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Protective Effect of Ursodeoxycholic Acid on Liver Function in Pediatric Patients with Seizure Treated with Phenobarbital

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ABSTRACT

Background: *Epilepsy is a common and devastating neurological disease. Its treatment, especially when using phenobarbital, causes liver complications, and it is therefore essential to identify a way to reduce liver complications. This study aimed to investigate the protective effect of ursodeoxycholic acid on liver function in pediatric patients with seizure treated with phenobarbital.*

Materials and methods: *The present study was conducted on 80 patients (40 in the placebo group and 40 in the ursodeoxycholic acid group). To assess the effect of intervention, liver enzyme levels after five weeks of treatment were recorded. Independent t-test and ANOVA repeated measures were used to compare the means.*

Conclusion: *The study results showed that the administration of ursodeoxycholic acid had a relative effect in improving liver function in patients with liver injury caused by phenobarbital.*

Keywords: ursodeoxycholic acid, liver function, liver enzymes, liver injury, phenobarbital.

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INTRODUCTION

A seizure is a sign of simultaneous, abnormal and intense neuronal activity in the brain, which can manifest as changes in the mental status, level of consciousness, tonic and clonic movements. Seizures may be provoked or unprovoked. Provoked seizures are caused by low blood sugar, alcohol withdrawal, blood sodium deficiency, fever, brain infection or brain injury (1). Unprovoked seizures caused by stress or lack of sleep may lead to continuous seizures (1, 2). Brain diseases, which have at least one seizure and an increased risk of seizures over a longer period of time, are collectively known as epilepsy, a condition that looks like an epileptic seizure but does not include fainting, non-epileptic psychotic events, and tremors (1). Studies have shown that after a seizure, the probability of a second seizure is about 50%. Also, almost 80% of people with epilepsy live in developing countries (3). These cases show the importance and prevalence of seizures. Phenobarbital is one of the most commonly prescribed drugs for the treatment of seizures. Animal experiments show that phenobarbital induces liver microsomal enzymes in dogs and causes the proliferation of the smooth endoplasmic reticulum of the liver and increases the weight of the liver, while also accelerating the metabolism of various drugs and endogenous compounds (4). In addition, these mechanisms cause elevated levels of liver enzymes. Affected enzymes include alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT) (5). Recent studies regarding the use of phenobarbital have shown results beyond enzyme induction in liver cells, so mice treated continuously with phenobarbital developed liver tumors (6). Several studies in the evaluation of ursodeoxycholic acid (UDCA) compared to the control group have acknowledged the reduction of liver enzymes such as ALT (7-9) and AST (10). Based on the above-mentioned information, the present study aimed to investigate the protective effect of ursodeoxycholic acid on liver function in pediatric patients with seizures treated with phenobarbital. ❑

MATERIALS AND METHODS

This clinical trial was carried out on 80 patients with seizure treated with phenobarbitals who were referred to Amir-Al-Momenin Hospital in Zabol, Iran, in 2022. Subjects were divided into two equal groups (40 in the placebo group and 40 in the UDCA group) using random allocation software (Figure 1). Given the short duration of the follow-up, we had no loss to follow-up. We used the following exclusion criteria: patients with non-epileptic seizures caused by hypoglycemia, fever, heatstroke, lack of sleep, stress and trauma; the use of certain drugs such as some antidepressants (Zyban and Wellbutrin); and seizures in patients undergoing treatment for mood disorders or who were taking painkillers (Ultram or tramadol) and penicillins (methicillin and oxacillin) used to treat skin infections, urinary tract infections, ear and respiratory tract infections. The sample size was calculated based on a study by Tabrizian *et al* (11) (mean±SD 19.4±5 for group 1, and mean±SD 22.8±7 for group 2) considering the statistical power of 0.80 and alpha of 0.05. The first group was given the appropriate dose of UDCA tablets, and the second group received a placebo. Before receiving the medicine and also after 72 hours and then every week for five weeks, blood samples were taken from all subjects and further analyzed for liver enzymes using the same standard laboratory kits.

