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Research Article

Protective Effects of Ursodeoxycholic Acid on Valproic Acid Induced Hepatotoxicity in Epileptic Children with Recurrent Seizure; A Double-Blinded Randomized Clinical Trial

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Abstract

Background: There are controversies regarding the protective role of ursodeoxycholic acid (UDCA) against valproic acid (VPA)-induced hepatotoxicity in children. In the present clinical trial, we assessed the potential role of UDCA in preventing VPA-induced fluctuations of hepatic enzymes in epileptic children with recurrent seizures.

Methods: Two-hundred children with epileptic seizures were randomly allocated into either intervention (VPA+UDCA) or control (VPA+ placebo) group. Fluctuations of liver enzymes were recorded at baseline, as well as 48 hours, 1 month, and 3 months following the interventions.

Results: The mean age of the patients was 7.33±2.96 years (the range of 4-16). Males and females constituted 43 (43%) and 57 (57%) subjects in each group respectively. There were no significant differences in the baseline levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) between the intervention and control groups. At 48 hours post-intervention, AST and ALT increased 1.7% and 11.05% (23.18±7.91 and 30.75±4.20 IU/l) in the intervention group and 21.3% and 35% (28.46±3.71 and 35.62±7.72 IU/l) in the control group respectively (P<0.0001). Both AST (P<0.001) and ALT (P=0.03) levels were significantly lower in the intervention than placebo group at 1-month post-intervention. At 3-month post-intervention; however, while AST level still was significantly higher in the control (29.87±5.41 IU/l) than intervention (21.63±6.87 IU/l, P<0.0001), ALT level was not significantly different between the two groups (32.72±5.59 IU/l and 32.01±7.89 IU/l respectively, P=0.5).

Conclusion: UDCA can be an effective drug to manage VPA-induced fluctuations of hepatic enzymes in children with recurrent epileptic seizures.

Introduction

Hepatocytes detoxify a wide range of chemicals produced in the body. These cells; however, are susceptible to drug-induced toxicities caused by many pharmaceutical agents. These adverse effects are generally subclinical and only traceable by biochemical analyses.[1,2]

Valproic acid (VPA); which is also known as sodium valproate (SV), is a common drug used to treat neurological and psychological disorders. Although VPA has an acceptable safety profile, examples of VPA-induced toxicity against kidneys, pancreas, gastrointestinal tract, endocrine system, and hepatocytes have been reported.[1,3] VPA-induced hepatotoxicity has been known for a long time.[4] Transient hepatotoxicity has been reported in 15-30% of patients treated with VPA.[5]

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid used for treating various liver disorders such as cholestasis,[6] non-alcoholic steatohepatitis (NASH),[7-9] non-alcoholic fatty liver disease (NAFLD),[10, 11] intrahepatic cholestasis of pregnancy (ICP),[12] primary biliary cirrhosis (PBC),[13] and hepatitis C virus (HCV) infection.[14,15] The protective effects of UDCA on biochemical and cytological parameters of liver function have been demonstrated.[16,17] Although the exact cytoprotective mechanisms induced by UDCA are not well understood, the roles of anti-apoptotic and anti-oxidative pathways have been proposed.[18] There are a few studies regarding the protective effects of UDCA against VPA-induced hepatotoxicity; especially in children.[19] Therefore, we here aimed to assess potential protective effects of UDCA against VPA-induced fluctuations of liver enzymes in children with epileptic seizures.

Materials and Methods

Patients

This was a double-blinded randomized clinical trial

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conducted on children with epileptic seizures who were under treatment with VPA. The study was performed in the pediatric ward of Amir-Al-Momenin Hospital of Zabol from February 2016 to June 2018. The patients were randomly assigned to either control or intervention group. The researcher and patients were blinded to the interventions (i.e. drug or placebo). The study was registered in the Iranian Registry of Clinical Trials (IRCT20181228042156N1).

Sample size

The sample size was calculated based on the below formula:

$$N = \frac{(r+1)(Z_{\alpha/2} + Z_{1-\beta})^2 \sigma^2}{rd^2} \quad \text{Eq. (1)}$$

In this equation; "Z_{α}" was 1.96 (P=0.05), "$Z_{1-\beta}$" was 0.84 (power of 80%). The "r" was the ratio between the two groups which was considered "1". According to a pervious report, the standard deviation (δ) of liver enzymes was considered 25 IU/l, and the effect size "d" was considered 10 IU/l.[20] The sample size in each group was calculated as 98 which was rounded up to 100.

Blinding

This study was a double-blinded trial in which patients who received the drugs and the researcher evaluating the outcomes were blinded to the administrated medications.

