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Examining the Effect of Ursodeoxycholic Acid on Abdominal Pains and Dyspepsia after Laparoscopic Cholecystectomy

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Abstract

Introduction: Bile acids decrease biliary cholesterol secretion and bile cholesterol saturation and dissolve cholesterol gallstones. Accordingly, this study is aimed at investigating the therapeutic effect of ursodeoxycholic acid (UDCA) on gastrointestinal pains and dyspepsia after cholecystectomy. **Materials and Methods:** The study was a double-blind randomized clinical trial and sampling was done though convenience sampling method. The sample size was 80 subjects and during the discharge from hospital, the patients in group A were treated with 300 mg UDCA three times a day for two months and the patients in group B received placebo. Both groups were evaluated during the first and second weeks after treatment. The obtained data were then analyzed in SPSS.19. **Results:** One week after the end of treatment, 14 patients in the intervention group and 12 patients in the placebo group (P = 0.633) reported pain and the same issue was reported by 10 patients in the intervention group and 9 patients (22.5%) in the placebo group (P = 0.793) 2 weeks after the end of the treatment. Moreover, one week after the end of treatment, 8 patients in the intervention group and 7 patients in the placebo group (P = 0.775) reported dyspepsia and the same issue was reported by 6 patients in UDCA group and 7 patients in the placebo group (P = 0.762) 2 weeks after the treatment. The decrease in the mean score of pain severity from the first to the second week was 0.9 ± 1.10 in UDCA group and 0.66 ± 0.86 in the placebo group, which was not statistically significant (P = 0.720). **Conclusion:** According to the results, the effect of UDCA on abdominal pain after laparoscopic cholecystectomy cannot be considered positive and calls for more studies.

Key words: UDCA, laparoscopic cholecystectomy, abdominal pain

Introduction

Gallstone is a relatively prevalent disease. About 20 million people suffer from gallstones in the United States, and about 500,000 cholecystectomies are done every year (Schwartz's principle of surgery, 2015). About 95% of the patients with cholecystitis symptoms have gallstones and 90% of acute pancreatitis occur because of gallstones (Schwartz's principle of surgery, 2015; Sabiston 2012). The symptoms associated with gallstones and their complications are among the most prevalent gastrointestinal diseases that end up in hospitalization costing the United States about 5 billion USD each year (Tint et al., 1982). The existing evidence shows that the incidence of gallstones has been drastically increased in recent decades and it is not yet known to have reached its final level. Considering this progressive increase, changes in lifestyle and new nutritional patterns along with other contributing factors seem to be effective in the prevalence of gallstones (Sabiston 2012).

There are some natural compounds in the body which hinder the production of cholesterol and prevent it from being absorbed in the intestine. UDCA is one of these compounds. UDCA is one of the secondary bile salts endogenously produced by intestinal bacteria. The primary and secondary bile salts digest fatty compounds. This compound contributes to the regulation of cholesterol in the body, which takes effect by reducing the absorption of cholesterol by enterocytes (Stefanini et al., 1974). As one of the bile salts, UDCA has been stated to reduce biliary colic pain in some studies (Tomida et al., 1999). However, biliary pancreatitis may be inhibited by treatment with UDCA. Thus, some studies state that these underlying mechanisms can resolve some of the gallbladder abnormalities, such as gallbladder movement disorders during fasting and that residual gallbladder volume after ingestion can be resolved by using UDCA (Festi et al., 1990; Portincasa et al., 1996). UDCA reduces cholesterol secretion in the bile, reduces cholesterol saturation, and eliminates cholesterol gallstones in human specimens (Stefanini et al., 1974; Perkins and Kehlet, 2000; Bodvall and Overgaard, 1967).

