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Usefulness of Ursodeoxycholic Acid in Management of Gallstone Disease in Children

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Abstract
Objective – The aim of the study is to assess the usefulness of ursodeoxycholic acid in management of gallstone disease in children. Materials and Methods – The prospective study aimed to assess the management of gallstone disease in children. We analyzed all new cases of cholelithiasis during the period from January 2016 to March 2020. Forty-eight new cases of cholelithiasis were enrolled in the study. The diagnosis was established by ultrasound examination due to different complaints in previously healthy patients, or during regular follow-up visits in patients with a chronic disease. A Student t-test, Fisher's test and $\chi 2$-test were used in the statistical processing, where appropriate. Results – A 6-month course of treatment with ursodeoxycholic acid was conducted in 72.9% of cases (N=35). In 27.1% (N=13) of patients this treatment was not administered. Successful dissolution of gallstones was observed in 31.4% (N=11) of treated patients (N=35), over a period of 1 to 6 months. In the group of nontreated patients (N=13), successful dissolution of gallstones was achieved in 38.5% (N=5). Cholecystectomy was performed in 10.4% (N=5) patients, and 1 patient underwent endoscopic retrograde cholangiopancreatography. No early complications, relapse or postcholecystectomy syndrome were observed in the 12-month follow-up period. Conclusion – Management of cholelithiasis in children can often be a challenge. In a selected patient group, conservative treatment may be successful. Use of ursodeoxycholic acid can lead to dissolution of gallstones in patients with preceding dehydration. The effectiveness of ursodeoxycholic acid, except in children with dehydration, was higher in patients with stones of smaller diameter. Proper timing for transference from conservative to surgical treatment is essential.

Key Words: Pediatric Gallstone Disease ▪ Ursodeoxycholic Acid ▪ MRI - Cholangiography ▪ Contrast Enhanced Ultrasound ▪ Cholecystectomy.

Introduction

Gallstone disease (cholelithiasis) has been affecting mankind since ancient times. The oldest known case of a patient with cholelithiasis is seen in evidence of gallstones in an Egyptian mummy from the time of the 11th dynasty (2025-1991 BC) (1). The first description of gallstones in medical literature was by the Florentine physician and pathologist Anthony Benivenius, in his book "De abditis nonnullis ac mirandis morborum et sanationum causis" (2). It is widely accepted that gallstone disease is more common in the adult population, and predominant in developed countries. The wide use of high frequency abdominal ultrasound should make the diagnosis of cholelithiasis in children more common. Gallstones can most often be found as an additional finding in children with other diseases - chronic hemolytic anemia, total parenteral nutrition, cystic fibrosis, celiac disease, Crohn's disease etc. (3).

The epidemiology in the general pediatric population remains unclear, with only limited published data. The calculated average incidence of

the disease in children in Italy is 0.13 – 0.2% (5). Similar data have been published for the pediatric population in Japan, 0.13%. Ultrasound screening in The Netherlands revealed an incidence of 1.9% (3, 4). In the Tertiary Pediatric Center in Bulgaria, the reported incidence was 0.03%. The disease incidence shows a bimodal distribution during childhood – a small peak in infancy and a pronounced predominance in adolescence (3).

Guidelines for management of patients with cholelithiasis are available for adults. There are no accepted forms for children (6). Recommendations for management of gallstone disease in children were published in 2011 in Bulgaria. These recommendations discussed only surgical management. Surgical treatment is indicated for patients with progressive mechanical jaundice and / or an associated inflammatory process (calculous cholecystitis with choledocholithiasis, calculous pancreatitis), cholelithiasis with protracted course, and frequent "bile colic" events. There are no recommendations for prevention and management in asymptomatic cholelithiasis and between attacks (18).

The increase in the incidence of children with chronic hemolytic anemias, obese patients, celiac disease, cystic fibrosis and inflammatory bowel disease, increases the risk and incidence of gallstone disease. The number of children using bariatric surgery because of obesity is also increasing. This type of surgery, as well as rapid changes in children's weight, are known to be predisposing factors for gallstone disease (6).