Inclusion and exclusion criteria

Inclusion criteria were considered as willing to participate in the study, definite diagnosis of epileptic seizures, and age of <18 years. Exclusion criteria were not willing to participate in the study, having systemic diseases, chronic hepatic (HBV and HCV infections and cirrhosis) diseases, diabetes, celiac disease, hypertension, cardiovascular and pulmonary disorders, renal insufficiency, age > 18 years, using hepatotoxic drugs and antibiotics, and finally not consuming > 10% of the administrated UDCA.

Randomization

The patients were randomized based on a sequence of random numbers (https://www.randomizer.org).

Study groups

In both the control and intervention groups, the patients were under treatment with oral VPA (15 mg/kg daily).

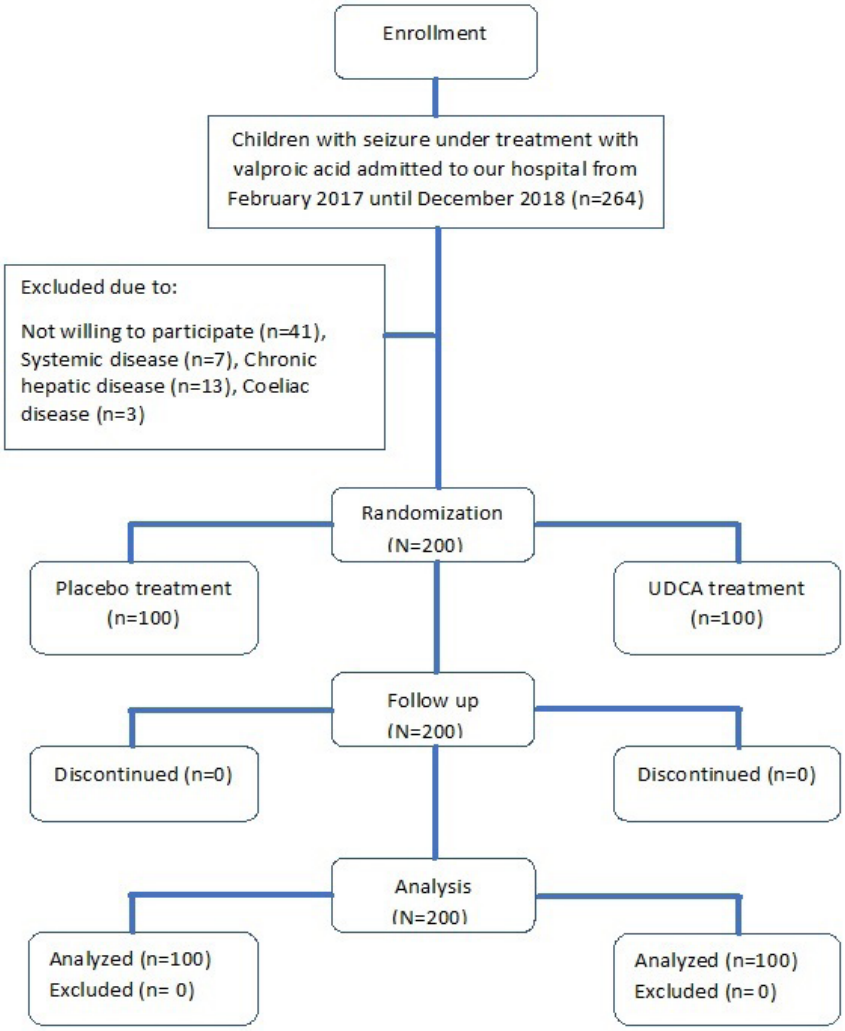

Figure 1. CONSORT diagram of the study.

The patients in the control group received placebo, while those in the intervention group were treated with 15 mg/kg daily oral UDCA (Dr. Abidi Co., Tehran, Iran). Liver functional tests in the both groups were measured at baseline, as well as 48-hour, 1-month, and 3-month post-intervention. Serum samples were separated from venous blood (5 ml), and liver enzymes levels were measured using specific ELISA kits manufactured by Pars Azmoun company (Iran). The sensitivities of AST and ALT kits were 2 IU/l and 4 IU/l respectively. The mean intra-assay and inter-assay precisions (low, normal, and high values) were 2.36% and 2.15% for the AST kit and 3.28% and 1.86% for the ALT kit, respectively.

Statistical analysis

The data was analyzed using SPSS 16 software. Mean, standard deviation, and frequency were used to describe the data. The Kolmogorov–Smirnov test was used to check normal distribution of quantitative variables. Independent samples student t-test was used to compare mean values between the intervention and placebo groups.

