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Is paracetamol responsible for fatal acute liver failure in pediatric patients after hip dysplasia surgery?

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Abstract. – OBJECTIVE: It is well known that local complications, such as avascular necrosis and arthrosis can develop after surgery for developmental dysplasia of the hip (DDH). Thus far, systemic complications that may develop in such cases have not been identified in the literature. This study is the first case series to evaluate acute liver failure (ALF) development after DDH surgery in pediatric patients.

PATIENTS AND METHODS: Six patients, five female and one male, who underwent DDH surgery were selected for this study. Perioperative fasting time, laboratory values, treatments, histopathological evaluations, and prognoses after ALF in these patients were evaluated retrospectively.

RESULTS: All the patients were administered paracetamol and sevoflurane in therapeutic doses. The patients were referred postoperatively to our pediatric emergency department after 5 ± 1.67 days (range = 3-7 days) on average. The average perioperative fasting time was 9.3 ± 0.82 hours (range = 8-10 hours). Due to the very high aminotransferases and use of paracetamol, intravenous N-acetylcysteine was administered alongside supportive treatments to all the patients. After liver transplantation, two of three patients with grade 3 encephalopathy, died in the early postoperative period. Histopathological evaluations of the three patients' explants were compatible with toxic hepatitis due to paracetamol.

CONCLUSIONS: Paracetamol is a commonly used analgesic after pediatric surgery. The therapeutic dose of paracetamol remains uncertain in children who have been fasting for a long time and have been exposed to hepatotoxic drugs due to previous surgery. In conclusion, caution should be exercised in the use of paracetamol in children with DDH who will undergo surgery, and careful perioperative clinical and laboratory monitoring for ALF is essential.

Key Words:
Developmental dysplasia, Paracetamol toxicity, Encephalopathy, Histopathological evaluation.

Introduction

The determination of etiology is important in patients with acute liver failure (ALF), and the frequency of the causes varies with age. In most patients, the cause cannot be identified. Metabolic causes are a more common cause of ALF among those under 1 year of age, whereas viral hepatitis is a more frequent cause of ALF for patients above this age[1,2]. Although ALF due to drug toxicity is less frequent, paracetamol is recognized worldwide as the most common agent causing ALF, and hence, it should be regarded as the causative factor when all other causes are excluded[3].

Since 2002, IV paracetamol (also known as acetaminophen) has been widely used for short-term treatment of pain and fever, especially after surgery[4]. Although it is well known that paracetamol can result in ALF in acute overdoses and chronic supratherapeutic doses, ALF rarely develops in therapeutic doses, although some rare cases have been reported[5-7].

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Local complications, such as avascular necrosis and osteoarthritis, are frequently encountered after surgical treatment of patients with developmental hip dysplasia (DDH)[8,9]. However, thus far, development of ALF in a patient after DDH surgery has not been reported in the literature. This study presents pediatric patients who underwent DDH surgery in different centers and developed ALF in the early postoperative period. Thus, the current study is the first series of cases in the literature presenting ALF after DDH surgery.

Patients and Methods

Ethical Approval

This retrospective study was approved by the Local Ethics Committee of Inonu University, Turkey (2018/4-7).

Patient Selection

Between September 2010 and September 2017, 204 patients who applied to the pediatric emergency clinic with a pre-diagnosis of ALF were investigated. Six patients (one at our clinic and five at other institutions) had undergone DDH surgery in the last one week before ALF pre-diagnosis were included in the study. Patients who had liver disease before surgery and those who developed liver toxicity after surgery but did not meet the criteria for ALF were excluded from the study.

Study Design

The required data were sourced from the patients' records in our hospital and records from other health centers where DDH surgeries were performed. Relevant information was also obtained from the patients' parents. The patients' age, sex, hip dysplasia degrees (according to Tönnis classification), and prognosis were investigated.

The diagnosis of ALF in the patients was made according to the criteria provided by the Pediatric Acute Liver Failure Study Group (PALFSG)[10]. In children who developed ALF, the decision to transplant was made according to the daily evaluation of important prognostic variables, such as the interval between the onset of jaundice and encephalopathy, degree of encephalopathy, level of bilirubin, prothrombin time (PT), international normalized ratio (INR), alanine aminotransferase (ALT) level, and ammonia (NH_3) level[11]. In addition, the King's College scoring system for acetaminophen toxicity was taken into account when making the decision to transplant[12].

