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Ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy: a multi-centered randomized controlled trial

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Abstract. – OBJECTIVE: Intrahepatic cholestasis of pregnancy (ICP) is a special complication of pregnancy characterized by skin pruritus, abnormal liver function tests and bile acids. To compare the efficacy of ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) monotherapy with their combined effect on intrahepatic cholestasis of pregnancy (ICP).

PATIENTS AND METHODS: Singleton pregnancies with ICP in five tertiary medical centers were randomly divided into three treatment groups: oral UDCA 4×250 mg daily (Group 1, n = 41), intravenous SAMe 1000 mg daily (Group 2, n = 38), and a combination of both drugs (Group 3, n = 41) until delivery. Paired t test, analysis of covariance and non-parametric test were used.

RESULTS: All therapies significantly and equally improved pruritus. The serum levels of total bile acids (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TB) in each group significantly decreased after treatment ($p < 0.05$). Group 1 was more effective than Group 2 in reducing TBA concentration ($p < 0.05$), Group 1 and Group 3 showed more effective than Group 2 in reducing AST and TB concentrations ($p < 0.05$), and Group 1 facilitated deliveries at term. No perinatal death or adverse drug reactions were observed.

CONCLUSIONS: UDCA and SAMe are both effective and safe in the treatment of ICP. UDCA monotherapy should be used as the first line therapy for ICP because it is more efficacious, cost-effective and convenient.

Key Words:
Intrahepatic cholestasis of pregnancy, Ursodesoxycholic acid, S-adenosylmethionine.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a special complication of pregnancy characterized by skin pruritus, abnormal liver function tests and bile acids, with or without different degrees of jaundice in the third trimester, all of them subsiding soon after delivery[1-3]. In China, the occurrence of ICP varies from area to area, and is especially high in Sichuan Province (5.2%) and Chongqing Municipality (6.0%)[4,5]. While the maternal prognosis of ICP is benign, ICP may exert serious impact on the fetus, leading to high risk of premature delivery, meconium-stained amniotic fluid, fetal distress, sudden intrauterine fetal death, stillbirth, and even neonatal death[6-8]. Therefore, woman with ICP should be considered high-risk pregnancy and strict fetal monitoring should be conducted throughout the last period of gestation.

The cause and pathogenesis of ICP is still unelucidated, and until now, optimal treatment mode of ICP is still controversial[9,10]. In recent 20 years, ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) have demonstrated in clinical trials and observational studies a beneficial effect on pruritus and serum biochemical abnormalities, further improving perinatal outcome[11-16]. UDCA is a naturally-occurring hydrophilic bile salt, which may increase the hydrophilic properties of the bile acid pool, thereby preventing damage to membranes by hydrophobic bile salts[17]. SAMe influences the methylation reactions, and subsequently

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increases the flow of bile and biliary lipid metabolism which was previously impaired by estrogen load produced by the placenta[18]. Two previous studies have shown that UDCA and SAMe may have synergistic action, and this effect might be due to their different biochemical mechanisms[19,20]. However, how to select medical treatment regimens is still controversial. A few randomized controlled studies compared curative effects of different treatment protocols of the two drugs, but these investigation were small and their conclusions were inconsistent[19-22].

Therefore, the aim of the present multi-centered randomized controlled study was to evaluate various medical treatment regimens of UDCA and SAMe for ICP.

Patients and Methods

After the protocol for this work was approved by the Ethics Committee of West China Second Hospital of Sichuan University, a multi-centered, open, randomized controlled trial was performed to compare the efficacy and safety of UDCA, SAMe, and combinations of the two drugs in the treatment of ICP. This clinical experiment was conducted in five tertiary medical centers in southwest China. The leading center was West China Second Hospital of Sichuan University, whereas the other participating centers were the First Affiliated Hospital of Chongqing Medical University, Xinqiao Hospital of Third Military Medical University, Affiliated Hospital of Luzhou Medical College, and Sichuan Provincial People's Hospital.

Diagnosis criteria of ICP were as follows: 1). Clinical manifestation: Skin pruritus occured in the torso and limbs during the third trimester of pregnancy in the absence of lesions attributable to dermatological diseases or any possible cause of pruritus besides ICP. Pruritus was scored by a semiquantitative scale of 0-4[15] (0 = no pruritus, 1 = occasional pruritus, 2 = intermittent pruritus every day with asymptomatic periods prevailing, 3 = intermittent pruritus every day with symptomatic periods prevailing, 4 = constant pruritus day and night). 2). Biochemical tests: Serum level of total bile acids (TBA) is elevated (> 10 μmol/L), concentration of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is slightly or moderately increased (> 50 U/L), and total bilirubin (TB) is normal or increased (> 21 μmol/L). No other causes could be found for the hepatic dysfunction.