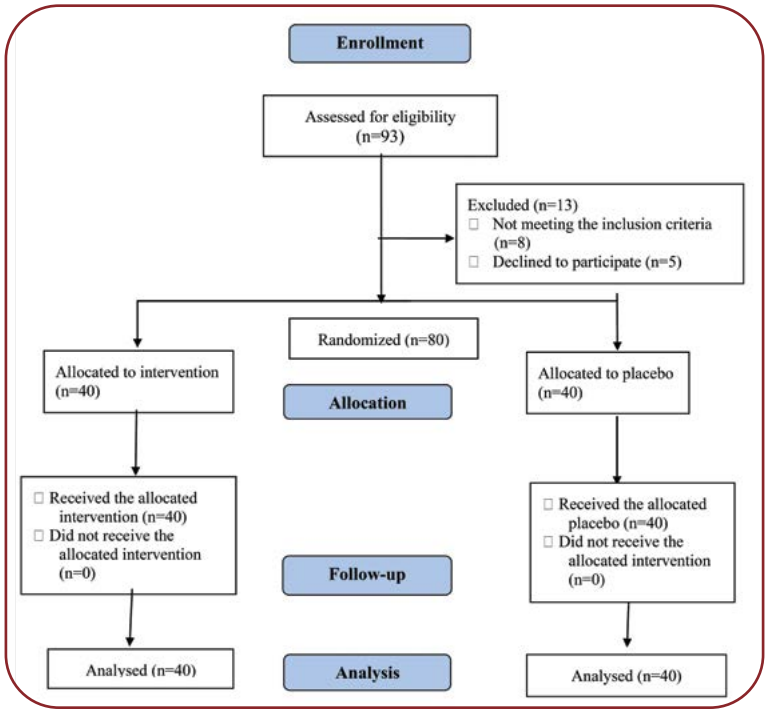

FIGURE 1. CONSORT flow diagram of the study design

Ethical consideration

The research was conducted in accordance with the tents of the Declaration of Helsinki. The study was approved by the Ethics Committee of Zabol University, Iran (IR.ZBMU.REC.1401.054). Accordingly, written informed consent was obtained from all participants before they received any intervention. This study was part of Fatemeh Mir's medical thesis prepared in Zabol University, Iran.

Data analysis

Data were analyzed using SPSS version 20. Mean and SD (standard deviation) were used to describe quantitative data, while frequency and percentage were used to describe qualitative data. In order to compare variables in the two groups, independent t-test and chi square test were used. Intra-group changing trend of enzymes was compared using ANOVA repeated measure. ❑

RESULTS

Study participants had a mean age of 8±3.51 years (range 1-17 years). Among all subjects, 29 (36.3%) were boys and 51 (63.8%) girls, without any significant difference between groups (P=0.816). There was no significant difference in age between the two groups (P=0.488) (Table 1).

TABLE 1. Comparison of age between the ursodeoxycholic acid and placebo groups

Variable		Mean	SD	P value
Age	Placebo	7.73	3.72	0.488
	Ursodeoxycholic acid	8.28	3.32	

The mean AST level before treatment was significantly higher in the UDCA group than the placebo one. Therefore, the time trend of AST after the intervention was compared between the two groups, and in the fifth week the mean AST level was found to be significantly lower in the UDCA group than the placebo group (P<0.001) (Table 2) (Figure 2).

The mean ALT levels before treatment and during the first week of treatment were signifi-

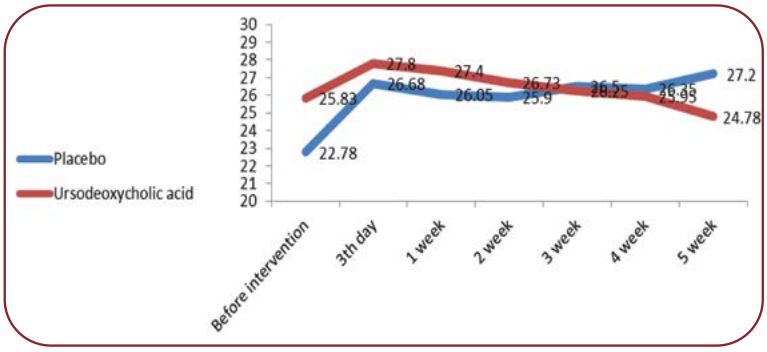

FIGURE 2. Time trend of AST levels in the ursodeoxycholic acid and placebo groups

