Effect of Rowachol and ursodeoxycholic acid in the prevention of postcholecystectomy pain after laparoscopic cholecystectomy

Original Article

Ahmed M. Elashry, Hossam A. Elfeki, Amir A. Eldawody and Hesham M. El-Gendy

Department of General Surgery, Faculty of Medicine, Mansoura University, Mansoura, Cairo, Egypt.

ABSTRACT

Background: Patients often experience various symptoms from the immediate postoperative period to even years after. Rowachol is a terpene mixture that enhances the solubility of cholesterol, calcium carbonate, and calcium phosphate, which makes it a potent choleretic agent. Ursodeoxycholic acid can improve gallbladder contractility by decreasing cholesterol content in the plasma membrane of muscle cells and can stimulate biliary secretion, leading to relieved cholestasis.
Aim: To determine whether Rowachol and ursodeoxycholic acid were useful in the prevention of postcholecystectomy pain.
Patients and Methods: This randomized, clinical trial included 225 patients who underwent laparoscopic cholecystectomy and were randomly distributed into three groups according to the type of interventions. Group A included 75 patients who received Rowachol at a dose of 100 mg three times daily for 3 months; group B included 75 patients who received ursodeoxycholic acid at a dose of 300 mg twice daily for 3 months, and the control group included 75 patients who did not receive any. Technical difficulties were assessed also using the Parkland grading scale, which assesses the initial view of the gallbladder. Postoperatively, the patients were assessed by biliary pain score.
Results: A higher percentage of patients in groups A and B had a Parkland score of more than II (21.3; 16%) compared to the control group. There were no statistically significant differences between the studied groups as regards postoperative complication incidence or postoperative pain grade. Mean Parkland grading was higher among intervention groups than the control group with a statistically significant difference. A higher percentage of patients in intervention groups experienced grades III and IV postoperative pain than the control group with a statistically significant difference. Mean values for postoperative pain grade were higher among the intervention group than the control group with a statistically significant difference.
Conclusion: In conclusion, both Rowachol and ursodeoxycholic acid did not have a significant effect on postlaparoscopic cholecystectomy pain incidence.

Key Words: Cholecystectomy, laparoscopic, postcholecystectomy pain, Rowachol, ursodeoxycholic acid.

Received: 18 January 2024, **Accepted:** 4 February 2024, **Publish:** 7 July 2024

Corresponding Author: Ahmed M. Elashry, MSc, Department of General Surgery, Faculty of Medicine, Mansoura University, Mansoura, Egypt. **Tel.:** 01021379959, **E-mail:** ahmed_elashry_00@yahoo.com

ISSN: 1110-1121, July 2024, Vol. 43, No. 3: 700-708, © The Egyptian Journal of Surgery

INTRODUCTION

In most patients, gallstones will stay asymptomatic. Approximately 20% of patients will experience symptoms, like a biliary colic, for which laparoscopic cholecystectomy (LC) is the preferred treatment. Therefore, LC is one of the most performed elective abdominal surgeries worldwide[1]. Nonetheless, following a cholecystectomy, patients frequently have a range of symptoms from the first postoperative day to years later, and these symptoms can independently predict changes in the prognosis, functional status, and quality of life[2]. Postcholecystectomy pain, or PCP, is the term used to describe chronic or recurrent discomfort that approximately one-third of cholecystectomy patients experience following surgery[3].

Anatomical factors may contribute to PCP and these include sphincter of Oddi dysfunction, cystic-duct remnant neuroma, and retained cystic-duct remnant calculi. However, the etiology for most of PCP remains unclear. As a result, the clinical management of these patients is frequently without an evidence-based approach[4].

Rowachol is a terpene mixture that enhances the solubility of cholesterol, calcium carbonate, and calcium phosphate, which makes it a potent choleretic agent. As a result, terpene preparations are effective in resolving biliary stones. However, the preventive effect of Rowachol as a choleretic drug for patients with PCP is unclear[4,5]. Ursodeoxycholic acid can be considered one of the least expensive, best tested, and safest of the drugs currently available. Ursodeoxycholic acid, in pharmacological

DOI: 10.21608/EJSUR.2024.357117

doses, markedly decreases biliary cholesterol saturation by 40–60%, by the inhibition of cholesterol absorption in the intestine, and cholesterol secretion into bile as indicated by a decrease in the cholesterol fraction of biliary lipids[6].