There are currently no generally accepted guidelines for surgical treatment of asymptomatic cholelithiasis. Some centers have adopted their own guidelines for cholecystectomy in the asymptomatic form of the disease. Most of them consider cholecystectomy to be justified only in cholelithiasis because of chronic hemolytic anemia (7). Schmidt et al. recommend that the indications for surgery should be carefully assessed, as its long-term effects in children are unknown. The recommendation is that cholecystectomy should be performed as concomitant manipulation in asymptomatic patients during another surgical intervention (8). Cholelithiasis is not a diagnostic challenge in most cases, but its etiological clarification and the optimal therapeutic approach remain unclear. Determining the exact moment for transition from conservative to surgical treatment is important for appropriate management of the disease.

The aim of this study is to assess the usefulness of ursodeoxycholic acid in management of gallstone disease in children.

Materials and Methods

A prospective cohort study was conducted in a single tertiary center. We collected data on patients who underwent treatment at the Department of Pediatrics and Pediatric Surgery of St. George's University Hospital from January 2016 to March 2020. We performed abdominal ultrasound examination in all children referred to the clinic with known predisposing factors for the development of cholelithiasis, recurrent abdominal pain and gallstone disease diagnosed accidentally in out-patients. A second ultrasound examination was performed by an independent radiologist for confirmation of the diagnosis. Subsequent follow-up ultrasound examinations were performed by the first scientist. We enrolled all children in the study with proven hyperechoic shadowing lesions in the gallbladder or bile tree. Initially, 59 patients were selected. Subsequently 11 patients were excluded from the study - 1 patient with a gallbladder polyp, 1 patient with a gallbladder clot due to haemobilia, and 9 patients due to failure to complete the 12-month follow-up period.

Two- and three-dimensional mode abdominal ultrasound was performed with a Philips EPIQ 7 ultrasound system for assessment of the size, number, and location of the gallstones. Convex C9-2 and C5-1 (9-2 MHz) probes and a sector X7-2 (7-2 MHz) probe were used. Contrast enhanced ultrasound (CEUS) was performed to distinguish gallbladder polyps from gallstones and sludge. Sonovue contrast agent was used in doses of 0.6, 1.2 and 2.4 ml, according to the age and weight of the patients. Abdominal plain x-ray was done

to confirm the presence of radiolucent gallstones. MRI-cholangiography, according to a standardized protocol, was performed in the case of a suspected bile tree abnormality or choledocholithiasis. All symptomatic children with confirmed gallstone disease were initially treated with spasmolytics, nonsteroidal anti-inflammatory drugs, crystalloids, proton pump inhibitor, and ursodeoxycholic acid (UDCA). Children with recurrent episodes of biliary colic (>2) were referred for cholecystectomy. Gallstone disease was defined as symptomatic (with complaints) and asymptomatic (without complaints), single (with a single stone visualized) or multiple (with more than one stone).

We defined "dehydration" as significant depletion of body water and electrolytes, in varying degrees, occurring in patients with enteral or parenteral losses. Grades of dehydration were defined as "mild" in case of loss of less than 5 % of body weight, "mild" loss of 5 – 10%, and "severe" in loss of >10%. Six-month treatment with UDCA was prescribed and an appropriate low-cholesterol diet was recommended to all children who were not indicated for cholecystectomy. Follow-up abdominal ultrasound examinations of patients were performed at 1, 3, 6 and 12 months.

Statistical Analyses

The data from the study were processed using the software products MS Excel 2007 (Microsoft, Redmond, WA, USA) and SPSS 19.0 (IBM, Chicago, IL, USA), based on the MS Windows 10 operational system (Microsoft, Redmond, WA, USA). The Student t-test, Fisher's test and χ2-test were used in the statistical processing, where appropriate. For all analyses, a significance level of the null hypothesis of $P<0.05$ and a confidence interval of 95 % were used.

Results

A total number of 48 new cases of cholelithiasis were registered and followed-up, 52% (N=25) were females and 48% (N=23) males. Overall, there was no significant difference in the sex distribution. The age range was from 1 mo to 17 y 5 mo (Me 7 y 5 mo, SD±4 y 2 mo).

