for 6 mo	1137	295	716	171	31.1	30.1	74	65	74	65	26	28	NA	NA
Sen,[38] 2020	Turkey	Cohort	Sleeve gastrectomy	Obesity	UDCA 500 mg for 6 mo	152	128	90	81	39.8	38	16	48	16	48	5	19	5	19
Vural,[37] 2020	Turkey	Cohort	Sleeve gastrectomy	Obesity	UDCA 500 mg	42	66	35	50	39	39.9	11	36	11	36	NA	NA	NA	NA
Nabil,[40] 2019	Egypt	RCT	Sleeve gastrectomy	Obesity	UDCA 500 mg for 6 mo	100	100	79	75	30.4	31.7	6	40	6	40	NA	NA	NA	NA
Bencini,[19] 2019	Italy	RCT	Gastrectomy	Malignancy	PC	65	65	27	28	67	69	0	4	1	4	0	3	0	1
Machado,[41] 2019	Brazil	Cohort	RYGB	Obesity	UDCA 300 mg for 5 mo	69	68	51	41	34.2	35.9	1	18	1	18	NA	NA	NA	NA
Coupaye,[42] 2019	France	Cohort	Sleeve gastrectomy	Obesity	UDCA 500 mg for 6 mo	143	46	119	40	40.9	43.2	5	13	5	13	2	5	2	5
Abdallah,[36] 2017	Egypt	Cohort	Sleeve gasterctomy	Obesity	UDCA 600 mg for 6 mo	247	159	169	113	32.4	30.7	0	8	0	8	0	0	0	0
Coupaye,[18] 2017	France	Cohort	Sleeve gastrectomy, RYGB	Obesity	UDCA 500 mg for 6 mo	231	168	194	151	42.2	41.4	13	36	25	51	21	24	7	25
Adams,[17] 2016	USA	RCT	Sleeve gasterctomy	Obesity	UDCA 600 mg for 6 mo	28	29	21	19	43.7	46.0	4	13	4	13	NA	NA	NA	NA
Amstutz,[35] 2015	Switzerland	Cohort	RYGB	Malignancy	PC	26	64	NA	NA	NA	NA	0	22	2	22	2	22	0	16

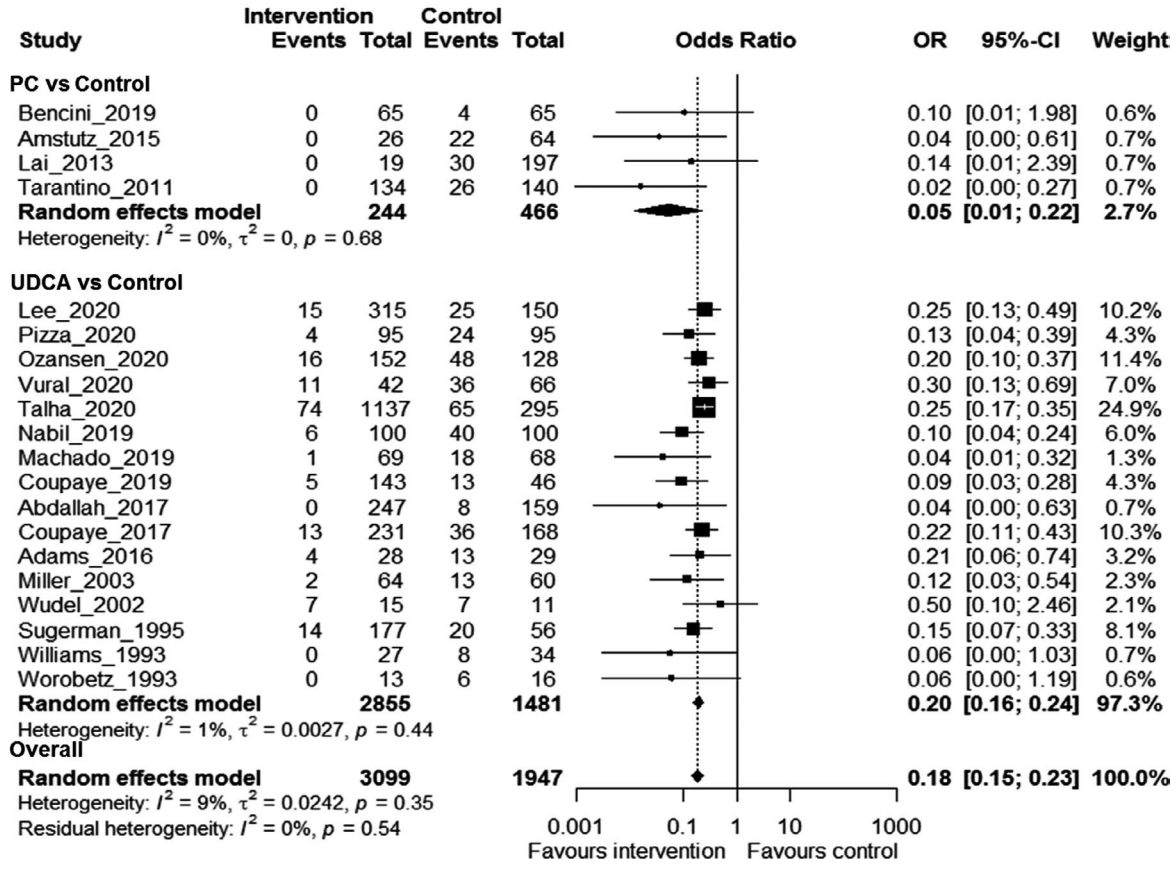
(Continues)