Post Cholecystectomy Syndrome (PCS) refers to a set of unpleasant complications after gallbladder surgery that can have causes similar to preoperative pain (Perkins and Kehlet, 2000). The syndrome can involve a range of symptoms from mild abdominal pain to severe abdominal pain attacks and jaundice (Stefanini et al., 1974, Bodvall and Overgaard, 1967). The etiology of this syndrome is unknown, although there are many assumptions regarding postoperative gallbladder pain, including sphincter of Oddi dysfunction, choledochal stones and gallstones formed after cholecystectomy (Perkins and Kehlet, 2000). According to the reports, Post Cholecystectomy (PCS) syndrome in 10 to 15% of the patients occurs after cholecystectomy, which causes discontent in many of these patients. In a study by

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McHardy, 7.5% of the patients with PCS symptoms needed hospitalization (McHardy 1959). One has to note that the risk of PCS has nothing to do with preoperative findings and can occur equally in all patients. Given the above as well as the high percentage of patients who can develop this complication, the present study was conducted to evaluate the therapeutic effect of UDCA on gastrointestinal pain and dyspepsia after cholecystectomy.

Materials and Methods

The study was a double-blind randomized clinical trial and sampling was done through convenience sampling method. The studied population was all patients undergoing laparoscopic cholecystectomy under the supervision of the researcher surgeon at Shahid Mohammadi Hospital in Bandar Abbas during a 6-month period from March 2017 to September 2018. The inclusion criteria were symptomatic chronic cholecystitis diagnosed in the gallbladder by ultrasound and being 18 to 70 years old. The exclusion criteria were gallstones in the bile duct confirmed by ultrasound or increased bilirubin (gallstones in the liver inside or outside ducts), comorbid metabolic abnormalities including diabetes, the patients admitted with pancreatitis on arrival (undergoing cholecystectomy because of acute pancreatitis), the patients with complications during surgery or had undergone surgery due acute cholecystitis and those without consent to participate in the study.

The sample size was determined with the help of Morgan table given the lack of similar studies (Indeed, when we are neither aware of the variance of the population nor the probability of variable success or failure, statistical formulas cannot be used to estimate sample size. Thus, Morgan table is used which gives the maximum number of samples). Hence, the highest sample size was obtained using the table to obtain accurate statistical information. The sample size was estimated to be 80 if the estimated population of the study was 100 in a 6-month period based on the experience of the professors of the surgery ward. The subjects were randomly divided into two groups according to the inclusion and exclusion criteria and the table obtained from Random Allocation software. After gaining the informed consent from the patients and during the discharge of patients from hospital, Group A was treated using UDCA manufactured by Amin Chemical & Pharmaceutical Co., Iran and the patients in Group B were treated with placebo (placebo was made upon request by Pharmaceutical Company that was quite similar to the original medicine). Both groups were evaluated and examined during the first and second weeks after the treatment. The patients were not charged for the treatment and paraclinic visits at all. The patients in group A were treated using 300 mg UDCA three times a day for two months and group B received the same amount and number of placebo. The blinding method was patients' unawareness with regard to the drug (being real or placebo).

The data collection tool was a researcher-made checklist including demographic information (gender, age, height, weight, and body mass index (BMI)), clinical assessment of abdominal pain, and dyspepsia. The patients' pain severity was evaluated according to Numerous Rating Scale (NRS): the highest possible pain score was 10 and total lack of pain 0 and the other scores were in this range (0 to 10), scored by the patient (Breivik et al., 2000). The obtained data were then entered into SPSS.19 for statistical analysis. The correlation between the variables was examined using Chi-square, Fisher's exact test, Independent T test and Pearson correlation coefficient. P-value less than or equal to 0.05 was considered significant.

Results

The study examined 80 patients randomly divided into two groups of 40 patients: UDCA and the placebo groups. In terms of gender distribution, the two groups were compared: 11 patients (27.5%) were males and 29 patients (72.5%) females in UDCA group and 13 (32.5%) patients were males and 27 (67.5%) females in the placebo group, with no statistically significant differences (P = 0.626), which showed the appropriateness of gender distribution between the two groups. The mean age of the two groups was compared, which was 52.22 ± 6.75 years in UDCA and 53.05 ± 5.34 years in the placebo group, not showing statistically significant differences (P = 0.546) and indicating a good age distribution between the two groups. Mean height in UDCA group was 1.66 ± 0.08 m and 1.65 ± 0.06 m in the placebo group, with no statistically significant differences (P = 0. 724). The mean weight in UDCA group was 75.67 ± 9.42 kg and 77.42 ± 27.26 kg in the placebo group was, which showed no statistically significant differences (P = 0.356). Moreover, the mean BMI in UDCA group was 27.31 ± 2.93 kg / m^2 and 28.22 ± 3.19 kg / m^2 in the placebo group, which showed no statistically significant differences (P = 0.188).