Ursodeoxycholic acid can improve gallbladder contractility by decreasing cholesterol content in the plasma membrane of muscle cells and can stimulate biliary secretion, leading to relieved cholestasis. Moreover, other mechanisms of action, such as protection of damaged cholangiocytes and stimulation of detoxification of hydrophobic bile acids, may contribute to ursodeoxycholic acid's effect. Therefore, ursodeoxycholic acid can be a good and safe alternative to prophylactic cholecystectomy[7]. So, this work aimed to determine whether Rowachol and ursodeoxycholic acid was useful in the prevention of PCP and for the improvement of symptoms after LC.

PATIENTS AND METHODS:

This randomized, clinical trial included 225 patients who underwent LC in the General Surgery Department of Mansoura University Hospitals. The study was conducted in the duration between February 2022 and February 2023.

Type of randomization

Study design: single-blind; patients were blinded to the treatment, but the treating physician was aware of it. Random allocation is a technique that allocates individuals for treatment groups and control groups solely by chance with no respect to the desire of researchers or patients' conditions and preferences. The closed-envelop technique was used to adopt the method. We started randomization 2 days postoperatively.

Patients

We included adult patients of both sexes over 18 years of age who had symptomatic gallbladder stone disease, noncalculous cholecystitis, and gallbladder polyps. But we excluded patients aged under 18 years, patients with severe psychiatric or neurologic diseases, patients who received immunosuppressive therapy days before enrollment, patients who received chemotherapy or radiotherapy within 4 weeks before the operation, pregnant or lactating women, patients with a history of any substance addiction, patients with LC converted to open cholecystectomy, and patients who underwent another open operation with LC in the same session such as paraumbilical hernia repair.

All patients were randomly distributed into three groups according to the type of interventions: group A included 75 patients who received Rowachol at a dose of 100 mg three times daily for 3 months, group B included 75 patients who received ursodeoxycholic acid at a dose of 300 mg twice daily for 3 months, and the control group included 75 patients who did not receive any treatment. The included patients received Rowachol orally at a dose of 100 mg and ursodeoxycholic acid orally at a dose of 300 mg.

Methods

Every patient was subjected to full history taking including personal history, complaint analysis, medical history, and history of previous operation and special attention to the cause of gallbladder disease.

Clinical examination included anthropometric measurements such as BMI, general examination with special attention to jaundice, and abdominal examination.

Laboratory investigations included serum creatinine measurement, complete blood count, liver enzymes (alanine transaminase and aspartate transaminase), and serum bilirubin. Radiological assessment included abdominal ultrasound and magnetic resonance cholangiopancreatography for certain cases.

Operative equipment

The equipment included two laparoscopic monitors, one laparoscope (5/10 mm, 0/30°) with a camera cord and light source, a carbon dioxide source with tubing for insufflation, 5–12 mm trocars (average three 5 mm working trocars and one 10 mm to 12 mm trocar), laparoscopic instruments (atraumatic graspers, Maryland grasper, clip applier, electrocautery), scalpel (11/15 blade), forceps, needle driver, and absorbable sutures.

Technique

The patient's health was optimized. Preoperatively, as per procedure, preoperative antibiotics were administered within 30 min of the incision. Initially, the abdomen was insufflated to a pressure of 15 mmHg using carbon dioxide and an optical trocar or Veress needle. The abdomen was then made into four small incisions (supraumbilical x1, subxiphoid x1, and right subcostal x2) to install the trocar. The gallbladder was retracted over the liver using lengthy instruments and a laparoscope camera. As a result, the suggested hepatocystic triangle region was made visible. A meticulous deconstruction process was used to obtain the crucial perspective of safety.

After obtaining a sufficient view, the operating surgeon could proceed with assurance that the cystic duct and cystic artery have been isolated. Both structures underwent meticulous cutting and slicing. The gallbladder and liver bed were then totally separated with electrocautery. The gallbladder was extracted from the abdomen and placed into a specimen pouch. Under direct visualization or with the installation of a subhepatic drain, all trocars were removed. To prevent incisional hernias during the recovery

phase, port sites had to be closed specifically to the surgeon, with fascial closure of trocar sites greater than 5 mm.

