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Research Article

The Effect of Ursodeoxycholic Acid in Liver Functional Restoration of Patients with Obstructive Jaundice after Endoscopic Treatment: A Randomized Controlled Trial

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Received: March 11, 2017; **Accepted:** May 30, 2017; **Published:** June 06, 2017

Abstract

Background: The aim of this study was evaluation of the effect of UrsoDeoxyCholic Acid (UDCA) in liver functional restoration of patients with obstructive jaundice in the early period after endoscopic intervention.

Methods: In this prospective, randomized, open-labeled, and controlled study, a total of 78 patients were randomly divided in the Investigation Group (IG; n= 40) in which has been administered UDCA, and in the control group (CG; n= 38). Inclusion criteria were: patients with obstructive jaundice, serum bilirubin level higher than 50μmol/l, 19+years of age, and written informed consent. UDCA administration started twenty-four hours after endoscopic treatment. It was administered at 750 mg/day, divided into three daily doses and lasted fourteen days. Serum-testing in patients with obstructive jaundice included determination of bilirubin (total and direct fractions), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Gama-Glutamil Transpeptidase (GGT), Alkaline Phosphatase (ALP), albumin, and Neutrophil/ Lymphocyte (N/L) ratio. These parameters were determined one day prior endoscopic intervention (day 0), and on the fifth, tenth, and fifteenth days after endoscopic intervention. The primary outcome measure in this trial was bilirubin (total and direct fractions), ALT, AST, GGT, and ALP serum levels decreasing rate. The secondary outcome was assessment liver functional parameters on which UDCA treatment has greater impact in terms of their improvement. Due to loss of follow-up, the data of 9 patients in the investigation group and 7 patients in the control group were not analyzed.

Results: The difference of the average values of total and direct bilirubin, between the groups, was statistically significant at day 0 (p<0.05), but at other evaluation days was not statistically significant, while the difference of the average values of ALT, AST, GGT, ALP, and N/L ratio, between the groups, was not statistically significant (p>0.05). The difference of the average values of albumin, between the groups, was statistically significant at the days 5, 10, and 15 (p<0.05). The decrease rate of total bilirubin, direct bilirubin, GGT, and N/L ratio, between the day 15 compared to day 0, was higher in the IG than in the CG (total bilirubin; 72.6% *vs* 67.6%, direct bilirubin; 78.1% *vs* 71%, GGT; 71.5% *vs* 63.4%, and N/L ratio; 29% *vs* 17%, respectively), while the decrease rate of ALT, AST, and ALP was higher in the CG than in the IG (ALT; 69.8% *vs* 67.7%, AST; 62.2% *vs* 59.5%, ALP; 50.8% *vs* 49%, respectively). The albumin level, in the IG, between the days 15 compared to day 0, was decreased 3.9%, while in the CG the albumin level was increased 5.4%.

Conclusion: UDCA has accelerated reducing the level of total bilirubin, direct bilirubin, GGT, and neutrophil/lymphocyte ratio, but did not decrease the level of ALT, AST, and alkaline phosphatase, and did not induce increasing of albumin level. UDCA had greater impact on GGT than in other functional liver parameters.

Trial registration: ClinicalTrials.gov NCT01688375.

Keywords: Obstructive jaundice; Ursodeoxycholic acid; Treatment with UDCA

Abbreviations

UDCA: Ursodeoxycholic Acid; IG: Investigation Group; CG: Control Group; ALT- Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gama-GlutamilTranspeptidase; ALP: Alkaline Phosphatase; N/L: Neutrophil/Lymphocyte; ERCP: Endoscopic Retrograde CholangioPancreatography; CT: Computed Tomography;

Citation: Fekaj E, Matveeva N and Jankulovski N. The Effect of Ursodeoxycholic Acid in Liver Functional Restoration of Patients with Obstructive Jaundice after Endoscopic Treatment: A Randomized Controlled Trial. Austin Dig Syst. 2017; 2(1): 1008.

MRCP: Magnetic Resonance CholangioPancreatography; SR: Stone Removal; SA: Stent Application; PSC: Primary Sclerosing Cholangitis; PBC: Primary Biliary Cirrhosis; ICP: Intrahepatic Cholestasis of Pregnancy; NASH: Non-Alcoholic SteatoHepatitis; CRC: Colorectal Cancer

Background

Obstructive jaundice results from biliary obstruction, which is blockage of any duct that carries bile from liver to gallbladder and then to small intestine [1].

The most common causes of obstructive jaundice are choledocholithiasis, strictures of the biliary tract, cholangiocarcinoma, carcinoma of pancreas, pancreatitis, parasites and primary sclerosing cholangitis [2]. Stone disease is the most common cause of obstructive jaundice [3,4]. Stones in the common bile duct occur in 10-15% of patients with gallstones. The prevalence of gallbladder and bile duct stones rises with age [5]. Up to 90% of patients with pancreatic head carcinoma exhibit the signs and symptoms of obstructive jaundice at the time of presentation [6].