Surgical procedures applied to the patients, medical treatments received, duration of surgical fasting, dose of paracetamol taken, date of admission to our hospital in the postoperative period, and tests for ALF etiology of the patients were recorded. No disease other than DDH was detected in the preoperative examinations and evaluations of all the patients. Three of the six patients (1st, 5th, and 6th) received medical treatment, and three (2nd, 3rd, and 4th) underwent liver transplantation.

Histopathological Examination

Tissue samples from the 2nd, 3rd, and 4th patients who underwent liver transplantation were examined histopathologically. The liver explants were fixed in 10% formaldehyde. All the segments and the hilar region (the vascular and main biliary ducts) were sampled macroscopically. After the macroscopic sampling, routinely processed formalin-fixed paraffin-embedded tissues were sliced to a thickness of 4 μm, and hematoxylin and eosin-stained slides were examined under a light microscope.

Results

The age, sex, degree of hip dysplasia, treatments, duration of surgical fasting, encephalopathy grade, and prognosis for each patient are presented in Table I. The patients were admitted to the hospital within 2 or 3 days after the surgery due to the development of vomiting, sleepiness, and seizure attacks. After an average of 5 ± 1.67 postoperative days (range = 3-7 days), they were referred to the pediatric emergency clinic of our center. The laboratory values of the patients when they first applied to the emergency room are presented in Table II. As soon as all the patients were admitted, intravenous N-acetylcysteine (NAC) treatment was started alongside supportive treatments.

The results of the viral and metabolic investigations performed to determine the etiologies at the time of the patients' first applications to the pediatrics emergency room were normal. Sevoflurane anesthesia was administered to all the patients during DDH surgery. Paracetamol was also used in therapeutic doses as an analgesic after the surgery.

Table I. Patient age, sex, hip dysplasia degree, surgeries applied, duration of fasting, encephalopathy grade, and prognosis.

No	Age / Sex (month)	Tönnis (R/L)	AIA (R/L)	Surgery	Fasting (hour)	EP grade	Prognosis
1	17/F	1/3	30/45	OR+IO	9	1	MT, live
2	18/F	2/2	38/36	IO	9	3	LTP, died
3	25/F	2/2	35/39	IO	10	3	LTP, died
4	19/F	3/3	47/43	OR+ IO	10	3	LTP, live
5	20/F	1/3	26/41	OR+IO	10	1	MT, live
6	8/M	2/1	33/26	A+CR	8	1	MT, live

F, female; M, male; AIA, acetabuler index angle; A, arthrography; CR, closed reduction; EP, encephalopathy; IO, iliac osteotomy; LTP, liver transplant; MT, medical treatment; OR, open reduction.

The histopathological findings of the 2nd, 3rd, and 4th patients who underwent liver transplantation were similar. Hepatocytic necrosis in the intermediate and pericentral zones (zones 2 and 3, respectively) was detected microscopically (Figure 1). The necrosis was coagulative in character and was not accompanied by inflammation. The periportal hepatocytes were partially intact, and hydropic degeneration and macrovesicular steatosis were observed (Figure 2). The current morphological picture was reported in the pathology report as paracetamol toxicity.

The mean follow-up period of the living patients was 4 ± 1.26 years (mean±SD) (range: 3-6 years), and they healed completely. Three of the patients who did not respond to medical treatment underwent living donor liver transplantation. The 4th patient who recovered after liver transplantation did not experience a major problem and is being followed up. However, the patient's parents did not accept our recommendation for secondary surgery to avoid the recurrence of hip dislocation due to the early termination of the cast on account of the emergency liver transplantation.

Discussion

Complications such as avascular necrosis and arthrosis may develop after DDH surgical treatment[8,9]. However, none of the studies in the current literature report systemic complications such as ALF that may develop after DDH surgery.

Viruses, metabolic diseases, and drugs are the most common causes of ALF in young children[13]. The most common drug causing ALF is paracetamol[10]. Thus, the role of paracetamol in ALF should be questioned after other etiological causes of liver failure are eliminated[3].

The recommended dose of paracetamol in children is 10-15 mg/kg every 4-6 hours, and the maximum daily dose should not exceed 50-75 mg/kg[6]. The development of liver failure from paracetamol is dose-dependent; hepatic failure is more likely with ingested dosages exceeding 150 mg/kg. All the patients included in this study received paracetamol at the therapeutic dose. However, children have a lower occurrence of liver failure from paracetamol overdose than adults, perhaps because of the effect of age on

Table II. Laboratory values of patients when they first applied to the emergency room.