TABLE 1 (Continued)

Study, year	Country	Type of study	Surgery	Indication	Intervention	Patients, n		Female, n		Mean age, years		Gallstone formation, n		Biliary problem, n		Symptomatic biliary problem, n		Subsequent cholecystectomy, n	
						E	C	E	C	E	C	E	C	E	C	E	C	E	C
Lai,[34] 2013	Taiwan	Cohort	Gastrectomy	Malignancy	PC	19	197	19	153	59.9	58.9	0	30	0	58	0	9	0	9
Tarantino,[43] 2011	Switzerland	Cohort	RYGB	Obesity	PC	134	140	101	101	40.7	43	0	26	0	29	0	29	0	26
Swartz,[33] 2005	USA	Cohort	RYGB	Obesity	UDCA	295	24	270	20	39.8	41.7	NA	NA	41	6	41	6	41	6
Miller,[32] 2003	Austria	RCT	Gastroplasty or gastric band	Obesity	UDCA	64	60	52	51	34.1	36.3	2	13	2	13	3	12	3	12
Wudel,[31] 2002	USA	RCT	RYGB	Obesity	UDCA	15	11	NA	NA	38	38	7	7	7	7	NA	NA	NA	NA
Sugerman,[30] 1995	USA	RCT	Gastric bypass surgery	Obesity	UDCA	177	56	141	44	36.5	37.4	14	20	14	20	1	2	1	2
Williams,[29] 1993	Canada	RCT	Gastroplasty or gastric band	Obesity	UDCA	27	34	NA	NA	NA	NA	0	8	0	8	NA	NA	NA	NA
Worobetz,[3] 1993	Canada	RCT	Gastroplasty or gastric band	Obesity	UDCA	13	16	NA	NA	33.5	33.9	0	6	0	6	0	2	0	2

Abbreviations: C, control group; E, experimental group; NA, not applicable; PC, prophylactic cholecystectomy; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; UDCA, ursodeoxycholic acid.