TABLE 2. Comparison of AST levels between the ursodeoxycholic acid and placebo groups

AST	Group	Mean	SD	P value
Before the intervention	Placebo	22.78	2.54	<0.001
	Ursodeoxycholic acid	25.83	4.03	
Three days after intervention	Placebo	26.68	1.92	0.544
	Ursodeoxycholic acid	27.80	2.76	
One week after intervention	Placebo	26.05	2.38	0.711
	Ursodeoxycholic acid	27.40	2.45	
Two weeks after intervention	Placebo	25.90	2.99	0.970
	Ursodeoxycholic acid	26.73	2.70	
Three weeks after intervention	Placebo	26.50	3.38	0.081
	Ursodeoxycholic acid	26.25	2.56	
Four weeks after intervention	Placebo	26.35	2.84	0.145
	Ursodeoxycholic acid	25.95	2.63	
Five weeks after intervention	Placebo	27.20	2.19	<0.001
	Ursodeoxycholic acid	24.78	3.33	

ALT	Group	Mean	SD	P value
Before the intervention	Placebo	27.53	3.21	<0.001
	Ursodeoxycholic acid	30.08	3.68	
Three days after intervention	Placebo	31.83	2.59	0.054
	Ursodeoxycholic acid	32.90	2.31	
One week after intervention	Placebo	30.78	2.94	0.047
	Ursodeoxycholic acid	31.90	1.90	
Two weeks after intervention	Placebo	30.88	3.09	0.455
	Ursodeoxycholic acid	31.33	2.18	
Three weeks after intervention	Placebo	29.95	3.43	0.398
	Ursodeoxycholic acid	30.60	3.41	
Four weeks after intervention	Placebo	29.25	3.29	0.778
	Ursodeoxycholic acid	29.05	3.02	
Five weeks after intervention	Placebo	29.10	3.24	0.388
	Ursodeoxycholic acid	28.48	3.19	

TABLE 3. Comparison of ALT levels between the ursodeoxycholic acid and placebo groups

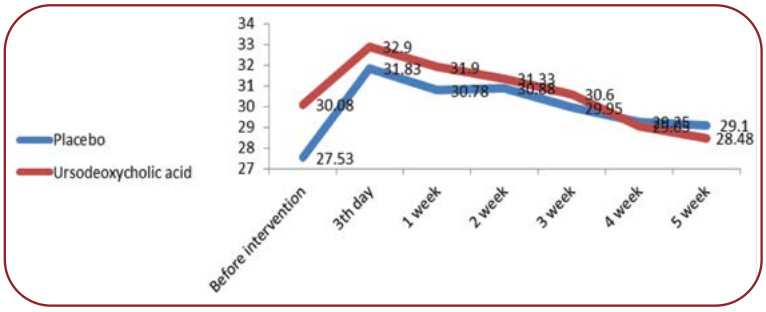

FIGURE 3. Time trend of ALT levels in the ursodeoxycholic acid and placebo groups

ALP	Group	Mean	SD	P value
Before the intervention	Placebo	399.13	109.408	0.040
	Ursodeoxycholic acid	343.20	128.762	
Three days after intervention	Placebo	399.13	109.408	0.040
	Ursodeoxycholic acid	343.20	128.762	
One week after intervention	Placebo	399.13	109.408	0.040
	Ursodeoxycholic acid	343.20	128.762	
Two weeks after intervention	Placebo	381.28	129.353	0.178
	Ursodeoxycholic acid	342.95	128.239	
Three weeks after intervention	Placebo	399.13	109.408	0.040
	Ursodeoxycholic acid	343.20	128.762	
Four weeks after intervention	Placebo	399.13	109.408	0.038
	Ursodeoxycholic acid	342.95	128.239	
Five weeks after intervention	Placebo	399.13	109.408	0.038
	Ursodeoxycholic acid	342.95	128.239	

TABLE 4. Comparison of ALP levels between the ursodeoxycholic acid and placebo groups

cantly higher in the UDCA group than the placebo one. Therefore, we compared the time trend of ALT levels between the two groups after the intervention by testing them before the inter-