Table 1. Predisposing Factors

Predisposing factor	N (%)
Previous ileum resection	1 (2.1)
Total parenteral nutrition	2 (4.2)
Biliary system malformation	5 (10.4)
Family history	2 (4.2)
Obesity	13 (27.1)
No predisposing factors	25 (52)

The incidence of children with cholelithiasis was 2.3% (48/2131) among those admitted to the Department of Pediatric Gastroenterology. Predisposing factors were found in 48% (N=23) of patients, and in 52% (N=25) they were not reported. The most common predisposition in the studied patients was overweight, found in 27.1% (N=13). There was no significant difference between the factors predisposing children to gallstone disease. The predisposing factors are summarized in Table 1.

The most common complaint was isolated abdominal pain in 31.3% (N=15). In the remaining patients, pain was accompanied by vomiting 16.7% (N=8), cholestasis 10.4% (N=5) and fever 6.3% (N=3). A moderate degree of dehydration was registered in 27.1% (N=13). Dehydration was observed due to acute vomiting and diarrhea in 8/13 patients with acute gastroenteritis, and in 5 patients due to severe vomiting. Of these patients, 2/13 had a cyst in the common bile tract, 2/13 had pyruvate dehydrogenase deficiency, and 1/13 were on total parenteral nutrition. In 35.4% (N=17) of patients, cholelithiasis was asymptomatic.

A medical history of previous biliary colic had been reported in 39.6% (N=19) of the children, and the number of cases of colic varied from 2 to 14. In 25% (N=12) of the cases, biliary colic was observed once at the onset of the disease but did not recur. In 35.4% (N=17) of the children there was no history of biliary colic. There was no significant difference regarding the type of complaint and the presence of biliary colic.

Multiple gallstones were registered in 64.6% (N=31) of the cases but in 35.4% (N=17) only one was found. The maximum gallstone size measured by ultrasound was 30 mm, and the minimum was 2 mm (Me 5.9, SD±4.2). In all patients, the gallstones were found to be radiolucent. All symptomatic children, 64.6% (N=31), received treatment with spasmolytics and intravenous fluid infusion. Additional analgesia with a non-steroidal anti-inflammatory drug was administered in 56.3% (N=27), and there was no case that required opioid analgesia. In 10.4% (N=5) of the cases antibiotic treatment was used due to clinical and laboratory signs of inflammation.

In all patients treatment with UDCA was initiated at a standard dose of 10-15 mg/kg. In 27.1% (N=13) of the children treatment was discontinued during the hospital stay due to various reasons – the refusal of the child to take the drug, parental disagreement with the treatment, or severe diarrhea as a side effect. The treatment with UDCA was continued for a 6-month period in 72.9% (N=35) of the patients after discharge.

Complete dissolution of the gallstones was registered in 31.4% (P=0.03, N=11/35) within 1 to 6 months in the group of patients receiving treatment. In those who did not receive UDCA therapy, gallstone dissolution was recorded in 38.4% (P=0.79, N=5/13). There was no statistically significant difference (P=0.17) in gallstone dissolution between the children treated with UDCA and those without treatment. The evolution of cholelithiasis in the 6 months period after establishing the diagnosis is shown in Fig. 1.

There was a significant difference in the incidence of gallstone dissolution between the group of children with previous dehydration, 83.3% (N=10, P=0.03), and the group without dehydration, both receiving UDCA treatment. Dissolution of the stones was observed within 1-3 months of initiation of the therapy. In only two children did the stones persist for more than 12 months. In children without dehydration, dissolution of gallstones was observed in only 1 patient.

A significant difference was found between the groups with different sizes of gallstones, as shown in Fig. 2. In 62.5% of the patients receiving UDCA therapy, and in 18.8% of patients without UDCA therapy, the dissolved gallstones were less than 5 mm in size. Gallstones larger than 5 mm were found in 1 patient receiving UDCA, and in 2 without therapy. One of the latter 2 patients had a gallstone larger than 10 mm.