The frequency of 1-week post-treatment pain was compared between the two groups. In UDCA group, 14 patients (35%) and in the placebo group 12 patients (30%) reported pain, but the differences were not statistically significant (P = 0.633). Moreover, regarding the frequency of 2 weeks post-treatment pain, 10 patients (25%) in UDCA group and 9 patients (22.5%) in the placebo group reported pain but the difference was not statistically significant (P = 0.793). Additionally, the frequency of 1-week post-treatment dyspepsia was compared between the two groups: 8 patients (20%) in the UDCA group and 7 patients (17.5%) in the placebo group reported dyspepsia, with no statistically significant differences (P = 0.775). Concerning the frequency 2 weeks post-treatment dyspepsia, 6 patients (15%) in the UDCA group and 7 patients (17.5%) in the placebo group reported dyspepsia, but the difference was not statistically significant (P = 0.762) (Table 1).

Table 1: Comparison of abdominal pain and dyspepsia between the two studied groups

Variable	Sub-group	The groups studied				P-value
		UDCA group		Placebo group		
		Frequency	Percent	Frequency	Percent	

1 week post-treatment pain	Yes	14	35	12	30	0.633
	No	26	65	28	70	
2 weeks post-treatment pain	Yes	10	25	9	22.5	0.793
	No	30	75	31	77.5	
1 week post-treatment Dyspepsia	Yes	8	20	7	17.5	0.775
	No	32	80	33	82.5	
2-weeks post-treatment Dyspepsia	Yes	6	15	7	17.5	0.762
	No	34	85	33	82.5	

Moreover, the mean pain severity scores of 1 week post-treatment pain were compared between the two groups: UDCA group 3.92 ± 0.82 and placebo group 4.08 ± 0.99 in the, which was statistically insignificant (P = 0.669). The mean score of pain severity of 2 weeks post-treatment pain was 3.00 ± 0.66 in UDCA group and 3.44 ± 0.72 in the placebo group, which was statistically insignificant (P = 0.182). The decrease in the mean score of pain severity from the first to the second week was 0.9 ± 1.10 in UDCA group and 0.66 ± 0.86 in the placebo group, which was not statistically significant (P = 0.720). However, 1 week post-treatment pain was reported in 12.5% of the males and 41.1% of females, which was statistically significant (P = 0.018). Moreover, there was no statistically significant relationship between 1 week post-treatment pain with 1 and 2 weeks post-treatment dyspepsia (P = 0.763 and P = 1.000) (Table 2).

Table 2: Comparison of pain one week later according to gender, pain two weeks later, and dyspepsia

Variable	Sub-group	Pain one week later				P-value
		Yes		No		
		Frequency	Percent	Frequency	Percent	
Gender	Male	3	12.5	21	87.5	0.018
	Female	23	41.1	33	58.9	
2 weeks post-treatment pain	Yes	19	100	0	0	0.000
	No	7	11.5	54	88.5	
1 week post-treatment Dyspepsia	Yes	4	26.7	11	73.3	0.763
	No	22	33.8	43	66.2	
2 weeks post-treatment Dyspepsia	Yes	4	30.8	9	69.2	1.000
	No	22	32.8	45	67.2	

