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Original Article

Trend of Pediatric Cholecystectomy: Clinical Characteristics and Indications for Cholecystectomy

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Purpose: Number of pediatric cholecystectomy has been recently showing a gradually increasing trend. The purpose of this study was to investigate the clinical features of patients who underwent pediatric cholecystectomy, and the latest trend in cholecystectomy.
Methods: In the present study, we conducted a retrospective chart review on 47 patients who had undergone cholecystectomy at a single center. The entire patient population was divided into two groups, according to the time of cholecystectomy (early group, January 1999 to December 2006; late group, January 2007 to August 2014).
Results: The comparison between the early and late groups showed that the number of cholecystectomy increased from 13 to 34 cases representing a 2.6-fold increase. The mean patient age also increased from 5.94±4.08 years to 10.51±5.57 years (p=0.01). Meanwhile, laparoscopic surgery also increased from 15.4% to 79.4%, respectively ($p<0.001$). However, sex, mean body mass index, comorbidities, indications of cholecystectomy, and previous total parenteral nutrition were not statistically significant.
Conclusion: The results of this study showed that pediatric cholecystectomy cases are increasing, particularly in the 10 to 19 years age group and laparoscopic cholecystectomies are also being performed at an increasing rate. When the patients were compared according to the time of cholecystectomy, there were no differences in other risk factors or indications for cholecystectomy.

Keywords: *Pediatric, Cholecystectomy, Cholelithiasis*

INTRODUCTION

Gallbladder disease in children is relatively rare, and the prevalence of cholelithiasis in children younger than 16 years was reported to be 0.15% in the 1950s [1]. Since then, the prevalence gradually increased and was reported to be 1.9% to as high as 4.0% through 2000 in several studies [2-4]. According to one study, the number of cases with laparoscopic or open cholecystectomy registered at the US national KID (Kid's Inpatient Database) increased from 4,767 cases in 1997 to 7,652 cases in 2009 [5].

Cholecystectomy is one of the common surgical procedures most often performed in adults, but is rarely performed in children because the prevalence of gallbladder disease is lower in children and the natural course of disease is different between children and adults [3]. Well-known risk factors for pediatric cholelithiasis are puberty (in girls), long-term use of total parenteral nutrition (TPN), hemolytic anemia, and obesity [2]. In the past, the comorbidity rate of hemolytic anemia in patients with gallstone disease was reported to be as high as 20% to 25%, but recently it has shown a decreasing trend. In contrast, the prevalence of non-hemolytic gallstone disease has been shown to increase as the prevalence of obesity increases [6,7].

One reason for the increase in the frequency of pediatric cholecystectomy may be that laparoscopic cholecystectomy is commonly accessible. Laparoscopic cholecystectomy is the first choice when performing cholecystectomy in adults and has also been utilized in pediatric cholecystectomy [5,8].

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Because the etiology and the trend of pediatric gallbladder disease have changed with time, in this study we aimed to examine the characteristics of patients in whom cholecystectomy was performed at a single center, to identify the indications for cholecystectomy, and to investigate whether they changed over time.

METHODS

We retrospectively reviewed the medical charts of patients who underwent cholecystectomy between January 1999 and August 2014 at Seoul National University Children's Hospital (Seoul, Korea). A total of 56 patients underwent cholecystectomy during the time period, and 47 patients of those in whom primary cholecystectomy was performed were included in the study, after excluding all cases in which cholecystectomy was performed along with other procedures due to conditions such as congenital biliary anomaly, hepatoblastoma, etc.

The following characteristics of 47 patients were analyzed; sex, age, time period of the procedure, symptoms and diagnosis at the time of the procedure, comorbidities, the presence or absence of TPN prior to the procedure, method of the procedure, height, weight, body mass index (BMI), clinical course, and complications.