All enrolled patients satisfied the following inclusion criteria: (1) The case complies with the ICP diagnosis criteria. (2) It is a singleton pregnancy between 28 and 35 weeks of gestation (Gestational age was ultrasonographically confirmed.). (3) No treatment has been received prior to the study. (4) The patients acceded to participate in the trial and gave their informed consent. The exclusion criteria were as follows: viral hepatitis (all participants were screened for hepatitis virus A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus infections using serologies), chronic liver disease, acute fatty liver, gallbladder diseases (inflammation and symptomatic cholelithiasis), skin diseases, neuropsychiatric disorders, allergic diseases, infections requiring the use of antibiotics, diabetes mellitus, pre-eclampsia, etc.

The study was planned in the expectation that a 2-week therapeutical period could be completed in 135 patients. This sample size was calculated to show a significant difference in TBA levels after two weeks of treatment between the three groups with $\alpha = 0.05$ (two-tails) and $\beta = 0.2$. A computer-generated random number table of medical statistics was obtained by a professional (Haike Lei, who is specialized in Health Statistics of West China Center of Medical Sciences of Sichuan University) using SAS 9.1 statistical software. The leading center randomly distributed the numbered and sealed envelopes containing the treatment protocol to the participating centers. The enrolled patients in each study center were randomly divided into three treatment protocols on a 1:1:1 ratio. All study centers gave the enrolled patients the drugs corresponding with the sealed and numbered envelopes based on the order of enrollment.

All the enrolled women in each study center have given written informed consent and this study was approved by the Institutional Ethics Committee of Sichuan University. The participants were randomly divided into three groups by closed envelope system. The woman in Group 1 received oral UDCA (Xinyi Pharmaceutical Factory of Shanghai Pharmaceutical Group Co. Ltd, China) 4×250 mg daily until delivery. Group 2 was given intravenous SAMe (Hospira S.r.l., Naples, Italy) 1000 mg daily until delivery. Finally, Group 3 was treated with the combination of these two drugs in the same dosage until delivery. According to ethical principles, patients of ICP should not be left untreated. Thus, no blank control group was formed. All enrolled patients were treated for at least two weeks. Cross over

was not contemplated even in presence of persistent symptoms and no concomitant medications were used to relieve pruritus or improve liver function tests. All patients were admitted to the Obstetrics Department for high-risk pregnancies. The severity of pruritus and biochemical parameters (standard liver function tests and serum total bile acids) were evaluated immediately prior to treatment and subsequently every week. Fetal movement counting was used routinely for assessment of fetal wellbeing. The fetus was also monitored by non-stress test twice weekly and amniotic fluid volume determination weekly beginning at 32 weeks. A biophysical profile was performed if the non-stress test was non-reactive. We also monitored the treatment tolerance and occurrence of adverse effects of the applied drugs on the mother and the fetus. The decisions to induce labor and carry out cesarean sections were decided by the attending obstetricians in accordance with the institutional guidelines. The newborn's status was monitored by pediatricians. Follow up assessments of mothers and babies were lasted six months after delivery.

Statitsical Analysis

Data were analyzed with the statistical software SAS 9.1. All statistical analyses were two-tailed tests. A p value < 0.05 was considered to be statistically significant. Quantitative data in each group were statistically described as mean ± standard deviation or median (range). Paired t-test was used to compare the differences between the results before and after treatment within the group. The differences of curative results between the three groups were compared using analysis of covariance. The ordinal data and Apgar scores of the newborns in three groups were compared using non-parametric test.

Results

From July 2009 to December 2011, a total of 135 pregnant women met the inclusion criteria and chose to participate in the study, and they were randomized to Groups 1, 2 and 3 on a 1:1:1 ratio. During treatment, 4 patients in Group 1, 7 in Group 2 and 4 in Group 3 withdrew or violated the study protocol prior to study completion. 8 patients deliveries before two weeks of treatment, 4 patients dropped out due to individual reasons, 3 patients took polyene phosphatidylcholine capsules (a drug used to improve liver function). Finally, the study included 120 cases with complete clinical information. A total of 41 were randomized to group 1, 38 to group 2 and 41 to group 3. Table I displayed the baseline characteristics of patients at enrollment. Randomization resulted in no significant differences between the three groups immediately before medication with regard to maternal age, gestational age, pruritus score and serum levels of TBA, ALT, AST and TB.