The results showed no statistically significant relationship between 2 weeks post-treatment pain with gender, and 1 and 2 weeks post-treatment Dyspepsia (P = 0.157, P = 1.000 and P = 1.000). Mean age in the group that reported 1 week post-treatment pain was 53.84 ± 6.46 years and in the group that did not report pain was 52.05 ± 5.83 years, but the difference was not statistically significant (P=.0218). The mean BMI in the group that reported 1 week post-treatment pain was 28.66 ± 3.70 kg / m^2 and in the group that did not report pain 27.34 ± 2.67 kg / m^2, but the difference was insignificant (P = 0.073). Mean age in the group that reported 2 weeks post-treatment pain was 55.63 ± 5.96 years and in the group that did not report pain 51.70 ± 5.83 years, which was statistically significant (P=0.013). Mean BMI in the group that reported 1 week post-treatment pain was 28.20 ± 4.00 kg / m^2 and in the group that did not report pain 27.63 ± 2.76 kg / m^2, but the difference was statistically insignificant (P= 0.488). There were no statistically significant differences in mean pain severity score 1 week post-treatment in both genders (P = 0.504) and 1 and 2 weeks post-treatment dyspepsia (both P-values equal to 0.067). There were no significant differences in mean pain severity score 2 weeks post-treatment in both males and females and 1 and 2 weeks post-treatment dyspepsia (all three P-values equal to 0.216).

In this study, the correlation between pain severity score with age and BMI was evaluated, and the results are presented in Table 3.

Table 3: Correlation analysis between pain severity score with age and BMI

Correlation between the two variables	**Pearson correlation coefficient**	**P-value**
1 week post-treatment mean pain intensity with mean age	-0.055	0.788
1 week post-treatment mean pain intensity with mean BMI	0.251	0.216
1 week post-treatment mean pain intensity with 2 weeks post-treatment mean pain intensity	0.330	0.167
2 weeks post-treatment mean pain intensity with mean age	0.032	0.896
2 weeks post-treatment mean pain intensity with mean BMI	0.057	0.817

Discussion

In the present study, 11 male patients, 29 female patients in UDCA group, 13 male patients, and 27 female patients in the placebo group were examined, with no statistically significant differences. According to the results, it seems that the number of laparoscopic cholecystectomy cases in the female population is about 3 times that of the male population. In a study by Middelfart et al. (1998) to examine pain and dyspepsia after elective and acute cholecystectomy, the female to male ratio was 2.11. In the present study, this ratio was 56 to 24 equal to 2.33, which is in line with the study by Middelfart et al. (1998). The results show that the hypothesis stating that female gender is a risk factor for gallstones is somewhat justified (Marschall and Einarsson, 2007). The mean age of the two groups was compared, which was 52.22 ± 6.75 years in UDCA and 53.05 ± 5.34 years in the placebo group, not showing statistically significant differences. In the study by Middelfart et al., the median age in the acute cholecystectomy group was 69 years with a range of 24 to 98 years and in the gallbladder group was 66 years with a range of 21 to 94 years. The mean age in that study was somewhat higher than the present study, which may be because of the inclusion criteria: 18 to 70 years of age. Concerning mean BMI, it was 27.31 ± 2.93 kg / m^2 in UDCA group and 28.22 ± 3.19 kg / m^2 in the placebo group, which showed no statistically significant differences. The studied population has a relatively high BMI and are in overweight category (BMI ranging from 25 to 29.99). Indeed, obesity is considered a risk factor for gallstones as well (Marschall and Einarsson, 2007).

Concerning pain existence frequency, 1 week post-treatment, there were 14 patients in UDCA group and 12 patients in the placebo group. 2 weeks post-treatment, there were 10 patients in UDCA group and 9 patients in the placebo group, but the difference was statistically insignificant. 4 patients in the intervention group and 3 in the placebo group did not have pain one week post-treatment. Concerning the prevalence of dyspepsia 1 and 2 weeks post-treatment, 8 patients in UDCA group and 7 patients in the placebo group reported dyspepsia. Two weeks later, 6 patients in UDCA group and 7 patients in the placebo group reported dyspepsia, but the difference was statistically insignificant. In fact, only 2 patients in the intervention group had no dyspepsia 1 week post-treatment. The decrease in the mean score of pain severity from the first to the second week was 0.9 ± 1.10 in UDCA group and 0.66 ± 0.86 in the placebo group, which was not statistically significant. Although mean age and BMI were significantly higher in the group reporting pain one week post-treatmnet compared to the group with no pain, it was statistically insignificant.