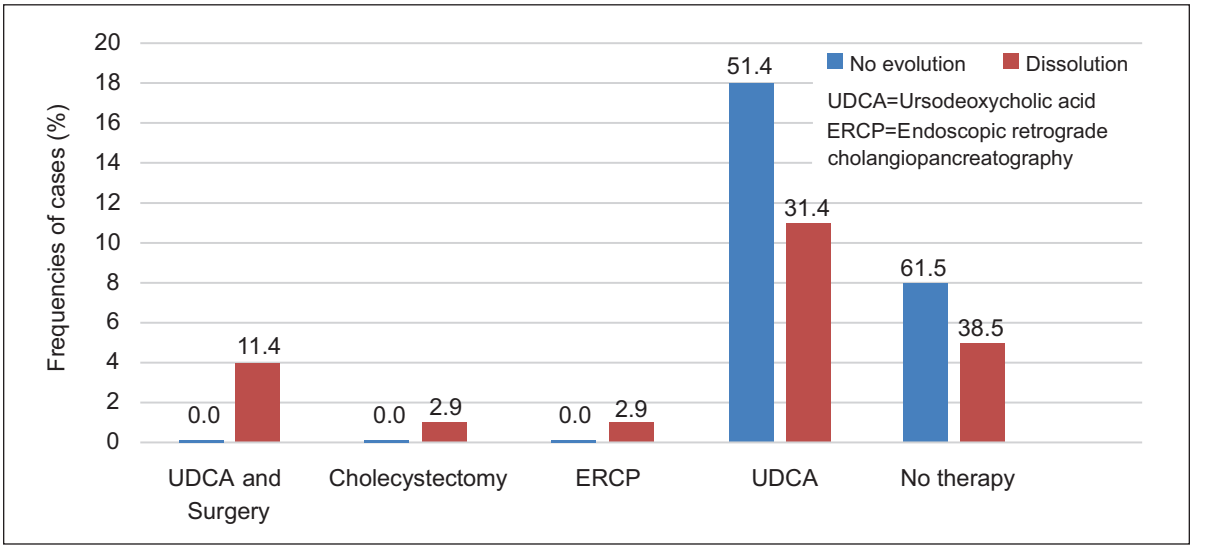

Fig. 1. *Evolution of gallstone disease.*

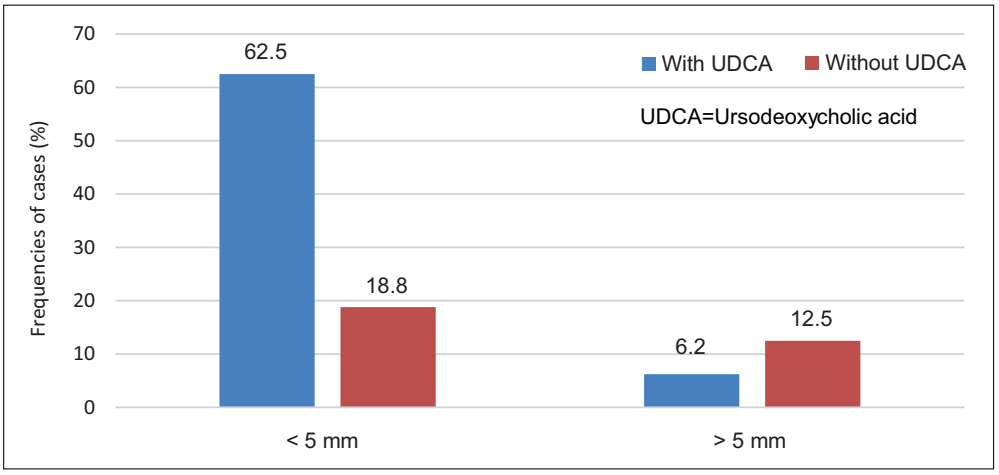

Fig. 2. *Initial size of dissolved gallstones in UDCA and non-UDCA groups.*

Table 2. Disease at Admission in Patients with Dissolved Gallstones

Disease/Predisposing factor	Therapy	
	With UDCA* N (%)	Without UDCA* N (%)
Total parenteral nutrition in newborn	1 (6.3)	-
Acute gastroenteritis	8 (50)	-
Cyst of the common bile duct	1 (6.3)	1 (6.3)
Obesity	1 (6.3)	1 (6.3)
Pyruvate dehydrogenase deficiency	-	2 (12.5)
Coeliac disease	-	1 (6.3)

*Ursodeoxycholic acid.