Diagnosis prior to the procedure was determined based on symptoms, physical examination, and imaging studies. The surgical indications were classified as follows: gallstone, gallbladder polyp, obstructive disease with choledocholithisis or the presence of jaundice, or the diagnosis of common bile duct dilation, acalculous cholecystitis, gallbladder abscess, and gallbladder associated tumor. BMI and BMI percentiles were determined by using the Korea National Health and Nutrition Examination Survey [9]. For comorbidities, hematologic disorders including hemolytic disease, heart disease, liver disease, malignancy, gastrointestinal disease, neurologic disease, renal disease, pulmonary disease, and thyroid disease were investigated, and also the use of TPN for longer than 4 weeks prior to the procedure was examined.

To investigate any trend over time, we divided the patients into two groups, using the midpoint of the study period as a cutoff (early group, January 1999 to December 2006; late group, January 2007 to August 2014), and compared the groups by patient characteristics, indications for cholecystectomy, comorbidities, and clinical course. Additionally, we compared differences between patient groups with and without comorbidities.

Statistical analyses were conducted using IBM SPSS Statistics 21 (IBM Co., Armonk, NY, USA). Mean scores were compared using 2 independent sample t tests for continuous and normally distributed data, and Mann-Whitney U test for non-normally distributed data.

This study was approved by Institutional Review Board at Seoul National University Hospital (IRB file No. 1602-069-740).

RESULTS

The mean age of 47 patients who underwent cholecystectomy was 9.24±5.53 years (range, 2 months to 18 years). There were 22 boys (46.8%) and 25 girls (53.2%). Concerning indications for cholecystectomy, gallstones were the indication of cholecystectomy in 31 cases (66.0%), which was the most common indication, followed by 5 cases (10.6%) with obstructive disease including choledocholithiasis. When overlap was allowed in case of several symptoms, patients with initial symptom of vague abdominal pain were 24, patients with nausea and vomiting were 12, patients with fever were 11, patients without symptoms but the cases of incidental diagnosis were 7, patients with right upper quadrant pain were 6, patients with jaundice were 4, and patient with dyspepsia was 1. In 3 of the 5 cases with obstructive disease, open cholecystectomy was performed and during the procedure, choledocholithiasis was removed, and in 1 of those cases, T-tube choledochostomy was performed. In the other 2 cases with obstructive disease, laparoscopic cholecystectomy was performed. In both cases, intraoperative choledochoscopy was performed because the presence of a tiny stone in the distal common bile duct was suspected on pre-procedure imaging, but no abnormality was found, and thus it is believed that the stone was passed. In a case of a 9-year-old patient who underwent surgery for an inflammatory myofibroblastic tumor found in the gastric antrum, the tumor metastasized to the gallbladder and a cholecystectomy procedure was performed. A total of 27 patients (57.4%) had comorbidities, of which

hematologic disorders were the most common, found in 11 patients (23.4%) including 5 children (10.6%) with hemolytic disease, followed by heart disease in 8 patients (17.0%) (Table 1).

Table 1. Characteristics of the Patients (n=47)

Variable	Value
Sex	
Male	22 (46.8)
Female	25 (53.2)
Mean age (yr)	9.24±5.53
Age category (yr)	
0–3	7
4–7	12
8–11	9
12–15	12
≥16	7
Surgical indications	
Gallstone	31 (66.0)
Gallbladder polyps	3 (6.4)
Obstructive disease	5 (10.6)
Chronic cholecystitis	3 (6.4)
Gallbladder abscess	4 (8.5)
Gallbladder tumor	1 (2.1)
Comorbidities	27 (57.4)
Hematologic disorder	11 (23.4)
Hemolytic disease	5 (10.6)
Heart disease	8 (17.0)
Liver disease	6 (12.8)
Malignancy	5 (10.6)
Gastrointestinal disease	4 (8.5)
Neurologic disease	2 (4.3)
Renal disease	1 (2.1)
Pulmonary disease	1 (2.1)
Thyroid disease	1 (2.1)
None	20 (42.6)

Values are presented as n (%), mean±SD, or n only.