Obstructive jaundice can lead to pathophysiologic disorders including functional lesions of the liver and kidney, functional disturbance of blood coagulation, gastric mucous membrane injury, reduced immune function and dysfunction of liver regeneration [7].

Current pathophysiological studies on obstructive jaundice have shown that the damage to the liver, kidney, and immune system of the patients are closely related to endotoxemia [8].

In patients with obstructive jaundice bile acids can induce liver cells apoptosis [9].

There are a many studies, where Ursodeoxycholic Acid (UDCA) was administrated in patients with cholestatic liver diseases. UDCA is a tertiary bile acid which is more and more frequently used in the treatment of different cholestatic diseases. It is normally present in humane bile, but in a low concentration of only 3% of total bile acids. UDCA is the major component of bile acids in black bear bile [10]. UDCA has been used as part of a traditional Chinese medicine from the time of the Tang Dynasty (618-907 AD) for the treatment of jaundice. Its therapeutic use was report in Japan in 1961, followed by the publication of the first controlled trial in patients with primary biliary cirrhosis in 1989 [11]. Mechanisms of action of UDCA are: 1) Protection against cell death induced by cytotoxic bile acids, 2) Modulation of the expression of liver transporters and enzyme systems, 3) Modulation of cholangiocyte transport and ductular bile flow, and 4) Immunosuppressive and anti-inflammatory properties of UDCA [12-16]. The aim of this study was investigation of the effect of UDCA in liver functional restoration of patients with obstructive jaundice in the early period after endoscopic intervention.

Methods/Design

Study objectives

This trial was a prospective, open-labelled, randomized, and controlled study. The objective was to evaluate the effect of UDCA in liver functional restoration in patients with obstructive jaundice in the early post-endoscopic phase.

The study was conducted to the department of abdominal surgery and endoscopy at University Clinical Centre of Kosovo (January 2015- November 2016).

Study design

After diagnosis, eligible patients with obstructive jaundice who met inclusion criteria were divided into two groups: (A) the investigation group in which has been administered UDCA in the early phase after endoscopic treatment, and (B) control group, in which no treatment has been applied with UDCA.

Diagnostic methods were: Clinical history, biochemical findings, ultrasound examination, Endoscopic Retrograde CholangioPancreatography (ERCP), CT-scan and Magnetic Resonance CholangioPancreatography (MRCP).

Inclusion criteria were

Patients with obstructive jaundice: choledocholithiasis, benign and malign strictures, serum bilirubin level higher than 50μmol/l, 19+years of age, and written informed consent.

Exclusion criteria were

Patients with cholangitis, acute pancreatitis, pregnant women, women during the breastfeeding, suspected or proven primary liver diseases, complications after endoscopic treatment: massive bleeding, acute pancreatitis, cholangitis, my family members, and patients who were unable to understand our study purpose.

Power of the study

A clinically relevant improvement of liver functional tests was defined as an improvement of 70% of liver functional tests in test group, and an improvement of 50% in control group. In our study, to have an 80% chance (power= 0.80) of detecting a difference between two groups on improvement of liver functional tests at an alpha level of 0.05, the power calculation indicates that each of the two groups should have at least 31 patients.

Outcomes

The primary outcome measure in this trial was bilirubin (total and direct fractions), ALT, AST, GGT, and ALP serum levels decreasing rate. The secondary outcome was assessment liver functional parameters on which UDCA treatment has greater impact in terms of their improvement. Follow-up measures were collected prior endoscopic intervention, and on the fifth, tenth, and fifteenth days after endoscopic intervention.

Randomization

Patients assigned an informed consent for the involving in the trial on the day of endoscopic procedure before ERCP treatment. Randomization was performed at the time of transfer to the endoscope room according to a random number table, which was established before the study began, using random number generator at http:// www.stattrek.com. To minimize observational bias we have been screened by two independent observers. Our study has had clear rules and procedures. This trial was precisely designed in terms of data collection and duration of the study.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by Ethics and Professional Committee at the University Clinical Centre of