Results

Overall, 200 patients (100 cases and 100 controls) were enrolled in the study (Figure 1). The patients' mean age was 7.33±2.96 (the range of 4-16) years. Males and females constituted 43 (43%) and 57 (57%) subjects in each group, respectively. There were no significant differences regarding baseline clinical parameters between the intervention and placebo groups (Table 1). However, significant differences were observed in the mean levels of AST, ALT, and ALP at 48-hour (Table 2), and 1-month (Table 3) post-intervention. At 3-month post-intervention, while AST level was significantly higher in the control (29.87±5.41 IU/l) than intervention (21.63±6.87 IU/l) group (P<0.0001), ALT level showed no significant difference between the two groups (Table 4).

Table 1. Baseline parameters in children with epilepsy treated with sodium valproate who received either UDCA or placebo.

Parameters	Groups		P-value
	Intervention N=100	Placebo N=100	
Total protein (mg/dl)	7.09 ± 0.89	7.26±0.93	0.22
GGT	35.93±10.49	36.72±8.76	0.60
Albumin (mg/dl)	42.48±7.08	40.98±5.27	0.12
Direct Bilirubin (mg/dl)	0.11±0.03	0.12±0.04	0.3
Total Bilirubin (mg/dl)	0.96±0.08	0.96±0.082	0.9
ALP (IU/l)	78.65±19.95	78.34±16.87	1
AST (IU/l)	22.79±7.93	23.45±4.92	0.39
ALT (IU/l)	27.69±6.07	26.38±4.45	0.23

GGT; gamma glutamyltransp peptidase, ALP; Alkaline phosphatase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase.

Table 2. Liver enzymes in children with epilepsy under treatment with valporic acid and either UDCA or placebo at 48 hours after treatment.

Parameters	Groups		P-value
	Intervention N=100	Placebo N=100	
ALP (IU/l)	77.55±19.68	79.91±16.26	0.4
AST (IU/l)	23.18±7.91	28.46±3.71	<0.001
ALT (IU/l)	30.75±4.20	35.62±7.72	<0.001

ALP; Alkaline phosphatase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase.

Table 3. Liver enzymes in children with epilepsy under treatment with valporic acid and either UDCA or placebo at 1-month after treatment.

Parameters	Groups		P-value
	Intervention N=100	Placebo N=100	
ALP (IU/l)	76.86±19.61	81.72±16.74	0.08
AST (IU/l)	21.63±7.13	28.08±2.71	<0.001
ALT (IU/l)	33.12±8.04	36.02±4.32	0.03

ALP; Alkaline phosphatase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase.

Table 4. Liver enzymes in children with epilepsy under treatment with valporic acid and either UDCA or placebo at 3-month after treatment.

Parameters	Groups		P-value
	Intervention N=100	Placebo N=100	
ALP (IU/l)	76.45±19.34	81.61±18.32	0.08
AST (IU/l)	21.63±6.87	29.87±5.41	<0.001
ALT (IU/l)	32.01±7.89	32.72±5.59	0.5

ALP; Alkaline phosphatase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase.

Discussion

The protective effects of UDCA have been shown in patients with cholestatic liver injury.[6] In this study, we assessed the protective effects of UDCA on VPA-induced hepatotoxicity in children with epileptic seizures. Compared with baseline values, we observed significant alternations in AST and ALT levels in both intervention and placebo groups at 48-hour (AST: +1.7% vs +21.3% and ALT: +11.05% vs +35% respectively) and 1-month (AST: - 5.08% vs +19.7% and ALT: +19.6% vs +36.5% respectively) post-intervention. At 3-month post-intervention, the patients in the intervention group preserved significantly lower AST level compared with control group. However, there was no significant difference between the groups comparing the mean ALT level following 3 months of interventions. Therefore, the patients who received concomitant VPA and UDCA showed significantly smaller elevations in AST and ALT levels than controls at 48-hour and 1-month post-intervention indicating alleviating effects of UDCA against VPA-induced acute hepatotoxicity.

UDCA has been traditionally used to study hepatotoxic effects of various pharmaceutical and non-pharmaceutical agents such as VPA.[1] The hepatotoxic effects of VPA have been associated with elevated levels of inflammatory (tumor necrosis factor-α), apoptotic (caspase 3), and oxidative stress (malondialdehyde-MDA) markers as well as attenuated activities of anti-oxidative enzymes (e.g. glutathione peroxidase and superoxide dismutase).[1] VPA also induces leukocyte infiltration and cytoplasmic vacuolization in hepatocytes of rats.[21] Furthermore, the hepatotoxic effects of VPA have been associated with depressed levels of serum zinc and selenium contributing to oxidative damage, as well as histological and biochemical defects in hepatocytes of rats.[22] In another report, VPA treatment reduced the cell viability of HepG2 hepatic cancer cell line and increased the release of ALT and AST from these cells.[23] On the other hand, the cytotoxic effects of VPA have been modulated by genetic variations in Cytochrome P450 2C9 (*CYP2C9*) and Acyl-CoA Synthetase Medium Chain Family Member 2A (*ACSM2A*) genes.[24] Regardless of these pathologic effects of VPA and the role of modulating factors, it seems that clinically tolerable doses of VPA have low hepatotoxic capacities in patients who have no serious liver diseases.