(a) Gallstone formation



(b) Subsequent cholecystectomy

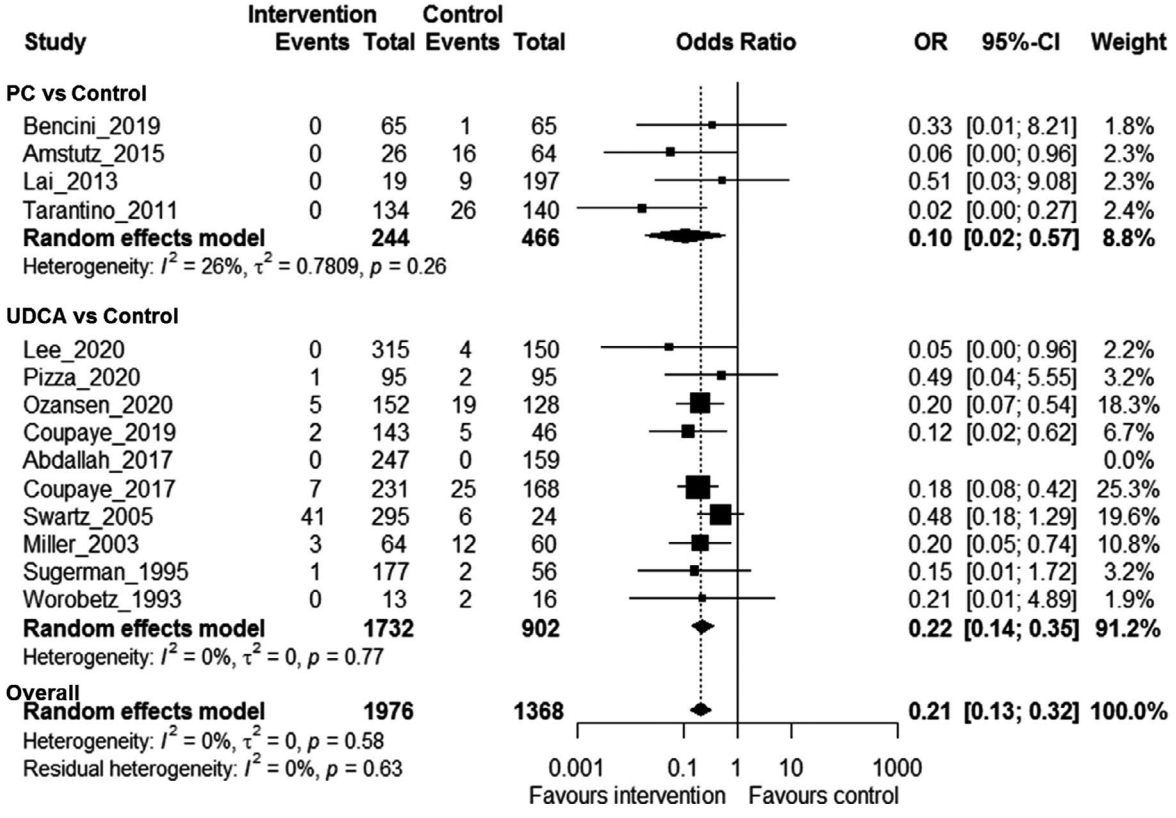


FIGURE 1 Comparison of clinical outcomes following gastric surgery according to prophylactic strategies. A, Efficacy for gallstone formation B, Efficacy for subsequent cholecystectomy. OR, odds ratio; PC, prophylactic cholecystectomy; UDCA, ursodeoxycholic acid

one RCT showed no statistically significant OR results (OR 0.33 [95% CI 0.01, 8.21]) (Supplementary Figure S3C).

3.3 | Indirect comparison of the efficacy of prophylactic cholecystectomy and UDCA for gallstone formation and subsequent cholecystectomy

Figure 2 and supplementary Table S2 show the results of direct and indirect comparison of PC to the control and UDCA by using network meta-analysis. When we compared the UDCA group with the PC group, the UDCA group showed a tendency to generate more gallstones (OR 3.74 [95% CI 0.88, 15.82]) and the need for SC (OR 2.19 [95% CI 0.47, 10.14]) although no statistical significance was observed. Gallstone formation (OR 18.88 [95% CI 4.53, 78.75]) and the need for SC (OR 9.86 [95% CI 2.28, 42.65]) occurred more in the control group on direct comparison than in the PC group.

3.4 | Quality and publication bias

Supplementary Table S3 describes the quality assessment for each of the RCTs' outcomes and those of the non-RCTs, according to the Cochrane collaboration tool for randomized trials and the Newcastle-Ottawa Assessment Scale.