Technical difficulties were assessed using the Parkland grading scale, which assesses the initial view of the gallbladder. The Parkland grading scale included grades I, II, III, etc. Grade I is the normally appearing gallbladder; II is minor adhesion at gallbladder neck, otherwise normal, III is presence of hyperemia, pericholecystic fluid, adhesions, or distension, IV is presence of adhesions obscuring the majority of gallbladder, grades I–III with abnormal liver anatomy, intrahepatic gallbladder, or impacted stone, and V is presence of perforation, necrosis, inability to visualize the gallbladder due to adhesions (score of '0' was given for 'no' and 1 point was given for 'yes'.

Postoperative assessment

The follow-up was up to 3 months, and all patients were asked to assess the presence of complications or abdominal pain. Regarding the pain, the patient determined the location, duration, severity, and frequency of abdominal pain. The patient assessed the severity of pain on a scale from 0 to 10 called the visual analog scale (VAS). Patients were given a score from 1 to 5 according to pain frequency (biliary pain). The biliary pain is defined as 1 is pain-free, 2 is pain occasionally (less than twice a month), 3 is pain weekly (once every week; a few times a month), 4 is pain frequently (a few times a week but not every day), and 5 is pain daily (at least one or more every day).

Biliary pain:

Score	Frequency
1	Pain-free
2	Pain occasionally (less than twice a month)
3	Pain weekly (once every week; a few times a month)
4	Pain frequently (a few times a week but not every day)
5	Pain daily (at least one or more every day)

Postoperative complications included bleeding, infection, and damage to the surrounding structure.

Statistical methods

Statistical analysis was conducted using SPSS (version 21; SPSS Inc., Chicago, Illinois, USA). Qualitative data were presented as number and percentage, while quantitative parametric data (normally distributed) were presented as mean and SD, and quantitative nonparametric data (abnormally distributed) were presented as median (minimum, maximum). χ^2 test was used to compare categorical data. Student's t test was used to compare normally distributed quantitative data between two groups. Mann–Whitney test was used to compare abnormally distributed quantitative data between two groups. Analysis of variance was used to compare normally distributed data between more than two groups. Kruskal–Wallis was used to compare abnormally distributed qualitative data between more than two groups. A *P value* less than 0.05 was considered statistically significant.

RESULTS:

The study included 225 patients who were planned to be operated by LC. The included patients had a mean age of 42.1±12.6 years. Most of the included patients were females (78.2%), while 21.8% were males. The commonest associated comorbidities were hypertension (21.8%), diabetes (15.1%), and cardiac diseases (9.3%). The mean operative time of the included patients was 49.8±9.41 min. Most of the included patients had intraoperative difficulties in Parkland grade I (45.3%) or II (42.2%). Intraoperative difficulties grade III was reported in 11.1% and grade IV in 1.3% of patients only. The mean parkland grade was 1.68±0.7. Postoperative complications were reported in 0.9% of patients (two patients only). About 102 (45.3%) patients experienced grade II postoperative pain, 33.3% (75 patients) experienced grade I postoperative pain, 18.7% experienced grade III postoperative pain (42 patients), and only six patients experienced grade IV postoperative pain (2.7%). The mean postoperative grade was 1.9±0.8 (Table 1).

Table 1: Demographic, medical disorders, and intraoperative and postoperative assessment

	Total cohort (N=225)
Age (years)	
Mean±SD	42.1±12.6
Sex [n (%)]	
Male	49 (21.8)
Female	176 (78.2)
Associated medical disorders [n (%)]	
Hypertension	49 (21.8)
Diabetes	34 (15.1)
Hepatic	4 (1.8)

Renal	0
Cardiac	21 (9.3)
Operative time (min) (mean±SD)	49.8±9.41
Intraoperative difficulties (Parkland grading) [n (%)]	
Grade I	102 (45.3)
Grade II	95 (42.2)
Grade III	25 (11.1)
Grade IV	3 (1.3)
Parkland grading (mean±SD)	1.68±0.7
Postoperative complications [n (%)]	2 (0.9)
Postoperative pain grade [n (%)]	
Grade I	75 (33.3)
Grade II	102 (45.3)
Grade III	42 (18.7)
Grade IV	6 (2.7)
Postoperative pain grade (mean±SD)	1.9±0.8