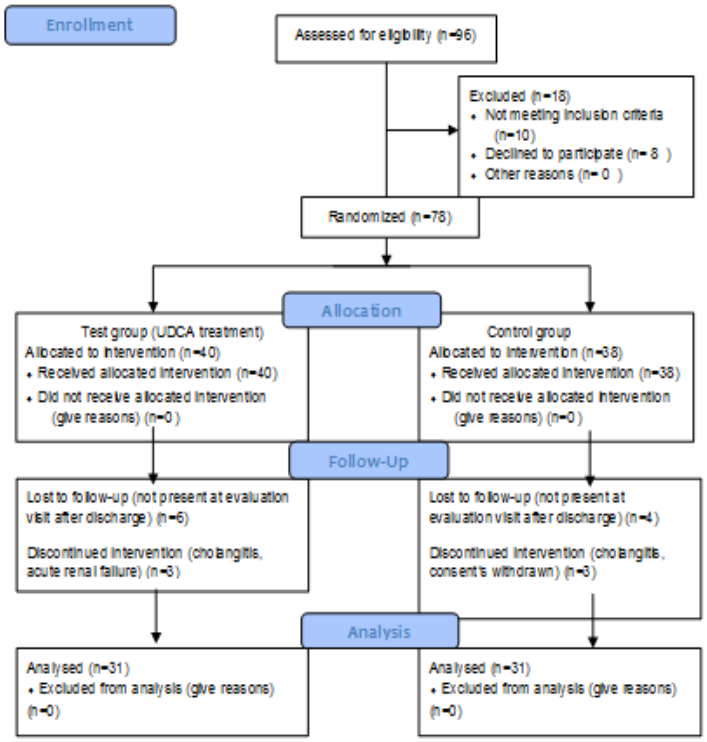

Figure 1: Flow diagram of patients included in the study.

Kosovo. Informed consent was obtained from all participants.

ERCP procedure

Patients with obstructive jaundice were treated by ERCP. The ERCP procedures were performed with the patient under topical pharyngeal anaesthesia with 2% lidocaine and after administration of sedation (midazolam 2-3 mg). Patients received intravenously infusion of 300 to 500 ml of 0.9 % saline solution and 10 mg Scopolamine butylbromide (Buscopan®). The material used to perform ERCP consisted of a video duodenoscope model TJF-Q180F (Olympus™), traction sphincterotome, needle scalpel to perform the pre-cut sphincterotomy, hydrophilic guide wire *via* the bile duct, Dormia basket, ballon catheter for stone extraction, and non-ionic water- soluble contrast 20-40 ml in concentration 1:1 (Omnipaque®) for opacification of the biliary and pancreatic ducts. In patients with ductal stones, by ERCP, ductal stones have been extracted. In those with benign or malign strictures, after sphincterotomy and balloon dilatation, procedure was finished by plastic stent (Olympus®) application. All patients were monitored continuously during the procedure, with measurements of heart rate, respiratory rate and arterial oxygen saturation.

Patients were kept under surveillance in the endoscopy recovery area for twenty-four hours. They were discharged to home by recommendation to come back for visits and serum-testing of liver biochemical markers on the day 5, 10, and 15 after endoscopic procedure.

Biochemical testing

Serum-testing in patients with obstructive jaundice included determination of bilirubin (total and direct fractions), ALT, AST, GGT, ALP, albumin, and N/L ratio. These parameters were determined one day prior endoscopic intervention, and on the fifth, tenth, and fifteenth days after endoscopic intervention.

The normal values of these biochemical markers are taken as follows: total bilirubin (5.0- 20.0 μmol/l), direct bilirubin (<7.0μmol/l), ALT (<42 U/l), AST (<37 U/l), GGT (M: 11-53 U/l, F: 9-37 U/l), ALP (70-306 U/l), and albumin (35-53g/l).

UDCA administration

UDCA administration started twenty-four hours after endoscopic procedure for the patients in the investigation group and lasted fourteen days. UDCA dose was administered at 750 mg/day, divided into three daily doses.

Data collection and statistical analyses

Statistical analysis was made in statistical programs: STATISTICA 7.1; SPSS 17.0: Data including serum-test results are collected and

Table 1: Patients demographics and characteristics.

	control group- CG	investigation group-IG
Age (Mean ± SD)	57.3±16.16	64.9±14.83
Sex		
Female (N/%)	13/41.9	18/58.1
Male (N/%)	18/58.1	13/41.9
Procedure		
SR (N/%)	18/58.1	13/41.9
SA (N/%)	13/41.9	18/58.1

SD: Standard deviation; SR: Stone removal; SA: Stent application; N: Number of patients

Table 2: The average values of the evaluated parameters in the investigation and the control group.