The only clinical manifestation of ICP is a variable degree of skin itching. The severity of pruritus diminished during treatment in most women of all three groups. Comparison of pruritus scores prior to and after treatment within each group showed statistically significant difference ($p < 0.05$), but the differences in relieving pruritus between the three groups were statistically insignificant ($p < 0.05$) (Table II).

Tables III and IV show the mean changes in liver function tests and TBA before and after treatment with the different treatment protocols, in each group and between the three groups. As compared to pretreatment, the TBA levels in Group 1 and Group 3 decreased significantly after a one-week treatment, and further decreased significantly after two weeks of treatment. The

Table I. Characteristics of the patients at enrollment[a].

	Group 1 (n = 41)	Group 2 (n = 38)	Group 3 (n = 41)	Statistical value	p
Maternal age (y)	27.85 ± 3.56	28.08 ± 3.76	28.95 ± 4.39	F = 0.89	0.413
Gestational week at diagnosis (wk)	29.94 ± 3.44	31.60 ± 2.38	30.95 ± 4.06	F = 1.40	0.254
Gestational week at randomization (wk)	30.30 ± 3.50	32.00 ± 2.29	31.11 ± 4.01	F = 1.45	0.241
Pruritus score	1.93 ± 0.93	2.03 ± 1.10	2.34 ± 0.99	Z = 5.16	0.076
TBA (μmol /L)	46.30 ± 49.53	36.83 ± 25.44	49.29 ± 45.20	Z = 0.95	0.390
ALT (U/L)	241.29 ± 168.45	262.89 ± 187.71	274.22 ± 165.99	Z = 0.38	0.686
AST (U/L)	162.17 ± 105.23	194.50 ± 143.21	206.32 ± 126.98	Z = 1.35	0.263
TB (μmol /L)	19.74 ± 14.39	23.11 ± 20.05	24.52 ± 21.94	Z = 0.68	0.508

Abbreviations: TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TB: total bilirubin. [a]Values are given as mean ± SD.

Table II. Comparison of pruritus score before and after treatment[a].

Groups	Pruritus score before treatment	Pruritus score after one-week treatment	Pruritus score after two-week treatment	p^{b1}	p^{b2}	p^{c1}	p^{c2}
Group 1 (n = 41)	1.93 ± 0.93	1.3 ± 0.73	0.81 ± 1.12	< 0.001	< 0.001		
Group 2 (n = 38)	2.03 ± 1.10	1.61 ± 0.64	1.19 ± 0.89	< 0.001	< 0.001	> 0.05	> 0.05
Group 3 (n = 41)	2.34 ± 0.99	1.58 ± 0.62	1.05 ± 0.78	< 0.001	< 0.001		

[a]Values are given as mean ± SD. [b1]Comparison within the group after one-week treatment. [b2]Comparison within the group after two-week treatment. [c1]Comparison between the three groups after one-week treatment. [c2]Comparison between the three groups after two-week treatment.

TBA levels in Group 2 also reduced after one-week treatment. However, the difference was statistically insignificant. After two weeks' treatment, it further decreased and showed significant difference (Table III). The covariance analysis showed that the differences of the curative effect on decreasing TBA levels between the three groups were not statistically significant after one-week treatment. After two weeks' treatment, Group 1 was more effective compared to Group 2, whereas the results of Group 1 compared to group 3 and Group 2 to Group 3 were not statistically different (Table IV).

As compared to pretreatment, the ALT levels in each group decreased significantly after one week of treatment and, then, further decreased significantly after two weeks of treatment (Table III). The covariance analysis showed Group 1 and Group 3 were significantly more effective than Group 2 in reducing ALT levels after a one-week treatment, but the difference became obscure after two weeks of treatment. The differences of curative effects between Group 1 and Group 3 were indeterminable (Table IV).

Compared to pretreatment, the AST and TB levels in each group decreased significantly after one-week treatment and then further decreased significantly after two weeks' treatment (Table III). The covariance analysis between the three groups indicated that Group 1 and Group 3 were significantly more effective than Group 2 in reducing AST and TB concentrations after one week and two weeks of treatment. Whereas the curative results of Group 1 compared to Group 3 were not statistically different (Table IV).

Table V showed the outcomes of the pregnancies and the status of the newborns. There were no perinatal deaths. All types of the treatment were very well tolerated by the pregnant women and no adverse side effects were recorded in the mothers or their babies.