There was a statistically significant difference between the studied groups as regards mean age (*P=0.04*). Mean age was higher significantly among the Rowachol group (group A) than the control group with a statistically significant difference (*P=0.01*). While group A and group B had comparable ages, group B and the control group also had comparable ages. There was a statistically significant difference between the studied groups as regards sex distribution with higher male percent among groups A and B and higher female percent among the control group (*P=0.014*). There was no statistically significant difference between the studied groups as regards associated comorbidities. There was no statistically significant difference between the studied groups as regards mean operative time. Mean Parkland grades for intraoperative difficulties were higher among group A and lower among the control group with a statistically significant difference (*P<0.001*). Most of the patients in group A had Parkland grade I (41.3%) or II (37.3%). In group B, most of the patients had Parkland grades II (46.7) and I (37.3%). A higher percentage of patients in groups A and B had Parkland scores more than II (21.3; 16%) compared with the control group (0%). In the control group, most of the patients were of Parkland grade I (57.3%) and the rest were of grade II (42.7%). There were no statistically significant differences between the studied groups as regards postoperative complication incidence or postoperative pain grade (Table 2).

Table 2: Demographic, associated comorbidities, and intraoperative and postoperative assessment differences between the studied groups

	Group A (Rowachol) (N=75)	Group B (ursodeoxycholic) (N=75)	Control group (N=75)	*P value*
Age (years)				F=2.9
Mean±SD	43.8±12.8	42.8±14.6	39.6±9.8[a]	*P=0.04*
Sex [n (%)]				
Male	22 (29.3)	19 (25.3)	8 (10.7)	χ^2=8.5
Female	53 (70.7)	56 (74.7)	67 (89.3)	*P=0.014*
Associated medical disorders [n (%)]				
Hypertension	17 (22.7)	15 (20)	17 (21.8)	0.9
Diabetes	9 (12)	14 (18.7)	11 (14.7)	0.5
Hepatic	1 (1.3)	3 (4)	0	0.17
Cardiac	8 (10.7)	8 (10.7)	5 (6.7)	0.6
Operative time				F=1.9
Mean±SD (min)	49.6±9.2	51.5±12.5	48.4±6.3	*P=0.14*
Intraoperative difficulties [n (%)]				

Parkland grading				
Grade I	31 (41.3)	28 (37.3)	43 (57.3)	
Grade II	28 (37.3)	35 (46.7)	32 (42.7)	χ^2=23.04
Grade III	13 (17.3)	12 (16)	0	*<0.001*
Grade IV	3 (4)	0	0	
Parkland grading				F=10.09
Mean±SD	1.84±0.86	1.79±0.7	1.43±0.49	*P<0.001*
Postoperative complications [n (%)]	0	2 (2.7)	0	χ^2=4.04 *P=0.13*
Postoperative pain grade [n (%)]				
Grade I	24 (32)	23 (30.7)	28 (37.3)	
Grade II	32 (42.7)	32 (42.7)	38 (50.7)	χ^2=7.98
Grade III	17 (22.7)	16 (21.3)	9 (12)	
Grade IV	2 (2.7)	4 (5.3)	0	*P=0.24*
Postoperative pain grade (mean±SD)	1.96±0.8	2.01±0.86	1.75±0.66	F=2.78 P= 0.065

F, analysis of variance (ANOVA) test: (a) post hoc analysis; *P value* against group A less than 0.05, χ test, level of significance less than 0.05.

All factors were entered in a linear regression model to be adjusted for confounders for the predictors of postoperative pain grades. Only Parkland grade showed statistical significance as a predictor for postoperative pain with statistically significant differences between grade II and I and grade III and I (Table 3).