IG/ treatment with UDCA	Mean	Minimum	Maximum	SD
0 day Total bilirubin	224.1	72.4	506.7	121.4601
0 day direct bilirubin	142.1	50.7	445.9	103.3737
5 day Total bilirubin	115.7	9.5	476.0	108.2620
5 day direct bilirubin	64.1	2.1	298.0	65.4191
10 day Total bilirubin	82.7	13.5	341.68	86.0599
10 day direct bilirubin	45.5	2.8	278.0	59.6096
15 day Total bilirubin	61.5	10.6	293.0	68.2012
15 day Direct bilirubin	31.3	2.2	216.0	42.9294
0 day ALT	174.3	33.0	463.0	113.4528
0 day AST	115.9	28.0	247.0	57.4506
0 day GGT	407.8	71.5	972.0	272.3756
0 day ALP	905.6	113.0	3353.2	745.3801
5 day ALT	86.7	15.0	343.0	69.1212
5 day AST	65.3	17.0	121.0	28.7381
5 day GGT	228.2	16.8	718.0	166.5587
5 day ALP	582.9	110.6	1506.0	378.9780
10 day ALT	68.5	14.8	198.0	46.8374
10 day AST	53.0	11.6	131.0	29.3872
10 day GGT	172.6	15.9	897.0	172.3221
10 day ALP	491.9	79.8	1609.0	328.3887
15 day ALT	56.3	11.6	178.0	41.7123
15 day AST	46.9	9.9	134.0	31.0861
15 day GGT	116.3	18.7	596.6	114.0191
15 day ALP	461.6	84.8	1819.0	412.0311
0 day Albumin	38.4	28.3	46.5	5.2152
0 day Neutrophil/lymphocyte ratio	4.8	1.67	23.7	4.2695
5 day Albumin	38.3	26.9	49.4	4.8115
5 day Neutrophil/lymphocyte ratio	3.1	1.2	7.27	1.8009
10 day Albumin	38.3	24.0	53.0	6.3945
10 day Neutrophil/lymphocyte ratio	3.3	1.21	10.1	2.2368
15 day Albumin	36.9	17.9	52.1	6.9815
15 day Neutrophil/lymphocyte ratio	3.4	1.12	21.8	3.8487
0 day Total bilirubin	170.2	50.0	450.5	102.9929
0 day direct bilirubin	85.9	10.3	215.6	58.0630
5 day Total bilirubin	94.7	7.66	389.58	103.1656
5 day direct bilirubin	48.5	2.86	264.0	59.0792
10 day Total bilirubin	70.9	8.9	290.0	79.7369
10 day direct bilirubin	37.8	1.5	183.0	49.6957
15 day Total bilirubin	55.2	8.2	293.0	67.6517
15 day Direct bilirubin	24.9	1.95	167.0	36.1103
0 day ALT	233.3	26.0	616.0	165.0666
0 day AST	154.5	30.0	392.0	89.8719
0 day GGT	434.4	88.0	2112.0	410.8447
0 day ALP	787.6	111.8	2734.0	636.9884
5 day ALT	107.8	22.0	305.0	76.6672
5 day AST	79.5	22.0	198.0	47.7248
5 day GGT	268.2	42.0	1226.8	245.2529
5 day ALP	570.8	121.0	1521.0	400.3219
10 day ALT	80.1	26.5	234.0	48.1684
10 day AST	62.7	23.0	148.85	32.3363
10 day GGT	185.9	23.0	782.5	174.0336
10 day ALP	453.4	78.0	1637.0	337.8345
15 day ALT	70.4	20.0	344.0	64.6117
15 day AST	58.4	14.2	250.0	49.0668
15 day GGT	159.2	24.0	1309.0	241.5278
15 day ALP	387.1	48.0	1610.0	372.3182
0 day Albumin	39.0	31.0	47.0	4.6997
0 day Neutrophil/lymphocyte ratio	3.5	0.92	8.33	1.7729
5 day Albumin	41.7	32.56	51.2	4.2857
5 day Neutrophil/lymphocyte ratio	2.9	0.87	6.14	1.5410
10 day Albumin	41.1	30.64	49.0	4.4141
10 day Neutrophil/lymphocyte ratio	2.6	0.63	5.92	1.5560
15 day Albumin	41.1	29.26	49.0	4.8317
15 day Neutrophil/lymphocyte ratio	2.9	0.6	10.3	2.1196

stored in a computer secured study platform. The collected data are processed using the following statistical methods: Data Types are formed using specific computer programs for this purpose. Their processing is performed using standard descriptive and analytical methods. Qualitative statistical series are analyzed by determining the ratio of relations, proportions, rates and determine the statistical significance between the discovered differences - Difference test. The quantitative series are analyzed with measures of central tendency and measures of dispersion of data (mean and standard deviation). In numerical series in which there was no deviation from the normal distribution, the significant difference was tested with Student t- test. In numerical series in which there were deviations from the normal distribution, to test the significant difference of the average values between the groups was used Mann-Whitney U Test. Statistical significance of more than two variables, differences was analyzed with Analysis of Variance - ANOVA. After ANOVA-test when it has given statistically significant results, we used Post hoc Tukey HSD test.ANOVA -Repeated Measures Analysis of Variance were used for measures the parameters which were repeated more than twice. The Shapiro-Wilk`s test examined the normal allocation-distribution of variables. The level of p less than 0.05 was considered as the cut-off value for significance.

Results

A total of 96 patients with obstructive jaundice were assessed if they were eligible to participate in the study. Eighteen patients were excluded from the study: serum bilirubin level lower than 50μmol/l, 10 patients; and declined to participate in the study, 8 patients.

Of the 78 patients enrolled in the study, 40 were randomized in

the Investigation Group (IG) and 38 were randomized to the Control Group (CG). Of 40 patients randomized to the IG, 31 were completely analysed. Six patients were not presented for further evaluation after discharge, and 3 patients discontinued the investigation: cholangitis, 2 patients; and acute renal failure, 1 patient. Of 38 patients randomized to the control group, 31 were completely analysed. Four patients were not presented for further evaluation after discharge, and 3 patients discontinued the investigation: cholangitis, 1 patient; and consent's withdrawn, 2 patients (Figure 1).