No	INR 0.8-1.2	PT second 11-14.5	DB mg/dL 0-0.5	TB mg/dL 0.2-1.2	NH3 µg/dL 31-123	AST U/L 5-34	ALT U/L 0-55	LDH U/L 125-243	PC mg/L 10-30	Lactate mmol/L 4.5-19.8	pH 7.35-7.45
1	2.8	31.3	1.12	1.46	199	6792	5477	6650	–	–	7.48
2	6.3	73.3	9.96	16.09	985	11057	8078	12818	–	82.6	7.14
3	3.7	42.1	2.68	4.45	873	22933	8083	33622	–	82.2	6.92
4	4.05	47.9	3.75	5.28	413	4202	4113	1995	15.5	55	7.43
5	2.41	28.2	6.03	9.81	71	993	1689	951	5.5	–	–
6	3.4	39.8	2.14	2.69	174	5509	2994	3325	42	–	7.10

DB, direct bilirubin; TB, total bilirubin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PC, paracetamol; pH, power of hydrogen.

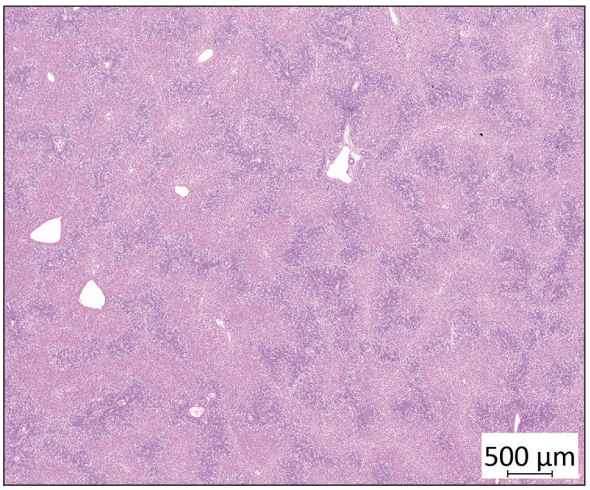

Figure 1. Necrosis areas (pale areas) in zone 3 and zone 2 (H&E,×10).

glutathione production[14]. Although ALF is rare in young children, it can be difficult to diagnose clinically. Encephalopathy, which is essential in the diagnosis of ALF in older children and adults, is difficult to detect in young children and often occurs in the advanced stages of the disease[15]. The late transfer of transplanted patients from other hospitals to our institution is likely to be related to the delay in the diagnosis of ALF due to their young age.

Although there is no definitive definition of ALF in children, it has been described by PALFSG as a condition with biochemical evidence of acute liver injury, inability to correct coagulopathy despite vitamin K treatment, the presence of encephalopathy, and the absence of previously known chronic liver disease. In addition, ALF is defined in patients without encephalopathy when INR > 2 or PT > 20 seconds, and in patients with encephalopathy when INR > 1.5 or PT > 15 seconds[10]. These criteria were also used to confirm the diagnosis of ALF in the patients in this study.

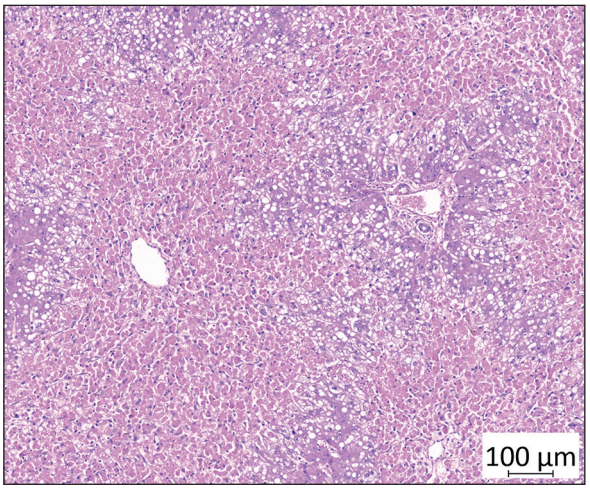

Figure 2. Fatty cell changes in periportal hepatocytes (H&E, ×50).