Table 3: Multivariate analysis for predictors of postoperative pain

	95% confidence interval			
	B estimate	Lower	Upper	*P* value
Age	−0.004	−0.01	0.006	0.43
Sex	−0.9	−0.35	0.17	0.5
Hypertension	−0.03	−0.34	0.31	0.79
Diabetes	−0.32	−0.68	0.03	0.074
Hepatic	0.45	−0.4	1.33	0.3
Cardiac	0.31	−0.11	0.74	0.15
Parkland grade				
II vs. I	0.29	0.065	0.52	*0.012*
III vs. I	0.42	0.03	0.81	*0.033*
IV vs. I	0.68	−0.24	1.6	0.15
III vs. II	0.12	−0.25	0.51	0.51
IV vs. II	0.39	−0.53	1.3	0.4
IV vs. III	0.26	0.7	1.23	0.59
Medications				
Rowachol vs. control	0.13	−0.16	0.37	0.45
UDCA vs. control	0.17	−0.086	0.43	0.19
Rowachol vs UDCA	−0.06	−0.3	0.19	0.6

UDCA, ursodeoxycholic acid.

DISCUSSION

LC is a very effective treatment for gallbladder disease, but PCP is not uncommon. Approximately 30–50% of patients who undergo cholecystectomy remain symptomatic, where the management of PCP can be quite challenging. The efficacy of choleretic drugs is questioned[8].

Thus, Rowachol treatment for patients with PCP might be beneficial[9].

It has been reported that remnant gallbladder after partial cholecystectomy or cystic duct calculi can be a source of recurrent biliary pain. Another possible explanation for PCP is that intraoperative damage to nerves innervating visceral structures during the operation causes postoperative pain[10].

This study aimed to evaluate the efficacy of Rowachol and ursodeoxycholic acid in the prevention of post-LC pain.

The study showed the absence of a beneficial effect of either Rowachol or ursodeoxycholic acid in the prevention of postoperative pain after LC.

The study included 225 LC patients with a mean age of 42.1±12.6 years. In concordance with the present study, Lee *et al*.[11] demonstrated that the mean age for patients who underwent LC was 42.3±4.5 years[11]. Shrestha *et al*. in their study on 200 patients found that the mean age for LC patients was 41±5.8 years[12]. Han *et al*.[2] showed that the mean age for 475 LC patients included in his study was 50.3±13.7 years.

In the present study, the mean age of the included patients was higher among the intervention group than the control group with statistically significant differences (*P=0.036*). However, both Rowachol and ursodeoxycholic acid patients had comparable age and sex distribution. On the contrary, Han *et al*.[4] tried to assess the effect of Rowachol in the prevention of postoperative pain and included 138 patients who were randomly divided into two groups. He did not report significant age and sex differences between Rowachol and control groups.

Most of the included patients in the present study were females representing 75% of patients. Similar to this study, Lee *et al*.[11] showed that 71% of patients who underwent LC in this study were women. Also, Han *et al*.[2] and Han *et al*.[4] showed that 53% of LC patients were females. On the contrary, Unalp-Arida *et al*.[13] reported in their demographic survey that 70% of patients in their study were males.

The commonest associated comorbidities were hypertension and diabetes (21.8 and 15.1%, respectively). Similarly, Han *et al*.[4] showed that the associated comorbidities with the highest frequencies were hypertension and diabetes among their study group. Han *et al*.[2] showed that 21.8% of LC patients were hypertensives. On the contrary, Unalp-Arida *et al*.[13] showed that the commonest associated medical disorders with gallstones were dyslipidemia and cardiovascular diseases.

The mean operative time in the included patients was 49.8±9.41 min. Likely, Han *et al*.[4] showed that the mean operative time for LC was 52.3±6.8 min. In a study by Shrestha *et al*.[12], the mean operative time was 55±3.4 min.

However, Wang *et al*.[14] reported a longer mean operative time among LC patients (62.3±6.5 min). Yuksekdag *et al*.[15] found that operative duration varied from 50±3.4 to 70.4±10.8 according to the timing of the operation after the incidence of cholecystitis.

There were no statistically significant differences between the intervention groups and control group as regards mean operative time. Similar to the present results, Han *et al*.[4], showed that the mean operative time was longer in the placebo group (58.8±30 min) than the Rowachol group (51.9±27.2) but with no statistically significant difference (*P=0.14*).

According to Parkland grading, intraoperative difficulties in grades I and II were found in 45.3 and 42.4% of patients in the present study. Mean Parkland grade value for intraoperative difficulties was 1.68±0.7. The Parkland Grading Scale for cholecystitis has been reported to be a reliable and accurate predictor of LC outcomes[16].