UDCA is particularly used to mitigate liver dysfunction in patients with chronic hepatic disorders. In patients with primary sclerosing cholangitis (PSC), UDCA dose-dependently decreased AST and ALT levels.[25] In individuals with ICP, UDCA treatment for 2-3 weeks decreased ALT level by 50% in approximately 80% and normalized this marker in 39.5% of the patients.[26] Other studies have also indicated beneficial effects of UDCA in patients with ICP.[27, 28] In another study on patients with PSC, the combination of UDCA and all-trans retinoic acid (ATRA) reduced ALT, but not ALP level.[29] In patients with liver cirrhosis; Tauroursodeoxycholic acid (TUDCA); a derivative of UDCA; decreased ALT, AST, and ALP levels while UDCA only decreased AST.[30] Post-transplant UDCA treatment for one month reduced ALT, AST, and GGT levels in liver transplanted patients.[31] Also, combined UDCA and vitamin E treatment normalized AST, ALT, and GGT levels in 80%, 70%, and 65% of patients with NASH, respectively.[8] The synergistic effects of UDCA have also been reported in combination with glucocorticoids in patients with autoimmune hepatitis-primary biliary cirrhosis (AIH-PBC).[32] UDCA treatment significantly attenuated isoniazid and rifampicin -induced liver injury and fluctuations of ALP and ALT in mice.[33] In another study by Mesdjian *et al.*, UDCA prevented ultrastructural changes of hepatocytes in rats treated with VPA and carbamazepine.[34]

The hepatoprotective effects of UDCA can be in part explained by its modulating effects on inflammatory processes.[35,36] Furthermore, UDCA treatment counteracted with both oxidative and nitrosative stresses in patients with PBC.[37] UDCA treatment also activated anti-apoptotic pathways via upregulating Bcl-2 and Bax in hepatocytes of mouse model of drug-induced liver injury.[33] The immune modulating effects of UDCA (i.e. decreasing IFN- γ, IL-4, and IL-6 levels) have been noted in patients with PBC.[38] Moreover, UDCA treatment normalized glutathione (GSH) pool, increased myeloperoxidase (MPO) activity, and decreased MDA level in hepatocytes of rat model of liver injury induced by amoxicillin-clavulanic acid.[39] Other possible hepatoprotective mechanisms of UDCA are yet to be divulged.

The therapeutic efficiency of UDCA can be modulated by a variety of factors. Patients with NASH harboring the variant (A) allele of -308G>A polymorphism of *TNF-α* gene better responded to UDCA therapy than those with GG genotype.[40] In another study on PBC patients, the duration of treatment was indicated as an important predictor of biochemical response to UDCA as the highest response rate was observed following 3 years of treatment.[13] Other factors modulating therapeutic response to UDCA have been noted as the severities of underlying diseases[37] and the duration of follow up period post-treatment.[13] Furthermore, differential responses may be seen in individual biochemical markers as different patterns were reported for ALP and AST compared with ALT, bilirubin and albumin in long-term follow up.[13] Differences in biochemical responses to UDCA may also be explained by variable diseases stages,[41] and different durations,[42] and doses[43] of UDCA therapy. Considering multifactorial hepatoprotective mechanisms recruited by UDCA,[44] its therapeutic efficiency should also be interpreted considering multiple determinants.

As a limitation of this study, we did not assess other liver functional indices (e.g. albumin, INR, and bilirubin) and relevant clinical manifestations. Therefore, it is recommended to assess these biochemical responses in parallel to clinical picture.

Conclusion

UDCA can be used as an effective therapeutic to prevent adverse hepatotoxic effects of VPA in children with recurrent epileptic seizures. The long-term effects of UDCA on VPA-induced hepatotoxicity; however, should be elucidated in future studies.

Ethical issues

The study was approved by the Ethical Committee of Zabol University of Medical Sciences (IR.ZBMU.REC. 1397.116). All the parents were requested to sign informed consent forms.

Data sharing

Applicants can obtain data by contacting the corresponding author.

Conflict of interest

The authors declare that there is no conflict of interest.

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