The primary cause of the obstructive jaundice was as follows: choledocholithiasis, 31 patients (13 patients in the IG, and 18 patients in the CG); and malign stenosis of extrahepatic biliary tree, 31 patients (18 patients in the IG, and 13 patients in the CG); cholangiocarcinoma, 19 patients; pancreatic cancer, 11 patients; and carcinoma of the ampulla of Vater, 1 patient. Patient characteristics are shown in Table 1. The difference between the mean age of patients between the two groups was not statistically significant for $p > 0.05$ ($p = 0.058107$). There was no significant difference between the genders in both groups for $p>0.05$ ($p = 0.2020$). Also, the percentage difference between the procedures in both groups was not statistically significant for $p>0.05$ ($p=0.2020$). The average values of all evaluated parameters in both groups are shown in Table 2.

The difference of the average values of total bilirubin, direct bilirubin, ALT, AST, GGT, ALP in the IG and CG, between the day 0 (before ERCP) and the days 5, 10, and 15 (after ERCP), was statistically significant for $p<0.05$ (total bilirubin, $p=0.000000$, $p = 0.000006$; direct bilirubin, $p=0.000000$, $p= 0.000121$; ALT, $p= 0.000000$, $p=0.000000$; AST, $p=0.000000$, $p=0.000000$; GGT, $p = 0.000000$, $p= 0.000830$; and ALP, $p= 0.002725$, $p=0.006027$, respectively).

The difference of the average values of albumin and N/L ratio in the IG and CG, between the four measurements, was not statistically significant ($p>0.05$) (Table 3).

According multiple comparisons of total bilirubin, direct bilirubin, ALT, AST, GGT, and ALP in the IG and CG, there was an overall significance due to the statistical significance between the day 0 versus the 5^{th}, 10^{th} and 15^{th} days after the procedure for $p<0.05$ (Table 4).

The difference of the average values of total bilirubin and direct bilirubin, between the groups, was statistically significant for $p< 0.05$ (total bilirubin, $p = 0.034706$; and direct bilirubin, $p=0.033173$, respectively) at day 0, but at the other days was not statistically significant ($p>0.05$). The difference of the average values of ALT, AST, GGT, ALP, and N/L ratio, between the groups, was not statistically significant ($p>0.05$), while the difference of the average values of albumin, between the groups, was statistically significant at days 5, 10, and 15 (after ERCP) ($p=0.007722$; $p=0.020353$; $p=0.002547$) (Table 5).

The index dynamics showed that decrease rate of total bilirubin, direct bilirubin, GGT, and N/L ratio, between the day 15 compared to day 0, was higher in the IG than in the CG (total bilirubin; 72.6% *vs* 67.6%, direct bilirubin; 78.1% *vs* 71%, GGT; 71.5% *vs* 63.4%, and N/L ratio; 29% *vs* 17%, respectively), while the decrease rate of ALT, AST, and ALP was higher in the CG than in the IG (ALT; 69.8% *vs* 67.7%, AST; 62.2% *vs* 59.5%, ALP; 50.8% *vs* 49%, respectively).

The albumin level, in the IG, between the days 15 compared to day 0, was decreased 3.9%, while in the CG the albumin level was increased 5.4%.

Discussion

In a study by Hsu et al. was shown that UDCA seemed not to benefit patients with severe obstructive jaundice after successful drainage [17]. This study has failed to demonstrate the beneficial effect of UDCA.

To our knowledge, no previous study has evaluated the effect of UDCA in patients with obstructive jaundice after endoscopic treatment.

In this study was evaluated the effect of UDCA in functional liver restoration in patients with obstructive jaundice after endoscopic treatment. The patients randomly were divided in two groups: in the Investigation Group (IG) and in the control group. The patients in the IG were treated with UDCA, while the patients in the CG were not treated with UDCA. Also, in this study was observed the impact of UDCA in functional liver tests.

The study showed that the difference of the average values of total bilirubin and direct bilirubin between the day 0 (before ERCP) and the days 5, 10, and 15 (after ERCP) was statistically significant in both groups. The difference of the average values, between the groups, was statistically significant at day 0, but was not at other days. The decrease rate of total and direct bilirubin, between the days 15 compared to day 0, was higher in the IG than in the CG. The difference of the average values of ALT, AST, GGT, ALP, and N/L ratio between the day 0 and the days 5, 10, and 15 was statistically significant in both groups, but the difference between the groups was not statistically significant. The decrease rate of GGT and N/L ratio, between the day 15 compared to day 0, was higher in the IG than in the CG, while ALT, AST, and ALP reduced higher in the CG than in the IG. The higher decrease rate of ALP in the CG maybe was due to a large number of patients with choledocholithiasis than with malign stenosis in this group.

It was shown that the difference of the average values of albumin between the day 0 and the days 5, 10, and 15 was not statistically significant in both groups. The albumin level, in the IG, between the day 15 compared to day 0, was decreased, while in the CG the albumin level was increased. It may be explained due to a large number of patients with choledocholithiasis than with malign stenosis in the CG. The difference of the average values of albumin, between the groups, was statistically significant at days 5, 10, and 15.