Supplementary Figure S4 shows the results of funnel plots for evaluating publication bias categorized by study outcomes such as gallstone formation and cholecystectomy, and methodologies such as conventional meta-analysis and network meta-analysis. Regardless of study outcomes, there was no potential publication bias via visual inspection or Egger's regression test for the funnel plot (Supplementary Figure S4A,B) and the comparison specific funnel plot (Supplementary Figure S4C,D).

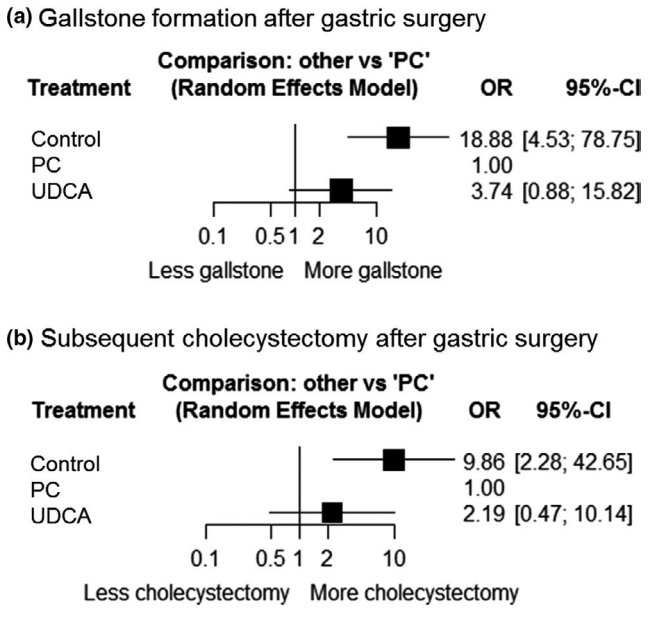


FIGURE 2 Comparison of prophylactic cholecystectomy and other prophylactic methods for clinical outcomes following gastric surgery using network meta-analysis. OR, odds ratio; PC, prophylactic cholecystectomy; UDCA, ursodeoxycholic acid

4 | DISCUSSION

Patients may suffer from gallstones following gastric surgery, but there seems to be a dilemma regarding the need for a PC with its invasiveness, because the incidence of symptomatic cases needing invasive treatment is quite low.[9,10] The prophylactic efficacy of UDCA for gallstone formation following gastric surgery, which is without severe clinical burden to the patient, is well-proven to be superior to the control groups in recent RCTs, regardless of the indication for the gastric surgery.[20,39,40] However, no solid evidence has been suggested that might persuade those who insist on the need for a PC, concomitant with gastric surgery, to use UDCA instead, despite the poor cost-effectiveness of a PC. We expected that patients receiving a UDCA in this study would show a clearly superior outcome over patients without any preventive methods. We tried to evaluate whether the efficacy of UDCA is comparable to a PC to arrive at a more convincing clinical implication.

This meta-analysis study suggested that prophylactic UDCA might be a reasonable preventive method for postsurgical gallstone formation or for SC. The UDCA group also showed an excellent preventive effect as compared to a PC done for gallstone formation (OR 0.18). There were many cases where fewer SCs performed in UDCA group as compared to the control group (OR 0.22). The indirect comparison between the PC and the UDCA groups revealed no statistically significant differences between them, although the UDCA group showed a greater tendency to develop gallstones (OR 3.34) and had a greater need for SC (OR 2.19). To the best of our knowledge, this is the first time that indirect comparison results can be interpreted as being fairly meaningful evidence of UDCA's excellent prophylactic efficacy for gallstone formation and SC following gastric surgery, as well as being comparable to a PC, regardless of the indication for the gastric surgery.