Liu *et al*.[16] reported a mean score of 2.57±2.77. He reported that 44.8% had grade I difficulties but only 21.5% were of grade I. Shrestha *et al*.[12] found that 32.5% of patients were of grade I and 36.4% of patients were of grade II. On the contrary, Han *et al*.[2] in their study on 475 patients showed that the mean Parkland score was 3.3±2, which was higher than that reported in the present study.

According to the present results, surprisingly, intraoperative difficulties of higher Parkland gradings (III and IV) were reported at higher frequencies among the intervention group than the control group with a statistically significant difference (*P<0.001*). Also, grade II intraoperative difficulties were reported at a higher rate among the ursodeoxycholic acid group (46.7%) while most of the patients in the Rowachol group had grade I intraoperative difficulties (41.3%).

On the contrary, Han *et al*.[4] showed that the incidence of intraoperative difficulties was higher among the placebo group than the Rowachol group with a statistically significant difference (41.7 vs. 10.4%; *P=0.03*).

Postoperative complications were reported by 0.9% of patients only. In agreement with the this study, Han *et al*.[4] demonstrated the incidence of postoperative complications in only 1 patient and he was in the placebo group. Gin *et al*.[17] also reported low postoperative complication rates (1.2%) and it was affected mainly by the intraabdominal pressure.

Postoperative complication incidence was comparable between Rowachol and ursodeoxycholic acid groups. In concordance with the present study, Han *et al*.[4] did not find a statistically significant difference between Rowachol and placebo groups as regards postoperative complication incidence.

According to the present study, the mean postoperative pain grade was 1.9±0.8. Postoperative significant pain was presented in 66.7% of patients. Most of the patients experienced postoperative pain grade II (45.3%), while 18.8% of patients had grade III and 2.7% experienced grade IV postoperative pain. In agreement with the present study, Han *et al*.[2] reported that 50% of LC patients experienced PCP, which affected the quality of life in their study on 475 patients. Thistle *et al*.[18] also showed that 50–60% of LC patients had significant postoperative pain after LC.

In a study by Akturk and Serinsöz[19], the mean VAS for PCP was 1.9±0.3. Ergin *et al*.[20] found that the mean VAS after 24 h was 1.7±1.9. On the contrary, Gin *et al*.[17] reported a higher mean pain score among LC patients (3±1.3).

There were no statistically significant differences between Rowachol and ursodeoxycholic acid in comparison to each other or in comparison to the control group as regards postoperative pain grades. In agreement with the present study, Han *et al*.[4] reported no statistically significant differences between Rowachol and placebo groups as regards postoperative pain despite the lower rate among the Rowachol group (4.7%) than the placebo group (14.3%). They described the significance as a marginal difference, but it was insignificant (*P=0.08*).

Very low to low-quality evidence indicated that pharmacological agents, such as NSAIDs, lidocaine, parecoxib, nefopam, dexamethasone, and magnesium sulfate, could decrease pain intensity in patients undergoing LC. Moreover, moderate to high-quality evidence showed that intravenous infusion of ketamine and opioids, as well as pregabalin, was effective in pain control[21].

In the present study, we evaluated the predictors for postoperative pain. Only intraoperative difficulties represented the most statistically significant predictor for postoperative pain. In agreement with the present study, Han *et al*.[4] showed that intraoperative difficulties represented a significant predictor for postoperative pain.

Also, Han *et al*.[2] showed that mean values for intraoperative difficulties grade were higher among patients who experienced PCP (1.96±0.4) than those who did not experience PCP (1.38±0.6) with statistically significant difference (*P=0.04*). This may be because difficulty in dissection of the triangle formed by the common bile duct, cystic duct, and liver (Calot's triangle) may cause intraoperative nerve damage innervating the visceral structures[22].

The analysis of postoperative pain in this study revealed the absence of a significant correlation between receiving Rowachol or ursodeoxycholic acid and the incidence of postoperative pain (*P=0.45*; 0.19). On the contrary, a multivariate analysis of postoperative pain in a study by Han *et al*.[4] reported that the absence of postoperative Rowachol treatment (hazard ratio=2.54, 95% confidence interval=1.10–10.39, *P<0.05*) was an independent risk factor for the development of PCP.