The effect of UDCA was evaluated in primary sclerosing cholangitis, primary biliary cirrhosis, and in other diseases. Ursodeoxycholic acid, a bile acid, is the most extensively studied drug for the management of Primary Sclerosing Cholangitis (PSC). When compared to placebo, UDCA significantly reduced the elevated levels of alkaline phosphatase in patients suffering from PSC [18]. Unlike Primary Biliary Cirrhosis (PBC), in which UDCA shows biochemical, histological and survival benefits, several studies aiming at determining the effectiveness of UDCA among PSC patients failed to show an improvement in outcomes [18-21].

Ursodeoxycholic acid is the most extensively used drug in patients with Primary Biliary Cirrhosis (PBC). However, some patients

Table 3: Comparison of average values of liver functional tests between the evaluated days in the Investigation Group (IG) and in the Control Group (CG).

	SS-Effect	Diff-Effect	MS–Effect	SS–Error	diff–Error	MS–Error	*F	P
Total bilirubin/IG	485748	3	161916	1144207	119	9615.2	16.83961	0.000000
Total bilirubin/CG	241311	3	80436.9	965562	120	8046.4	9.99669	0.000006
direct bilirubin/IG	211340	3	70447	574522	116	4952.8	14.22364	0.000000
direct bilirubin/CG	59726	3	19908.8	304005	115	2643.5	7.53116	0.000121
ALT/IG	262611	3	87537	638777	117	5459.6	16.03353	0.000000
ALT/CG	525507	3	175169.0	1186271	119	9968.7	17.57197	0.000000
AST/IG	91509	3	30503	177866	119	1494.7	20.40792	0.000000
AST/CG	186132	3	62043.9	414234	120	3451.9	17.97359	0.000000
GGT/IG	1406766	3	468922	4121905	115	35842.7	13.08279	0.000000
GGT/CG	1400149	3	466716.4	9358177	119	78640.1	5.93484	0.000830
ALP/IG	3565980	3	1188660	27386501	115	238143.5	4.99136	0.002725
ALP/CG	2608885	3	869628.4	22526920	113	199353.3	4.36225	0.006027
Albumin/IG	45	3	15	3869	110	35.2	0.42871	0.732829
Albumin/CG	108	3	36.1	2347	113	20.8	1.73966	0.162909
Neutrophil/lymphocyte ratio/IG	52	3	17	1207	115	10.5	1.63904	0.184231
Neutrophil/lymphocyte ratio/CG	13	3	4.5	360	115	3.1	1.43115	0.237334

*F- ratio in ANOVA test

respond poorly, and some authors were unable to demonstrate any significant effect of UDCA in all-cause mortality or liver transplantation, pruritus, or fatigue in patients with PBC. Bezofibrate developed as a drug for treatment of hyperlipidemia and used for the prevention for the cardiovascular diseases. Recently, this drug has come to be recognized as a potential anticholestatic medicine for the treatment of PBC that does not respond sufficiently to UDCA monotherapy.

A meta-analysis was performed to assess the efficacy and safety of UDCA and bezafibrate combination therapy in the treatment of PBC. As a result, in nine trials, which included 247 patients, combination therapy with UDCA and bezafibrate was more effective than UDCA monotherapy in decreasing the serum Alkaline Phosphatase (ALP). Also, seven trials, which included 194 patients, reported that combination therapy with UDCA and bezafibrate was more effective than UDCA monotherapy in decreasing Gama-Glutamil Transferase (GGT).

In four trials, which included 112 patients, combination therapy with UDCA and bezafibrate was more effective than UDCA monotherapy in decreasing the serum ALT.

In four trials, which included 97 patients, combination therapy decreased the serum bilirubin levels compared with UDCA monotherapy.

There were no significant differences between the two groups in serum AST levels. It was demonstrated in two trials, which included 39 patients.

This meta-analysis concluded that significant improvements of liver biochemistry indicators, such as ALP, GGT, immunoglobulin M, total cholesterol, bilirubin, ALT, and triglycerides, compared with UDCA monotherapy suggest that combination therapy is more favorable, although the survival rate was not significantly different between the groups [22].

Hosonuma K et al. [23], in a prospective, randomized, controlled, and multi-center study aimed to compare the long-term clinical results between combination therapy (ursodeoxycholic acid+bezafibrate) and UDCA monotherapy for Primary Biliary Cirrhosis (PBC) patients exhibiting dyslipidemia. The median treatment period in the UDCA and UDCA+BF groups was 107 and 110 months, respectively.

The serum Alkaline Phosphatase (ALP) levels and the Mayo risk score in the combination therapy group were significantly lower than those in the UDCA monotherapy group at 8 years after the beginning of the study ($p<0.05$).However, the survival rate was not significantly different between the groups [23].