The main mechanism of UDCA to inhibit cholelithiasis is to suppress the secretion of cholesterol and mucin to bile resulting in increasing bile acid concentration and decreasing bile saturation.[45] This clearly explains the preventive effect of UDCA on inhibition or dissolution of cholesterol stone by rapid body weight change and altered diet following bariatric surgery and gastrectomy. In addition, the other main culprit behind gallstone formation after gastrectomy seems to be the deterioration of gallbladder motility and cholestasis, which

were known to cause pigment stones.[46-48] Some additional physiological effects of UDCA such as intensification of gallbladder contractility[49,50] and improvement of bile secretion to relieve cholestasis would explain the preventive effect for cholelithiasis following gastectomy.[51] Also, UDCA protects damaged cholangiocytes and stimulates detoxification of hydrophobic bile acids.[52] Based on these physiological mechanisms including dissolution effect and improvement of cholestasis, UDCA seems to prevent cholelithiasis regardless of the type of gallstones following gastric surgeries.[20]

A recent RCT of PC for gastric cancer patients showed that a concomitant PC done during gastric surgery for malignancies is safe and without technical difficulties.[19,53] But the overall postsurgical morbidities of laparoscopic cholecystectomy, including wound infection, bile duct injury, bile leakage, and open conversion are still not negligible.[54] The history of upper abdominal surgery is known as being a risk factor for open conversion of cholecystectomy,[55] although abdominal surgical history is not a risk factor for difficult laparoscopic cholecystectomy for the experienced surgeon.[56] Moreover, a result from a large-scale study raises great concern that the mortality of patients who undergo a PC with bariatric surgery is nearly twice (OR 2.16) as high.[57] The less-invasive nature of prophylactic UDCA greatly compensates for several concerns about doing a PC. Such concerns are poor cost-effectiveness, postsurgical morbidity, and the medico-economic burden.[11,58,59] The considerably smaller number of patients needing an SC with a prophylactic UDCA may mean patients who suffer from cholecystectomy-related adverse events may become extremely rare, because UDCA efficacy seems to be close to that of a PC, according to the result of this study. Furthermore, contrary to the concerns of physicians who support a PC approach, a recent meta-analysis showed that the overall surgery-related complication rate following an SC was only 1.8%.[60] It seems quite reasonable to give UDCA for prophylactic purposes following a gastric surgery instead of doing a PC during gastric surgery, which seems to be selectively performed in patients with symptomatic biliary disease.

Our study has several limitations. First, several potential heterogeneities may exist, according to unspecified details such as type of surgery, indications for surgery, and the dosage of UDCA. Although it can be considered that integration without detailed classification can cause bias, no significant differences have been reported by type of surgery[18,32] or by different dosage of UDCA.[20] We found no statistical heterogeneity and no prominent significant differences in the results of subgroup analysis by study design and surgical indication in this study. Second, the included studies' observation periods were diverse and relatively short. Most studies evaluated outcomes at 12 months, which might not be considered to be a long enough period to evaluate de novo gallstone formation or SC for symptomatic cholelithiasis as outcomes. Cholelithiasis has been reported to occur mostly within the 2 years following surgery,[13] but it is hard to predict a sufficient duration of observation for occurrences of symptomatic cholelithiasis because of its inconsistency.[61] Nevertheless, it is meaningful to synthesize the evidence given so far and to provide a basis for the better management of the patient through such indirect comparisons, especially those hard-to-compare outcomes in RCTs because of ethical aspects such as comparing a PC with other prophylactic strategies.

In conclusion, prophylactic UDCA has been shown to significantly reduce the incidence of gallstones and SC following gastric surgery. Prophylaxis with UDCA for patients following gastric surgery seems to be a reasonable, less-invasive preventive method to ensure clinical benefit while reducing the burden on the patient as compared to a PC. In the future, large-scale long-term follow-up studies will be needed to provide more solid evidence on the long-term effect and appropriate administration strategies of prophylactic UDCA.

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CONFLICT OF INTEREST

The authors claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jin Ho Choi and Sang Hyub Lee had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jin Ho Choi, Sang Hyub Lee. Acquisition or interpretation of data: Jin Ho Choi. Draft of the manuscript: Jin Ho Choi, Sang Hyub Lee. Critical revision of the manuscript for important intellectual content: Sang Hyub Lee, In Rae Cho, Woo Hyun Paik, Ji Kon Ryu, Yong-Tae Kim. Administrative, technical, or material support: In Rae Cho, Woo Hyun Paik. Study supervision: Sang Hyub Lee, Ji Kon Ryu, Yong-Tae Kim.