The study had some advantages, being a randomized clinical trial, which minimized the risk of bias and allowed for better generalizability and reliability of the data. Another advantage is that the study is considered the first study to compare Rowachol and ursodeoxycholic acid in the management of PCP including also a control group. Generally, few studies evaluated the role of either Rowachol or ursodeoxycholic acid in comparison to placebo in the management and prevention of PCP. The study had a relatively large sample size in comparison to other studies that evaluated similar topics. The study had some limitations. Being a randomized clinical trial, it lasts for a relatively longer duration. Also, the study evaluated the pain as a main outcome, which is subjective and differs between variable individuals.

CONCLUSION

In conclusion, both Rowachol and ursodeoxycholic acid did not have a significant effect on post-LC pain incidence.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Carmen S S Latenstein, Sara Z Wennmacker, JudithJde Jong, Cornelis J H M van Laarhoven, Joost P H Drenth, Philip R de Reuve. Etiologies of long-term postcholecystectomy symptoms: a systematic review. Gastroenterol Res Pract 2019; 2019:4278373.

2. In Woong Han, Hyeon Kook Lee, Dae Joon Park, Yoo Shin Choi, SeungEunLee, Hongbeom Kim. Long-term patient-reported outcomes following laparoscopic cholecystectomy: a prospective multicenter observational study. Medicine (Baltimore) 2020; 99:e21683.

3. Jaunoo SS, Mohandas S, Almond LM. Postcholecystectomy syndrome (PCS). Int J Surg 2010; 8:15–17.

4. In Woong Han, O Choel Kwon, Min Gu Oh, Yoo Shin Choi, Seung Eun Lee. Effects of Rowachol on prevention of postcholecystectomy pain after laparoscopic cholecystectomy: prospective multicenter randomized controlled trial. HPB (Oxford) 2016; 18:664–670.

5. Tae Hoon Lee 1, Joung-Ho Han, Hong Ja Kim, Seon Mee Park, Sang-Heum Park, Sun-Joo Kim. Is the addition of choleretic agents in multiple double-pigtail biliary stents effective for difficult common bile duct stones in elderly patients? A prospective, multicenter study. Gastrointest Endosc 2011; 74:96–102.

6. MarceloGRoma,FlaviaDToledo,AndreaCBoaglio, CeciliaL Basiglio, FernandoACrocenzi, Enrique J Sánchez Pozzi Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. Clin Sci (Lond) 2011; 121:523–544.

7. Sang Hyub Lee , Dong Kee Jang , Moon-WonYoo , Sun-Hwi Hwang , Seong-YeobRyu , Oh Kyoung Kwon *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; 155:703–711.

8. Qandeel H, Nassar AHM, Ng HJ, El Zanati H. Laparoscopic cholecystectomy for gallbladder dysfunction and polyps: incidence and follow up. Jsls 2021; 25:2.

9. AlexanderPodboy, Srinivas Gaddam, KennethPark, Kapil Gupta, Quin Liu, Simon K Lo. Management of difficult choledocholithiasis. Dig Dis Sci 2022; 67:1613–1623.

10. SaketKumar, Nishant Kurian, Rakesh Kumar Singh, Venkat RaoChidipotu, Sanjay Kumar, Amarjit Kumar Raj *et al*. Surgical management of cystic duct stump calculi causing post-cholecystectomy syndrome: a prospective study. J Minim Access Surg 2023; 19:257–262.

11. Lee SH, Chung HW, Lee TY, Cheon YK. Effect of Rowachol on the gallbladder dysmotility disorder based on gallbladder ejection fraction. Medicina (Kaunas) 2023; 59:1.

12. AnupShrestha, AbhishekBhattarai, KishorKumarTamrakar, ManojChand, SamjhanaYonjanTamang, Sampada Adhikari *et al*. Utility of the Parkland Grading Scale to determine intraoperative challenges during laparoscopic cholecystectomy: a validation study on 206 patients at an academic medical center in Nepal. Patient Saf Surg 2023; 17:12.

13. Unalp-Arida A, Der JS, Ruhl CE. Longitudinal study of comorbidities and clinical outcomes in persons with gallstone disease using electronic health records. J Gastrointest Surg 2023; 27:2843.