Some authors assessed the statistical relationship between serum bilirubin and albumin concentrations during the natural course of PBC in untreated patients and further constructed a time model on their relation, since both are well-established independent predictors of survival and thus disease progression in PBC. They then compared the relationship seen in the reference cohort between albumin, bilirubin, and time since referral with that seen in published UDCA trials. Specifically, the reported reduction in serum bilirubin levels in UDCA trials was assessed in relation to an accompanying and corresponding slower reduction, stabilization or even increase in serum albumin concentration, consistent with improved prognosis.

As a higher concentration in serum albumin is associated with improved survival, and if UDCA not only lowers bilirubin, but also improves prognosis, one would expect to see a slower fall in the level of albumin. Therefore, if the observed albumin at the end of the trial's follow-up was lower than that predicted by the model, given the final bilirubin level and the length of follow-up, this would be consistent with UDCA having no effect on prognosis.

In all assessed trials, serum albumin did not significantly differ

Table 4: Comparison of total bilirubin, direct bilirubin, ALT, AST, GGT, and ALP values between the evaluation days in both groups (post- hoc Tukey HSD test).

a.Total bilirubin								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1} - M=224.09**	**{2} - M=115.72**	**{3} - M=82.654**	**{4} - M=61.474**	**{1} - M=170.16**	**{2} - M=94.693**	**{3} - M=70.921**	**{4} - M=55.187**
0 {1}		0.000313	0.000137	0.000136		0.006708	0.000285	0.000143
5 {2}	0.000313		0.554205	0.140602	0.006708		0.724424	0.310899
10{3}	0.000137	0.554205		0.830223	0.000285	0.724424		0.900597
15 {4}	0.000136	0.140602	0.830223		0.000143	0.310899	0.900597	
b. direct bilirubin								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1} - M=142.09**	**{2} - M=64.093**	**{3} - M=45.540**	**{4} - M=31.329**	**{1} - M=85.943**	**{2} - M=48.460**	**{3} - M=37.812**	**{4} - M=24.973**
0 {1}		0.000402	0.000139	0.000137		0.030534	0.003376	0.000206
5 {2}	0.000402		0.732666	0.270314	0.030534		0.853609	0.279454
10{3}	0.000139	0.732666		0.856656	0.003376	0.853609		0.768707
15 {4}	0.000137	0.270314	0.856656		0.000206	0.279454	0.768707	
c. ALT								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1}- M=115.95**	**{2} - M=65.303**	**{3} - M=53.005**	**{4} - M=46.965**	**{1} - M=154.45**	**{2} - M=79.453**	**{3} - M=62.713**	**{4} - M=58.366**
0 {1}		0.000142	0.000136	0.000136		0.000144	0.000136	0.000136
5 {2}	0.000142		0.601528	0.254511	0.000144		0.676955	0.493851
10{3}	0.000136	0.601528		0.927163	0.000136	0.676955		0.991443
15 {4}	0.000136	0.254511	0.927163		0.000136	0.493851	0.991443	
d. AST								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1}- M=115.95**	**{2}- M=65.303**	**{3}- M=53.005**	**{4}- M=46.965**	**{1}- M=154.45**	**{2}- M=79.453**	**{3}- M=62.713**	**{4}- M=58.366**
0 {1}		0.000142	0.000136	0.000136		0.000144	0.000136	0.000136
5 {2}	0.000142		0.601528	0.254511	0.000144		0.676955	0.493851
10{3}	0.000136	0.601528		0.927163	0.000136	0.676955		0.991443
15 {4}	0.000136	0.254511	0.927163		0.000136	0.493851	0.991443	
e. GGT								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1}- M=407.79**	**{2} - M=228.23**	**{3} - M=172.55**	**{4} - M=116.31**	**{1} - M=434.43**	**{2} - M=268.22**	**{3} - M=185.85**	**{4} - M=159.22**
0 {1}		0.002616	0.000159	0.000137		0.100621	0.004206	0.001261
5 {2}	0.002616		0.666632	0.111181	0.100621		0.655456	0.422805
10{3}	0.000159	0.666632		0.653249	0.004206	0.655456		0.982160
15 {4}	0.000137	0.111181	0.653249		0.001261	0.422805	0.982160	
f. ALP								
	IG/ treatment with UDCA				**CG**/ treatment without UDCA			
day	**{1}- M=905.63**	**{2} - M=582.91**	**{3} - M=491.96**	**{4} - M=461.60**	**{1} - M=787.61**	**{2} - M=570.81**	**{3} - M=453.41**	**{4} - M=387.07**
0 {1}		0.062690	0.008845	0.003875		0.264647	0.028575	0.005484
5 {2}	0.062690		0.888289	0.766468	0.264647		0.739122	0.386325
10{3}	0.008845	0.888289		0.994999	0.028575	0.739122		0.939314
15 {4}	0.003875	0.766468	0.994999		0.005484	0.386325	0.939314	

between UDCA and placebo-treated patients, despite the significant UDCA effect on serum bilirubin. They concluded that there is no evidence that UDCA acts on serum albumin concentrations in a way that is consistent with its effect on serum bilirubin levels [24].

Table 5: Comparison of the average values of evaluated parameters between the IG and the CG.