One week post-treatment pain was reported in 12.5% of the males and 41.1% of females, which was statistically significant. In a study by Middelfart et al. to examine pain and dyspepsia after elective and acute cholecystectomy, Abdominal pain after cholecystectomy was reported in 37% of the patients, which was 36% in acute cholecystectomy and 39% in gallstone groups. Abdominal pain was reported in 42% of the females and 29% of the males, which was statistically significant (Middelfart et al., 1998).

Conclusion

According to the results, the effect of UDCA on abdominal pain after laparoscopic cholecystectomy cannot be considered positive and needs more consideration

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Weak recommendations indicate that the desirable effects of adherence to a recommendation prob-ably outweigh the undesirable effects, but the panel is less confidentâ€™. Recommendations were based not only on the quality of evidence (high, moderate, low, very low) but also on the balance between wanted and unwanted effects, and on values and preferences13.Â Evidence is strong in support of TAP blocks for abdominal surgery in general, although the effect is evident only during the first 48 h after surgery and none of the evidence is from gastrectomies.Â Laparoscopic versus open distal gastrectomy for gastric cancer: a meta-analysis of randomized controlled trials and high-quality nonrandomized studies. Ann Surg 2012; 255: 446 â€“ 456. Ursodeoxycholic acid (UDCA), also known as ursodiol, is a secondary bile acid, produced in humans and most other species from metabolism by intestinal bacteria. It is synthesized in the liver in some species, and was first identified in bear bile, which is the derivation of its name Ursus. In purified form, it has been used to treat or prevent several diseases of the liver or bile ducts. Effect of cholecystectomy on bile acids as well as relevant enzymes and transporters in mice: Implication for pharmacokinetic changes of rifampicin // Eur J Pharm Sci. â€” 2017. â€” n 1. â€” Ñ€. 141â€“153. 42. Chiang L. T., Chen W., Chiang J. Y. PXR induces CY-P27A1 and regulates cholesterol metabolism in the intestine // Lipid Res. â€” 2007. â€” n 2. â€” Ñ€. 37â€“42.Â Postcholecystectomy pain syndrome: pathophysiology of abdominal pain in sphincter of Oddi type III // Gastroenterology. â€” 1999. â€” n 1. â€” Ñ€. 900â€“905. 45. Cotton P. B., Durkalski V., Romagnuolo J. et al.Â Effect of ursodeoxycholic acid on glycemic markers: A systematic review and meta-analysis of clinical trials // Pharmacol Res. â€” 2018. â€” n 135. â€” Ñ€. 144â€“149. Chronic abdominal pain is pain that is present for more than 3 months. It may be present all the time (chronic) or come and go (recurring). Chronic abdominal pain usually occurs in children beginning after age 5 years.Â Indigestion (dyspepsia) due to peptic ulcer or drugs such as aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Stomach irritation (caused by aspirin or NSAIDs, cola beverages [acidity], and spicy foods). Liver disorders, such as hepatitis.Â Whether the pain or other digestive upset occurs after eating or drinking dairy products is important because lactose intolerance is common, especially among blacks, Hispanics, Asians (particularly East Asian countries), and American Indians. Ursodeoxycholic acid (UDCA) has been used for the treatment of gall bladder stones since 1972. UDCA decreases stone formation and relieves symptoms by improving bladder muscle contraction and decreasing cholesterol levels in bile (6,7). The effects of UDCA on cholesterol stones are well known. However, there are no studies showing the effect on bile stones/sludge in pregnancy. The objective of this study is to evaluate the effect of UDCA for the treatment of symptomatic gall bladder stones and/or sludge during pregnancy. MATERIALS and METHODS. Study Design.Â After the dissemination of laparoscopic cholecystectomy with low morbidity and mortality rates, the use of medical treatment modalities became less common.