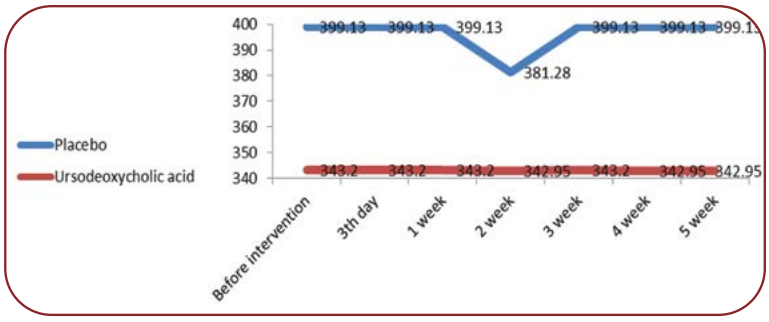

FIGURE 4. Time trend of ALP levels between the ursodeoxycholic acid and placebo groups

Albumin	Group	Mean	SD	P value
Before the intervention	Placebo	3.86	0.442	0.545
	Ursodeoxycholic acid	3.86	0.367	
Three days after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	
One week after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	
Two weeks after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	
Three weeks after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	
Four weeks after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	
Five weeks after intervention	Placebo	3.86	0.442	0.401
	Ursodeoxycholic acid	3.95	0.367	

TABLE 5. Comparison of albumin levels between the ursodeoxycholic acid and placebo groups

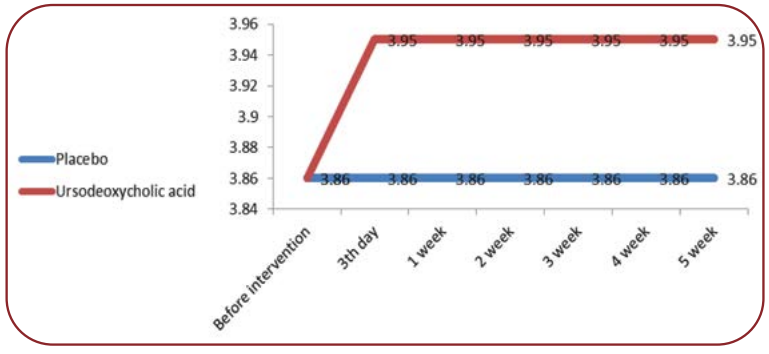

FIGURE 5. Time trend in albumin levels between the ursodeoxycholic acid and placebo groups

vention. There was no statistically significant difference during the remaining weeks (P<0.05). In general, the mean ALT value was not significantly different in the two groups during the study period (P=0.481) (Table 3) (Figure 3).

The mean ALP level before the intervention was significantly lower in the UDCA group than the placebo one. Therefore, the time trend of this enzyme was compared by us between the two groups after the intervention by testing them before the intervention. For the same reason, despite the significant difference in ALP level between the two groups, the overall difference between them was not statistically significant (p=0.250) (Table 4) (Figure 4).

Regarding albumin, there was no significant difference in its levels before the intervention and during the study period between the UDCA

and placebo groups (P=0.423) (Table 5) (Figure 5). ❑

DISCUSSION

The present study was conducted to investigate the protective effect of UDCA on liver enzymes in patients with seizures treated with phenobarbital. Our findings showed a significant decline in the mean AST levels during the fifth week of treatment with this drug, with no statistically significant difference being observed in post-treatment ALT, ALP and albumin levels among participants to the study groups. Therefore, it can be seen that the administration of UDCA does not affect the serum level of the majority of liver enzymes in patients receiving phenobarbital and can only cause a decrease in AST levels after five months.