14. Wang HH, Portincasa P, Liu M, Wang DQ. Effects of biliary phospholipids on cholesterol crystallization and growth in gallstone formation. Adv Ther 2023; 40:743–768.

15. SYuksekdag, GBas, IOkan, AKarakelleoglu, OAlimoglu, A Akcakaya *et al*. Timing of laparoscopic cholecystectomy in acute cholecystitis. Niger J Clin Pract 2021; 24:156–160.

16. Liu YQ, Wang C, Cai X, Zheng ZX, *et al*. Can the parkland grading scale predict the difficulty of laparoscopic cholecystectomy? A new approach to validation. BMC Surg 2023; 23:142.

17. Gin E, Lowen D, Tacey M, Hodgson R. Reduced laparoscopic intra-abdominal pressure during laparoscopic cholecystectomy and its effect on post-operative pain: a double-blinded randomised control trial. J Gastrointest Surg 2021; 25:2806–2813.

18. Johnson L Thistle , George F Longstreth, Yvonne Romero, Amindra S Arora, Julie A Simonson, Nancy N Diehl *et al*. Factors that predict relief

from upper abdominal pain after cholecystectomy. Clin Gastroenterol Hepatol 2011; 9:891–896.

19. Akturk R, Serinsöz S. Determining a method to minimize pain after laparoscopic cholecystectomy surgery. Surg Laparosc Endosc Percutan Tech 2022; 32:441–448.

20. Haipeng Liu, Weijie Jia, Jianyou Tian. Effectiveness of local anesthetic application methods in postoperative pain control in laparoscopic cholecystectomies; a randomised controlled trial. Int J Surg 2021; 95:106134.

21. Eftekhariyazdi M, Ansari M, Darvishi-Khezri H, Zardosht R. Pharmacological methods of postoperative pain management after laparoscopic cholecystectomy: a review of meta-analyses. Surg Laparosc Endosc Percutan Tech 2020; 30:534–541.

22. Morten Rune Blichfeldt-Eckhardt, Helle Ording, Claus Andersen, Peter B Licht, Palle Toft. Early visceral pain predicts chronic pain after laparoscopic cholecystectomy. Pain 2014; 155:2400–2407.

23. Helen H Wang, Piero Portincasa, Min Liu, Patrick Tso, David Q-H Wang, Similarities and differences between biliary sludge and microlithiasis: their clinical and pathophysiological significances. Liver Res 2018; 2:186–199.

24. Dragos Serban, Bogdan Socea, Simona Andreea Balasescu, Cristinel Dumitru Badiu, Corneliu Tudor, Ana Maria Dascalu Geta Vancea *et al*. Safety of laparoscopic cholecystectomy for acute cholecystitis in the elderly: a multivariate analysis of risk factors for intra and postoperative complications. Medicina (Kaunas) 2021; 57:3.

25. Geta Vancea, Radu Iulian Spataru, Alexandru Dan Sabau, Dan Sabau, Ciprian Tanasescu. The effect of biliary stenting with combined UDCA and Rowachol administration on retained CBD stones-multicenter study. Gastrointest Endosc 2008; 67:AB165–AB6.

26. Gustafsson S, Strömqvist M, Ekelund J, Engström Å. Factors influencing early postoperative recovery after laparoscopic cholecystectomy. J Perianesth Nurs 2020; 35:80–84.

27. GuillermoMedina-Diaz-Cortés, IrmaValeria Brancaccio-Pérez, IsaacEsparza-Estrada, FranciscoJoséBarbosa-Camacho, ClotildeFuentes-Orozco, PaolaGuadalupe González-Hernández *et al*. Differences in postoperative pain, nausea, and vomiting after elective laparoscopic cholecystectomy in premenopausal and postmenopausal Mexican women. World J Surg. 2022; 46:356–361.

28. Marcela Salazar-Parra, Bertha Georgina Guzman-Ramirez, Kevin Josue Pintor-Belmontes, Francisco José Barbosa-Camacho, AldoBernal-Hernández , Roberto Ulises Cruz-Neri *et al*. Gender differences in postoperative pain, nausea and vomiting after elective laparoscopic cholecystectomy. World J Surg 2020; 44:4070–4076.