In the group of patients with successfully dissolved gallstones receiving UDCA therapy, the most common disease was acute gastroenteritis in 50% of cases. The most common diagnose in the group without UDCA therapy and dissolved gallstones was pyruvate dehydrogenase deficiency, found in 2 children. All diagnoses at admission of patients with dissolved gallstones are summarized in Table 2.

Laparoscopic cholecystectomy was performed in 10.4% (N=5) children. In one case, the observed choledocholithiasis required endoscopic retrograde cholangiopancreatography (ERCP). No postcholecystectomy syndrome or recurrence of lithiasis was observed

Discussion

UDCA decreases biliary cholesterol saturation by 40 to 60% by inhibiting the intestinal absorption and biliary secretion of cholesterol. Also, UDCA increases water content in the bile, improving gravity dependent biliary flow (17).

In our study, UDCA treatment dissolved gallstones in children with dehydration. The possible reason is oversaturation of the bile with cholesterol and/or depletion of its water content during dehydration, and restoration of bile liquidity by UDCA. But the question why not all moderately or severely dehydrated children develop gallstones remains unclear. The presence of unknown additional factors in them is a possible explanation. We could not

find a report about the role of the dehydration in gallstone formation in children.

Successful dissolution was observed in the group with small-size gallstones. The same results were reported by Stawarski et al. and Lee et al. In their articles, the initial size of the dissolved gallstones was less than 5 mm, but there was no discussion about additional factors (16, 17). Corte et al. reported that the drug is not effective enough to dissolve gallstones in children. However, the use of UDCA improves subjective complaints such as abdominal pain, bloating and discomfort (5). Gökçe et al. consider that gallstones caused by ceftriaxone cannot always dissolve spontaneously. They observed that treatment with UDCA was ineffective in that group (9). Di Claudia et al. considered the benefits of UDCA in improving gallbladder emptying in patients with rapid weight loss (10). Portincasa et al. found the use of UDCA to be effective only in patients with small, pure cholesterol, radiolucent gallstones (11). Stokes et al. reported the protective effect of UDCA and a high fat diet in patients with rapid weight loss (12). The use of the drug to prevent the formation of gallstones is not recommended in children after heart surgery (13). UDCA has a limited effect in the prevention of gallstone formation in adults after bariatric surgery (14) or gastrectomy (15).

Our follow-up of asymptomatic patients and those without complaints after conservative treatment showed that they had no complications and no return of symptoms or relapse of dissolved gallstones within 12 months. Corte et al. postulated that patients may need follow-up for a longer period (5). Lee et al. reported recurrence rate up to 50% and 70% in 5- and 12-year periods, respectively (17). The possible explanation of the lack of relapses in our cohort is the short period of follow-up after discontinuation of UDCA treatment.

Limitations of the Study

The major limitation of our study is a small number of patients enrolled in it and the relatively short period of follow-up. More carefully designed randomized studies assessing the role of UDCA treatment in patients with gallstones and dehydration, enrolling a larger number of children, are needed.

Conclusion

The improvement in the diagnosis and the increase in the number of children with predisposing factors, has led to an increase in the incidence of gallstone disease in the pediatric population. Asymptomatic cholelithiasis is not indicated for surgical treatment. There is no significant difference in gallstone dissolvement in terms of UDCA treatment. In patients with previous episodes of dehydration, the probability of dissolving gallstones after treatment with UDCA is high. The effectiveness of ursodeoxycholic acid, except in children with dehydration, was higher in patients with stones of smaller diameter. The use of ERCP or surgery is indicated in a selected subgroup of symptomatic patients.

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Conflict of Interest: The author declares that he has no conflict of interest.

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