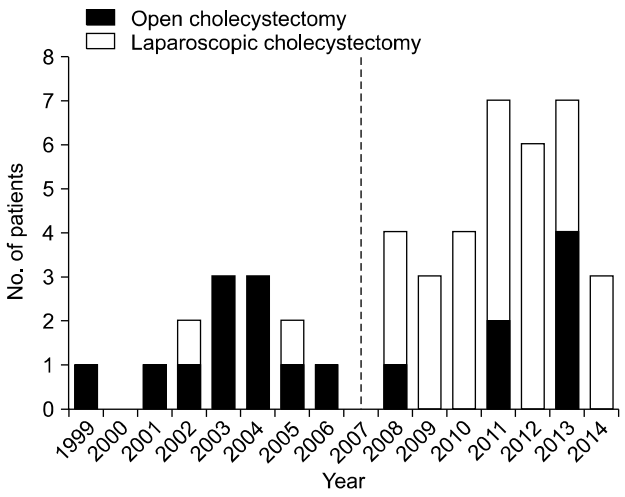

Fig. 1. Annual incidence for pediatric cholecystectomy.

When the time of procedure was divided into early and late, 13 patients underwent the procedure between 1999 and 2006 (early group, 27.7%), and 34 underwent the procedure between 2007 and 2014 (late group, 72.3%). The number of cholecystectomies performed in early period was increased more than double late period from 1999 to 2006 (Fig. 1).

The sex distribution was similar between the early and late groups (Table 2). The mean age in years at the time

Table 2. Comparison between Early and Late Groups (n=47)

	Early group (n=13)	Late group (n=34)	p-value
Male	7 (53.8)	15 (44.1)	0.392
Mean age (yr)	5.94±4.08	10.51±5.57	0.01
Age category (yr)			
0–3	3	4	0.377
4–7	6	6	0.065
8–11	2	7	>0.99
12–15	2	10	0.464
≥16	0	7	0.166
≥10 yr	2 (15.4)	21 (61.8)	0.008
Surgical indications			
Gallstone	8	24	0.728
Gallbladder polyp	0	2	>0.99
Obstructive disease	1	4	>0.99
Chronic cholecystitis	1	2	>0.99
Gallbladder abscess	2	2	0.304
Gallbladder tumor	1	0	0.277
Comorbidities	9 (69.2)	18 (52.9)	0.348
Hematologic disorder	3	8	>0.99
Hemolytic disease	1	4	>0.99
Heart disease	4	4	0.191
Liver disease	1	5	>0.99
Malignancy	1	4	>0.99
Gastrointestinal disease	–	4	0.564
Neurologic disease	–	2	>0.99
Renal disease	1	–	0.277
Pulmonary disease	1	–	0.277
Thyroid disease	–	1	>0.99
TPN (≥4 wk)	1	4	>0.99
Mean BMI (kg/m^2)	15.45±2.08	17.33±3.53	0.078
Categorized by percentile			
>95	0	1	>0.99
85–95	1	1	0.481
70–85	2	16	0.091
50–70	2	3	0.607
<50	8	13	0.197
Laparoscopy	2 (15.4)	27 (79.4)	<0.001
Complication	1	1	0.481

Values are presented as n (%), mean±SD, or n only.
TPN, total parenteral nutrition; BMI, body mass index.

of the procedure was 5.94±4.08 years in the early group and 10.51±5.57 years in the late group, a statistically significant difference (p=0.01). When age was categorized into groups of 0-3 years, 4-7 years, 8-11 years, 12-15 years, and 16 years or older, the distribution of age categories was similar between the early and late groups, but when only the proportion of patients of age 10 or older was examined, the late group showed a higher proportion (early group 15.4% vs. late group 61.8%; p=0.008). Gallstones were the most common indication for cholecystectomy in both groups, and there was no significant inter-group difference in any indications. Comorbidities were found in 69.2% of the early group and 52.9% of the late group, and the groups showed a similar distribution. The groups did not differ in terms of the number of cases with TPN administered longer than 4 weeks, either.