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REFERENCES

1. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Chatedaki C, Sioka E, et al. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: an

updated systematic review and meta-analysis. Obes Surg. 2017;27:3021–30.
2. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr. 1992;55:652–8.
3. Worobetz LJ, Inglis FG, Shaffer EA. The effect of ursodeoxycholic acid therapy on gallstone formation in the morbidly obese during rapid weight loss. Am J Gastroenterol. 1993;88:1705–10.
4. Brandão I, de Oliveira C, Adami Chaim E, da Silva BB. Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. Obes Surg. 2003;13:625–8.
5. Rehnberg O, Haglund U. Gallstone disease following antrectomy and gastroduodenostomy with or without vagotomy. Ann Surg. 1985;201:315–8.
6. Takahashi T, Yamamura T, Yokoyama E, Kantoh M, Kusunoki M, Ishikawa Y, et al. Impaired contractile motility of the gallbladder after gastrectomy. Am J Gastroenterol. 1986;81:672–7.
7. Inoue K, Fuchigami A, Hosotani R, Kogire M, Huang YS, Miyashita T, et al. Release of cholecystokinin and gallbladder contraction before and after gastrectomy. Ann Surg. 1987;205:27–32.
8. Portincasa P, Altomare DF, Moschetta A, Baldassarre G, Di Ciaula A, Venneman NG, et al. The effect of acute oral erythromycin on gallbladder motility and on upper gastrointestinal symptoms in gastrectomized patients with and without gallstones: a randomized, placebo-controlled ultrasonographic study. Am J Gastroenterol. 2000;95:3444–51.
9. Coupaye M, Castel B, Sami O, Tuyeras G, Msika S, Ledoux S. Comparison of the incidence of cholelithiasis after sleeve gastrectomy and Roux-en-Y gastric bypass in obese patients: a prospective study. Surg Obes Relat Dis. 2015;11:779–84.
10. Taylor J, Leitman IM, Horowitz M. Is routine cholecystectomy necessary at the time of Roux-en-Y gastric bypass? Obes Surg. 2006;16:759–61.
11. Sasaki A, Nakajima J, Nitta H, Obuchi T, Baba S, Wakabayashi G. Laparoscopic cholecystectomy in patients with a history of gastrectomy. Surg Today. 2008;38:790–4.
12. Gillen S, Michalski CW, Schuster T, Feith M, Friess H, Kleeff J. Simultaneous/Incidental cholecystectomy during gastric/esophageal resection: systematic analysis of risks and benefits. World J Surg. 2010;34:1008–14.
13. Fukagawa T, Katai H, Saka M, Morita S, Sano T, Sasako M. Gallstone formation after gastric cancer surgery. J Gastrointest Surg. 2009;13:886–9.
14. Kwon AH, Inui H, Imamura A, Kaibori M, Kamiyama Y. Laparoscopic cholecystectomy and choledocholithotomy in patients with a previous gastrectomy. J Am Coll Surg. 2001;193:614–9.
15. Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. Dig Dis Sci. 2007;52:1313–25.
16. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.
17. Adams LB, Chang C, Pope J, Kim Y, Liu P, Yates A. Randomized, prospective comparison of ursodeoxycholic acid for the prevention of gallstones after sleeve gastrectomy. Obes Surg. 2016;26:990–4.
18. Coupaye M, Calabrese D, Sami O, Msika S, Ledoux S. Evaluation of incidence of cholelithiasis after bariatric surgery in subjects treated or not treated with ursodeoxycholic acid. Surg Obes Relat Dis. 2017;13:681–5.
19. Bencini L, Marchet A, Alfieri S, Rosa F, Verlato G, Marrelli D, et al. The Cholegas trial: long-term results of prophylactic cholecystectomy during gastrectomy for cancer-a randomized-controlled trial. Gastric Cancer. 2019;22:632–9.
20. Lee SH, Jang DK, Yoo M-W, Hwang S-H, Ryu S-Y, Kwon OK, et al. Efficacy and safety of ursodeoxycholic acid for the prevention of gallstone formation after gastrectomy in patients with gastric cancer: the PEGASUS-D randomized clinical trial. JAMA Surg. 2020;155:703–11.
21. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–84.
22. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153–60.
23. Gerta Rucker UK, Konig J, Efthimiou O, Schwarzer G. netmeta: network meta-analysis using frequentist methods. R package version 1.2-0. 2019. Available from: https://CRAN.R-project.org/package=netmeta
24. Jørgensen L, Paludan-Müller AS, Laursen DR, Savović J, Boutron I, Sterne JA, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. Syst Rev. 2016;5:80.
25. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
26. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018;93:36–44.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
28. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001;323:101–5.
29. Williams C, Gowan R, Perey BJ. A double-blind placebo-controlled trial of ursodeoxycholic acid in the prevention of gallstones during weight loss after vertical banded gastroplasty. Obes Surg. 1993;3:257–9.
30. Sugerman HJ, Brewer WH, Shiffman ML, Brolin RE, Fobi MA, Linner JH, et al. 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. 1995;169(1):91–7.
31. Wudel LJ Jr, Wright JK, Debelak JP, Allos TM, Shyr Y, Chapman WC. Prevention of gallstone formation in morbidly obese patients undergoing rapid weight loss: results of a randomized controlled pilot study. J Surg Res. 2002;102:50–6.
32. Miller K, Hell E, Lang B, Lengauer E. Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238:697–702.