The appearance of prematurity in all groups was above the population average. Both gestational age at delivery and rate of preterm delivery (delivery prior 37th gestatin week) showed statistically significant differences between the three groups ($p < 0.05$) (Table V). The rate of preterm delivery of Group 1 was significantly lower than that of Group 2 and Group 3, whereas there were no significant differences between Group 2 and Group 3.

All babies had birth weights adequate for gestational age; therefore, the differences of birth weight between the three groups were generally statistically significant ($p < 0.05$) (Table V). The average birth weight of Group 2 was much lower than that of Group 1 and Group 3 ($p < 0.05$), but there were no significant differences between Groups 1 and 3.

The rate of cesarean section in all groups was significantly above the population average and it was similar in the three groups. The newborns' Apgar scores at 1st minute and 5th minute were not statistically different between the three groups. The rates of staining of the amniotic fluid and the rates of admission to the neonatal intensive care unit (NICU) showed no significant difference either (Table V).

Any remaining pruritus in all patients disappeared immediately after delivery. All the biochemical parameters had a significant reduction at 4 days after delivery in all groups and returned to normal values on the 42nd day postpartum. Furthermore, all newborns were thriving normally during a follow-up period that lasted six months after delivery.

Discussion

ICP is a relatively uncommon disorder of pregnancy associated with a variety of perinatal adverse outcomes. Since its pathogenesis is not fully understood, selection of optimal pharmacological

Table III. Comparison of biochemical parameters before and after treatment within each group[a].

Groups	Timepoint	TBA (μmol/L)	*p*	ALT (U/L)	*p*	AST (U/L)	*p*	TB (μmol/L)	*p*
Group 1 (n = 41)	Pretreatment	46.30 ± 49.53	–	241.29 ± 168.45	–	162.17 ± 105.23	–	19.74 ± 14.39	–
	One week[b]	27.52 ± 28.11	0.006	161.29 ± 101.47	< 0.001	110.56 ± 68.36	< 0.001	15.85 ± 7.04	0.011
	Two weeks[c]	18.66 ± 16.90	< 0.001	113.46 ± 86.93	< 0.001	80.76 ± 54.76	< 0.001	12.70 ± 6.89	< 0.001
Group 2 (n = 38)	Pretreatment	36.83 ± 25.44	–	262.89 ± 187.71	–	194.50 ± 143.21	–	23.11 ± 20.05	–
	One week[b]	31.92 ± 18.71	0.153	213.87 ± 175.36	0.013	155.34 ± 115.49	0.006	20.15 ± 13.59	0.006
	Two weeks[c]	25.80 ± 17.52	0.003	155.89 ± 118.82	< 0.001	120.11 ± 83.78	< 0.001	18.01 ± 12.28	0.018
Group 3 (n = 41)	Pretreatment	49.29 ± 45.20	–	274.22 ± 165.99	–	206.32 ± 126.98	–	24.52 ± 21.94	–
	One week[b]	29.26 ± 24.49	0.004	173.59 ± 87.81	< 0.001	118.15 ± 67.25	< 0.001	17.55 ± 9.10	0.008
	Two weeks[c]	21.64 ± 17.20	< 0.001	126.80 ± 100.07	< 0.001	88.12 ± 68.84	< 0.001	13.74 ± 4.90	0.002

Abbreviations: TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TB: total bilirubin. [a]Values are given as mean ± SD. [b]One week after treatment. [c]Two weeks after treatment.

therapy currently remains controversial. The gold standard for ICP treatment is drugs capable of reducing itching and liver function tests and improving the outcome of pregnancy with minimal side effects on the mothers and the fetuses.

UDCA and SAMe have been applied in the treatment of ICP for decades[23]. Previous reports have shown that both drugs are effective and safe, but available data are limited hitherto. We, therefore, performed a multi-centered, randomized controlled, open clinical trial to compare the efficacy of UDCA, SAMe, and a combination of the two drugs. There are four analogous clinical trials in the published literature and their main results are shown in Table VI[19-22]. However, the size of these studies was small and the results were inconsistent. Thus, to our knowledge, we have completed the largest randomized clinical trial comparing the efficacy of UDCA and SAMe in the treatment of ICP to date. In our study, both UDCA and SAMe were equally effective at alleviating pruritus. We have also found that the treatment by UDCA, either in monotherapy or in combination, is more effective than SAMe monotherapy in the improvement of biochemical parameters, whereas the results of combined therapy compared to UDCA monotherapy are not statistically different. As for fetal morbidity associated with ICP, we only found that UDCA monotherapy is more effective in extending gestational period than both SAMe monotherapy and combined therapy, and the other perinatal outcomes are similar in all groups.