Mean BMI was higher in the late group than in the early group, but the difference was not statistically significant (early group 15.45±2.08 kg/m^2 vs. late group 17.33±3.53 kg/m^2; p=0.078). On examination of BMI percentiles, there was 1 case with obesity higher than the 95th percentile in the late group, and there was 1 overweight patient with a percentile point between the 85th and 95th percentiles in each group. Most patients were classified as normal weight below the 85th percentile. Laparoscopic cholecystectomies were performed in 2 cases (15.4%) in the early group, and 27 cases (79.4%) in the late group, showing increasing trend (p<0.001).

Two patients died after the procedure, and in both cases, the death did not have a direct association with the operation. One of the patients was a 5-year-old child with aplastic anemia in the early group. The patient had gallbladder abscess and underwent open cholecystectomy and died 74 days after the procedure from the pneumonia the patient had prior to the operation. The other was an 18-year-old patient in the late group with aplastic anemia, like the first patient. The patient's lung condition prior to the procedure was poor due to pneumonia, and thus open cholecystectomy was performed. The patient died 35 days after the procedure due to worsening of the pneumonia (Table 2).

DISCUSSION

The prevalence of gallbladder disease is lower in children compared to that in adults; therefore, cholecystectomy is rarely performed. Recently, however, several studies reported that pediatric cholecystectomy is in an increasing trend. Walker et al. [5] reported in a single-center study that the frequency of cholecystectomy increased from 165 cases in 2003-2007 to 288 cases in 2008-2012, and also reported in 2012 that the number of cholecystectomies performed in a single center was 7.5 cases per year in period of 1980-1996 and 101 cases per year in 2005-2008 [7]. Such an increase in pediatric cholecystectomy may be a result of increases in the average BMI, non-hemolytic cholelithiasis, and biliary dyskinesia [5]. Between the two periods investigated in the present study, despite the number of total surgery was increased 1.3 times, the number of cholecystectomy in the late group increased 2.6 times compared to that in the early group.

In the study reported in 2013, cases accompanied with hemolytic disease among 453 pediatric patients with gallbladder disease decreased from 12.1% during period of 2003-2007 to 8.7% during the period of 2008-2012 [5]. This study also found hemolytic disease in 5 patients (10.6%) with gallbladder disease although the number was small, 4 of them had gallstones.

According to the literature on adult cholelithiasis, pregnancy and oral contraceptive are suggested as reasons for the higher prevalence of cholelithiasis in women than in men [10,11]. Additionally, hormonal changes during female puberty are known to play an important role in the formation of gallstones by increasing the cholesterol saturation of bile [12,13]. A study reported that due to these reasons, before puberty there was no sex difference in the occurrence of gallstone disease, whereas after puberty the rate was significantly higher in women (2.9%) than in men (0.9%) [14]. In the present study, 45.8% of the patients were girls under age 10 and 60.9% over age 10. Proportion of girl is higher in teenage but the difference was not statistically significant (p=0.385). The proportion of girls increased over time, with 46.2% in the early group and 55.9% in the late group. Although the difference was not significant, it is believed

that there may be an effect due to hormonal changes, as the mean age increased in the late group.

Adult obesity is known to cause gallstone disease by excessive hepatic cholesterol secretion and changed motility of the gallbladder [13]. Dittrick et al. [15] reported that obesity is a risk factor for gallbladder disease in children as well. In a study on pediatric cholecystectomy unrelated to hematologic disorders, being overweight or obese was found to be associated with complicated cholelithiasis [16]. However, in the present study, the prevalence of overweight or obese was relatively lower, 4% and 2%, respectively, compared to those (8.3% and 9.1%, respectively) in the Korea National Health and Nutrition Examination Survey. Although BMI was slightly higher in the late group, the difference between groups was not significant, and additionally, there was no significant inter-group difference in comorbidities. This medical center is a tertiary center among Korean medical facilities and has many patients with rare diseases. Of the total patients, 57.4% had underlying comorbid conditions and BMI tended to be lower in cases with comorbidities (17.87±3.33 kg/m^2 vs. 16.03±3.09 kg/m^2; p=0.056), which may explain why there were few overweight or obese patients in the study compared to that in a group of normal children.