33. Swartz DE, Felix EL. Elective cholecystectomy after Roux-en-Y gastric bypass: why should asymptomatic gallstones be treated differently in morbidly obese patients? Surg Obes Relat Dis. 2005;1:555–60.
34. Lai SL, Yang JC, Wu JM, Lai IR, Chen CN, Lin MT, et al. Combined cholecystectomy in gastric cancer surgery. Int J Surg. 2013;11:305–8.
35. Amstutz S, Michel JM, Kopp S, Egger B. Potential benefits of prophylactic cholecystectomy in patients undergoing bariatric bypass surgery. Obes Surg. 2015;25:2054–60.
36. Abdallah E, Emile SH, Elfeki H, Fikry M, Abdelshafy M, Elshobaky A, et al. Role of ursodeoxycholic acid in the prevention of gallstone formation after laparoscopic sleeve gastrectomy. Surg Today. 2017;47:844–50.
37. Vural A, Goksu K, Kahraman AN, Boy FN, Anil BS, Fersahoglu MM. Increased gallstone formation after sleeve gastrectomy and the preventive role of ursodeoxycholic acid. Acta Gastroenterol Belg. 2020;83:33–8.
38. Şen O, Türkçapar AG, Yerdel MA. Cholelithiasis after sleeve gastrectomy and effectiveness of ursodeoxycholic acid treatment. J Laparoendosc Adv Surg Tech A. 2020;30:1150–2.
39. Pizza F, D'Antonio D, Lucido FS, Tolone S, Del Genio G, Dell'Isola C, et al. The Role of Ursodeoxycholic Acid (UDCA) in cholelithiasis management after one anastomosis gastric bypass (OAGB) for morbid obesity: results of a monocentric randomized controlled trial. Obes Surg. 2020;30:4315–24.
40. Nabil TM, Khalil AH, Gamal K. Effect of oral ursodeoxycholic acid on cholelithiasis following laparoscopic sleeve gastrectomy for morbid obesity. Surg Obes Relat Dis. 2019;15:827–31.
41. Machado FHF, Castro Filho HF, Babadopulos R, Rocha HAL, Rocha JLC, Moraes Filho MO. Ursodeoxycholic acid in the prevention of gallstones in patients subjected to Roux-en-Y gastric bypass1. Acta Cir Bras. 2019;34:e20190010000009.
42. Coupaye M, Calabrese D, Sami O, Siauve N, Ledoux S. Effectiveness of ursodeoxycholic acid in the prevention of cholelithiasis after sleeve gastrectomy. Obes Surg. 2019;29:2464–9.
43. Tarantino I, Warschkow R, Steffen T, Bisang P, Schultes B, Thurnheer M. Is routine cholecystectomy justified in severely obese patients undergoing a laparoscopic Roux-en-Y gastric bypass procedure? A comparative cohort study. Obes Surg. 2011;21:1870–8.
44. Talha A, Abdelbaki T, Farouk A, Hasouna E, Azzam E, Shehata G. Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial. Surg Endosc. 2020;34:5331–7.
45. Mazzella G, Bazzoli F, Festi D, Ronchi M, Aldini R, Roda A, et al. Comparative evaluation of chenodeoxycholic and ursodeoxycholic acids in obese patients. Effects on biliary lipid metabolism during weight maintenance and weight reduction. Gastroenterology. 1991;101:490–6.
46. Vítek L, Carey MC. New pathophysiological concepts underlying pathogenesis of pigment gallstones. Clin Res Hepatol Gastroenterol. 2012;36:122–9.