Ursodeoxycholic acid as a primary bile acid without any toxic effects is considered to be an antioxidant (12-18). It has been used for centuries in traditional Chinese and Japanese medicine for the treatment of gallbladder and liver diseases (12, 13, 15). Ursodeoxycholic acid controls hypertransaminasemia following drug-related hepatotoxicity (17, 18). We found five case reports on the therapeutic effects of UDCA in the management of toxic hepatitis caused by amoxicillin, clavulanic acid, flutamide and sequential administration of cyproterone acetate, flutamide and Herbalife, respectively, which emphasized its potential efficacy in toxic hepatitis (19-23). In addition, some studies revealed the preventive role of UDCA in amoxicillin plus clavulanic acid and methotrexate-induced hepatotoxicity (24, 25). The mechanism of UDCA when used for the treatment of drug-induced hepatitis is likely due to its antioxidant properties, as reported by *in vivo* studies (17, 18). We did not notice any adverse reactions or drug intolerance in our patients.

Asgarshirazi *et al* investigated the effect of UDCA on 22 subjects with liver damage following the use of antiepileptic drugs. Their results showed that UDCA was effective and well tolerated in children suffering from drug-induced hypertransaminasemia, with no side effects being seen. Therefore, the authors suggested that the use of UDCA in patients with hepatotoxicity following antiepileptic drugs was a safe and effective medication (26).

Although we observed a decrease in the levels of liver enzymes in participants to our study, the general trend of changes was not significant. Importantly, as we conducted a placebo-controlled trial, our present research had more power than the aforementioned studies. Therefore, the difference between the results may be due to variations in the method of project implementation, sample size, control of confounding effect and follow-up duration. Da Jung Kim *et al* (27) investigated the effect of UDCA on the improvement of liver enzymes and concluded that UDCA was a metabolic byproduct of intestinal bacteria that had protective effects. However, its molecular mechanism is not known yet. The authors tested blood sample and urine samples of patients with obesity and liver dysfunction. Nine subjects were randomly divided into 10 vitamin E up to 400 IU twice a day and UDCA up to 300 mg twice a day for eight weeks. Four weeks following treatment with UDCA, the score of liver function improved and levels of serum microRNA-122 and liver deoxycholic acid decreased. Ursodeoxycholic acid was found to be effective in reducing uremic toxins. Besides, the use of vitamin E did not result in uremic toxin reductions like UDCA. Ursodeoxycholic acid and vitamin E are effective in liver function improvement by various mechanisms (15).

Although the design of the above-mentioned study was different from that of our research, its findings regarding the effect of UDCA in improving liver function were not in accordance with ours; also, the physiopathology of liver enzyme reduction was discussed by its author, which should be considered in future studies. We observed that AST levels decreased in our UDCA group and increased in the placebo group, but this trend of changes was not significant in the ANOVA test by repeating the observations, which may be due to the low sample size or the follow-up period of our study.

In a recent review which comprised 33 studies consisting of case reports and case series, Robles-Diaz *et al* (28) investigated the use of UDCA in patients with drug-induced liver injury (DILI) and assessed its effect in liver function improvement. In 18 of the 25 reported cases including 22 patients, an improvement of DILI was noted, with seven patients having no clinical/biochemical improvement following UDCA treatment. Also, four of the selected studies, inclu-

ding three cohort studies and one retrospective study, evaluated the effect of UDCA in patients with DILI.

Three studies showed that liver function improvement was associated with UDCA. Also, three out of four studies examining whether UDCA was effective in preventing DILI showed a lower increase in transaminases among patients receiving UDCA for DILI prevention. It seems that UDCA has benefits in the prevention of DILI. But the designs of the aforementioned studies do not guarantee a definitive conclusion regarding the efficacy of UDCA in DILI. Therefore, randomized clinical trials are required to check the precise effect of UDCA in DILI. Although our study was designed as a clinical trial, we did not observe any significant effects of UDCA in reducing the level of liver enzymes. However, we did see a decrease too, but given the presence of some confounders, especially the difference in baseline time (the time period before the intervention), low sample size and short duration of follow-up, our findings were not significant, and therefore future detailed studies should be done. ❑

CONCLUSION

The results of the present study showed that, at the end of the fifth post-intervention week, despite the high level of liver enzymes in patients receiving ursodeoxycholic acid, there was no significant difference in changes of other liver enzyme levels between the ursodeoxycholic acid and placebo groups, except for a decrease in AST level. Hence, the use of UDCA can have a partial effect on liver function improvement in patients suffering from phenobarbital-induced liver damage. ❑

Conflicts of interest: none declared.
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