Since pediatric laparoscopic cholecystectomy was first performed in 1990, its safety for children has been demonstrated. The procedure has advantages, such as that the length of hospital stay is shortened and that oral food intake is possible sooner [17]. The present study found that laparoscopic cholecystectomy was performed only in 15.4% of the early group, whereas it was performed in 79.4% of the late group. Previous studies reported that laparoscopic cholecystectomy took, on average, 70-90 minutes [18,19], and the present study found a similar result, a mean length of 72.0±58.8 minutes. Laparoscopic procedures have already been proven to be a safe and efficient treatment in pediatric patients with gallstone disease, and the use of laparoscopic procedures is expected to continuously increase.

In this study, the mean age of patients at the time of cholecystectomy increased from 5.94±4.08 years in the early group to 10.51±5.57 years in the late group, and also, the proportion of children over age 10, the approximate beginning of puberty, significantly increased. It is speculated that as the number of cholecystectomy increase, there will be an increase among patients in puberty, one of the aforementioned risk factors.

In addition, the prevalence of obesity tends to increase with age [20], which may have contributed to the higher mean age in the late group. In the study, 4 patients (8%) underwent cholecystectomy before the age of 1 year, and other studies have reported 6%-15% of their patients were under age 1 when they underwent the procedure [21,22]. During the formation of gallstones in newborn babies, the nucleation time is shorter and the cholesterol saturation index is higher, and therefore TPN administration has a greater impact than age [23]. However, in the present study TPN was not administered to any patients who underwent cholecystectomy under age 1, and 1 of the 4 patients under age 1 had a comorbidity of hematologic disease.

Biliary dyskinesia is characterized by nonspecific abdominal pain, and nausea in the absence of cholelithiasis, and is defined as abnormal gallbladder contractility on cholecystokinin-stimulated cholescintigraphy [24]. However, biliary dyskinesia is controversial in pediatric patients. Some studies have reported that cholecystectomy relieved symptoms of biliary dyskinesia in 72%-100% of cases [25-27]. However, another study with a median follow-up of 2.8 years, reported that only 44.2% patients were relieved of symptoms completely after cholecystectomy [28].

Srinath et al. [29] showed that pediatric patients with biliary dyskinesia who underwent cholecystectomy visited gastroenterology clinics more commonly and had more gastrointestinal symptom related hospitalizations than those with symptomatic cholecystolithiasis (OR 7.76, 95% CI 3.58-16.84). They insisted on treatment strategy used for other functional disorder rather than surgical approach, but the use of hepatobiliary scintigraphy is particularly of concern as it involves administration of radiopharmaceuticals to very young patients, infants, and neonates, who are at high potential risk of detrimental effects from ionizing radiation [30]. In our hospital, hepatobiliary scintigraphy in pediatric patients is not utilized frequently. Hence, the diagnosis of biliary dyskinesia is made rarely at out hospital.

The limitations of the study are as follows. It was retrospectively conducted with a small number of patients with a relatively short follow-up period. Although, cholecystectomy is controversial in pediatric patients with biliary dyskinesia, biliary dyskinesia makes up a large part of pediatric cholecystectomy cases [5]. Therefore, exclusion of biliary dyskinesia may be a limitation.

In conclusion, gallbladder disease is rare in children, and pediatric cholecystectomy is also rarely performed. The present study found that the number of cases in which primary cholecystectomy was performed over the recent 8 years has increased more than 2 fold compared to that in the previous period of the same length, and that patient age at the time of procedure also increased. There was no difference between the two time periods in terms of indications for cholecystectomy, and gallstones were the top indication in both periods. Comorbidities did not differ between periods, either. The mean BMI was in an increasing trend, although the inter-period difference was not statistically significant. The number of laparoscopic cholecystectomy has increased significantly during recent years. In consideration that the rate of obesity has increased in young children and children at puberty, follow-up research would be necessary to investigate risk factors for gallstone disease in pediatric patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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