47. Chijiiwa K, Makino I, Kozaki N, Tanaka M. Differences in gallbladder bile lithogenicity in patients after gastrectomy and colectomy. Eur Surg Res. 1996;28:1–7.
48. Kinoshita H, Imayama H, Hashino K, Aoyagi S. Study of cholelithiasis after gastrectomy. Kurume Med J. 2000;47:105–8.
49. van de Heijning BJ, van de Meeberg PC, Portincasa P, Doornewaard H, Hoebers FJ, van Erpecum KJ, et al. Effects of ursodeoxycholic acid therapy on in vitro gallbladder contractility in patients with cholesterol gallstones. Dig Dis Sci. 1999;44:190–6.
50. Guarino MP, Cong P, Cicala M, Alloni R, Carotti S, Behar J. Ursodeoxycholic acid improves muscle contractility and inflammation in symptomatic gallbladders with cholesterol gallstones. Gut. 2007;56:815–20.
51. Jazrawi RP, de Caestecker JS, Goggin PM, Britten AJ, Joseph AE, Maxwell JD, et al. Kinetics of hepatic bile acid handling in cholestatic liver disease: effect of ursodeoxycholic acid. Gastroenterology. 1994;106:134–42.
52. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Hepatology. 2002;36:525–31.
53. Bernini M, Bencini L, Sacchetti R, Marchet A, Cristadoro L, Pacelli F, et al. The Cholegas Study: safety of prophylactic cholecystectomy during gastrectomy for cancer: preliminary results of a multicentric randomized clinical trial. Gastric Cancer. 2013;16:370–6.
54. Wu XD, Tian X, Liu MM, Wu L, Zhao S, Zhao L. Meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2015;102:1302–13.
55. Hu ASY, Menon R, Gunnarsson R, de Costa A. Risk factors for conversion of laparoscopic cholecystectomy to open surgery - A systematic literature review of 30 studies. Am J Surg. 2017;214:920–30.
56. Menon A. A comprehensive review of the factors predicting technical difficulty in laparoscopic cholecystectomy. Int Surg J. 2017;4:1147.
57. Worni M, Guller U, Shah A, Gandhi M, Shah J, Rajgor D, et al. Cholecystectomy concomitant with laparoscopic gastric bypass: a trend analysis of the nationwide inpatient sample from 2001 to 2008. Obes Surg. 2012;22:220–9.
58. Liang TJ, Liu SI, Chen YC, Chang PM, Huang WC, Chang HT, et al. Analysis of gallstone disease after gastric cancer surgery. Gastric Cancer. 2017;20:895–903.
59. Shim JH, Park CH, Song KY. Can prophylactic cholecystectomy be justified? Gastric Cancer. 2013;16:445–6.
60. Warschkow R, Tarantino I, Ukegjini K, Beutner U, Güller U, Schmied BM, et al. Concomitant cholecystectomy during laparoscopic Roux-en-Y gastric bypass in obese patients is not justified: a meta-analysis. Obes Surg. 2013;23:397–407.
61. Shiffman ML, Sugerman HJ, Kellum JM, Moore EW. Changes in gallbladder bile composition following gallstone formation and weight reduction. Gastroenterology. 1992;103:214–21.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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