In our study, UDCA combined with SAMe failed to show a synergistic effect. In China, UDCA monotherapy costs only 13 dollars for two-week treatment, whereas SAMe monotherapy cost approximately 293 dollars. Thus, UDCA costs no more than 5% of SAMe, and oral medication is more convenient than intravenous route. Therefore, the use of UDCA monotherapy might be a more cost-effective and convenient treatment protocol. In 2012, Bacq et al[24] performed a meta-analysis to evaluate the effects of UDCA and they demonstrated that UDCA was effective in reducing pruritus and improving liver test results in patients with ICP, UDCA therapy might also benefit fetal outcomes.

Conclusions

It is tempting to use UDCA monotherapy as a first choice therapy for ICP. Future efforts will focus on optimized dosage regimens, including

Table IV. Comparison of change in biochemical parameters between the three groups by analysis of covariance.

	Group 1 vs Group 2		Group 1 vs Group 3		Group 3 vs Group 2	
	p[a]	p[b]	p[a]	p[b]	p[a]	p[b]
TBA (μmol/L)	0.140	0.020	0.851	0.478	0.197	0.099
ALT (U/L)	0.038	0.072	0.796	0.874	0.020	0.099
AST (U/L)	0.044	0.029	0.453	0.807	0.006	0.015
TB (μmol/L)	0.033	0.005	0.747	0.859	0.015	0.003

Abbreviations: TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TB: total bilirubin. [a]Comparison after one-week treatment. [b]Comparison after two-week treatment.

Table V. Perinatal outcomes[a].

	Group 1 (n = 41)	Group 2 (n = 38)	Group 3 (n = 41)	Statistical value	p
Gestational week at delivery (wk)	37.50 (34.14-39.71)	36.57 (35-37.57)	37.00 (35-38.14)	$\chi^2 = 19.058$	< 0.001
Preterm delivery (< 37 wks)	13 (31.71%)	26 (68.42%)	18 (43.90%)	$\chi^2 = 10.983$	0.004
Birthweight (g)	2925 (2210-3800)	2722 (2200-3450)	3002 (2365-4215)	$\chi^2 = 12.473$	0.002
Caesarean section	26 (63.41%)	29 (76.32%)	28 (68.29%)	$\chi^2 = 1.561$	0.458
Meconium stained amniotic fluid	9 (21.95%)	7 (18.42%)	6 (14.63%)	$\chi^2 = 0.733$	0.693
Apgar score at 1st min	9.68±0.53	9.63±0.67	9.56±0.63	Z = 0.927	0.629
Apgar score at 5th min	9.98±0.16	9.87±0.41	9.93±0.26	Z = 2.067	0.356
Admission to NICU	3 (7.32%)	4 (10.53%)	6 (14.63%)	$\chi^2 = 1.148$	0.563

Abbreviations: NICU: the neonatal intensive care unit. [a]Values are given as mean ± S.D. or median (range) or number (%).

Table VI. Similar study for ICP in the literature.

Year	Journal	Country	Groups[a]				Main conclusions
			1	2	3	4	
2006	J Perinat Med	Czech Republic	26	25	27	0	All therapies improved the pruritus. The treatment by UDCA, either in monotherapy or in combination, is more effective on biochemical parameters compared to SAMe monotherapy. UDCA and SAMe have probably a synergistic effect.
2004	Br J Obstet Gynecol	Italy	24	22	0	0	UDCA is more effective than SAMe at improving the concentration of serum bile acids and other tests of liver function, whereas both therapies are equally effective at improving pruritus.
1998	Br J Obstet Gynecol	Italy	8	8	8	8	A combination of UDCA and SAMe is more effective than placebo and than either drug alone.
1996	Eur J Obstet Gynecol Reprod Biol	Italy	10	10	0	0	UDCA has a positive effect in reversing pruritus and in reducing total bile acids compared with SAMe, but no effect of either drug in restoring liver function tests.

[a]Groups: 1 = treated by UDCA monotherapy; 2 = treated by SAMe monotherapy; 3 = treated by a combination of these two drugs; 4 = placebo-controlled.

dose and course, as well as on further elucidation of precise mechanisms of therapeutic effects of UDCA.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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