The child who developed ALF due to paracetamol had advanced and treatment-resistant coagulopathy, an excessively high serum ALT level, as well as an almost normal (slightly high) total bilirubin level (Table II). Encephalopathy is not common and is typically of grade 1 or 2. Centrilobular (zone 3) necrosis is generally detected with a biopsy[1,14]. The morphological findings in the explants of our patients who underwent liver transplantation were similar and showed pericentral (zone 3) coagulation necrosis, which was more specific for paracetamol toxicity (Figures 1 and 2). Although zonal coagulation necrosis has been observed in many etiologies, pure coagulation necrosis without inflammation is specific to paracetamol, halothane, and cocaine toxicity[16]. The patients in this study belonged to the pediatric age group and received only paracetamol as a postoperative pain reliever. Sevoflurane was administered as an anesthetic to all the patients. Sevoflurane has been used extensively in pediatric patients since the 1990s due to its low hepatotoxic effect[17]. On the other hand, halothane, which can cause necrosis in the liver and shares the same morphological picture as that of paracetamol, was not administered to these patients.

Of the three patients whose blood paracetamol levels could be checked, two showed normal values, probably due to the late admission to our emergency room after the initiation of their symptoms. The peak blood value of paracetamol occurs 4 hours after ingestion, and low values are attributable to elimination from the system if the test is performed after 24 hours[18]. Although five of our six patients did not show elevated paracetamol levels, paracetamol toxicity was considered as the ALF etiology in all our patients due to the use of paracetamol as an analgesic in the postoperative period, the elimination of viral and metabolic causes in the investigation, high transaminase levels, and compatible histopathological findings.

When paracetamol is administered, it is metabolized in the liver and forms a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI),

paracetamol itself is not toxic. Typically, the formed NAPQI is converted into non-toxic metabolites by glutathione. NAPQI, accumulates and may cause hepatocellular necrosis in cases involving paracetamol overdoses that decrease the reduced glutathione level, prolonged fasting, malnutrition, concomitant use of other hepatotoxic drugs, and metabolic stress with possible dehydration in the perioperative period[5-7,19]. In the case of our patients, paracetamol may have facilitated hepatotoxicity even at the therapeutic dose due to the long perioperative surgical fasting period. The risk of paracetamol toxicity, especially in young children, can be decreased if the healthcare team plans the surgery well such that a shorter fasting period is required.

The most important intervention affecting the prognosis of a patient with paracetamol toxicity is to start NAC orally or intravenously within the first 24 hours of detection[20]. Although NAC treatment was initiated in the emergency department in all the cases presented in this study, it was not effective in three patients with late referrals who had grade 3 encephalopathy (Table I).

Previous studies have emphasized that healthcare professionals or parents may inadvertently administer incorrect paracetamol doses to children[21,22]. Losek et al[22] reported that paracetamol administration *via* the rectum was significantly associated with supratherapeutic dosing. Sequential oral, rectal, and parenteral administrations of paracetamol to children should be recorded carefully, and every effort should be made to avoid exceeding the therapeutic dose.

Although the prognosis of ALF due to paracetamol is good[10], three patients were transplanted and two died because of the high level of hepatic encephalopathy, the high bilirubin, NH_3, INR, and PT blood values (Tables I and II), and the late referrals of these patients to our hospital. No scoring system exists for making the decision to transplant children with ALF, and the indications for transplants are not clear. It has been shown that the diagnostic value of daily evaluation of important prognostic variables when deciding about transplantation in children is superior to scoring systems such as King's College and MELD-Na used in adults[11]. Among the prognostic variables, the time between the onset of jaundice and encephalopathy; the degree of encephalopathy; the bilirubin, PT, INR, ALT, and NH_3 blood levels; and the number of white blood cells should be followed closely before the decision to transplant is made[12]. The urgent transfer of patients with ALF to the nearest pediatric hepatology clinic will reduce the need for transplantation and increase their survival rates.

This study has some limitations, it is a retrospective study and only a few cases were analyzed. In addition, the level of paracetamol in the blood has not been examined in all patients. Moreover, it has not been determined what makes these patients susceptible to paracetamol toxicity, and this issue needs to be explored.

Although paracetamol toxicity is dose dependent, the effects of long-term fasting, surgical interventions causing metabolic stress, dehydration and additional drug use on paracetamol metabolism have not been investigated in the studies that determine the relationship between dose and toxicity[5-7]. Well-designed prospective studies are thus needed to determine the most appropriate therapeutic dose of paracetamol in young children with DDH who have been fasting for a long time and also face the additional risks posed by the surgery.

Conclusions

Paracetamol, a commonly used analgesic after pediatric surgery[23], has rarely caused acute hepatic failure in therapeutic doses. The dosing recommendations of paracetamol in pediatric patients after DDH surgery may need to be reconsidered, and patients should be closely monitored for ALF in the first postoperative week, clinically and via laboratory testing.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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