	Rank Sum-IG	Rank Sum-CG	U	Z	*p*-value
0 day Total bilirubin	1127.000	826.0000	330.0000	2.111786	0.034706
0 day direct bilirubin	930.000	666.0000	260.0000	2.154869	0.031173
5 day Total bilirubin	1016.500	874.5000	378.5000	1.240657	0.214733
5 day direct bilirubin	1025.000	866.0000	370.0000	1.363280	0.172795
10 day Total bilirubin	1052.000	901.0000	405.0000	1.055893	0.291018
10 day direct bilirubin	1021.000	809.0000	374.0000	1.109448	0.267238
15 day Total bilirubin	1044.000	909.0000	413.0000	0.943264	0.345546
15 day Direct bilirubin	1065.500	887.5000	391.5000	1.245954	0.212782
0 day ALT	1069.500	883.500	387.5000	1.30227	0.192826
0 day AST	1082.500	870.500	374.5000	1.48529	0.137468
0 day GGT	893.000	877.000	428.0000	-0.09855	0.921493
0 day ALP	712.000	828.000	334.0000	-0.73236	0.463949
5 day ALT	1025.500	865.500	400.5000	0.92328	0.355862
5 day AST	1010.500	880.500	415.5000	0.70689	0.479638
5 day GGT	969.000	861.000	426.0000	0.34023	0.733683
5 day ALP	899.500	930.500	434.5000	-0.22177	0.824496
10 day ALT	1010.500	819.500	354.5000	1.40452	0.160165
10 day AST	1061.500	891.500	395.5000	1.18964	0.234189
10 day GGT	989.500	963.500	467.5000	0.17598	0.860308
10 day ALP	870.000	960.000	405.0000	-0.65791	0.510598
15 day ALT	1011.000	880.000	415.0000	0.71410	0.475166
15 day AST	1038.500	914.500	418.5000	0.86583	0.386583
15 day GGT	938.000	953.000	442.0000	-0.32459	0.745491
15 day ALP	855.000	1036.000	390.0000	-1.07476	0.282485
0 day Albumin	700.500	730.500	324.5000	0.44544	0.656005
0 day Neutrophil/lymphocyte ratio	853.500	1037.500	388.5000	-1.09639	0.272907
5 day Albumin	1106.000	664.000	258.0000	2.66399	0.007722
5 day Neutrophil/lymphocyte ratio	813.000	898.000	378.0000	-0.65315	0.513657
10 day Albumin	1053.500	716.500	281.5000	2.31978	0.020353
10 day Neutrophil/lymphocyte ratio	754.000	957.000	319.0000	-1.57068	0.116258
15 day Albumin	1150.000	680.000	245.0000	3.01770	0.002547
15 day Neutrophil/lymphocyte ratio	969.000	922.000	457.0000	0.10820	0.913840

IG- Investigation Group
CG- Control Group
[d]Estimated by Mann- Whitney U test

Currently, UDCA is the most promising treatment for Intrahepatic Cholestasis of Pregnancy (ICP). It is well tolerated by mothers and no adverse effects in newborns have been observed. Palma et al. [25] reported UDCA improved significantly serum biochemistry in patients with ICP. This study was followed by three small randomized controlled trials showing a significant reduction of pruritus and liver function tests after using UDCA in ICP [26-28].

Some studies tested UDCA monotherapy or UDCA in combination with other drugs for treatment of patients with Non-Alcoholic SteatoHepatitis (NASH). UDCA monotherapy was found to significantly improve liver function, including ALT, AST or GGT, in five studies. All five studies of UDCA combination therapy found significant improvements in liver function, with two also showing improvements in steatosis and inflammation. These data suggested that UDCA combination therapy was superior to UDCA monotherapy in the treatment of NASH [29].

The ratio of circulating Neutrophils to Lymphocytes (NLR) is an indicator of systemic inflammatory response and has been proposed as a routinely available preoperative indicator of prognosis in patients undergoing resection of primary colorectal cancer.

Subsequently, studies of patients with Primary Colorectal Cancer (CRC) have reported a statistically significant association between preoperative NLR and overall survival.

Associations have also been reported between NLR and recurrence-free survival, but not cancer-specific survival.

Ozdemir et al. [30] in their retrospective study concluded that high pretreatment NLR is a significant independent predictor of shorter survival in patients with colorectal cancer.

The neutrophil/lymphocyte ratio has been described as a marker for immune response to various stimuli including cancer.

Although these explanations, the meaning of elevated NLR remains unclear [30].

The limitation of this study was the significant differences at baseline levels (day 0) of total and direct bilirubin between the groups.

In the future, the effect of UDCA in functional liver restoration in patients with obstructive jaundice after endoscopic treatment should be assessed in a larger scale studies and, maybe, with higher daily doses of UDCA.

Conclusion

In summary, our results show that UDCA accelerates reducing the levels of total bilirubin, direct bilirubin, GGT, and neutrophil/lymphocyte ratio. UDCA does not decrease the level of ALT, AST, and alkaline phosphatase, and does not induce increasing of albumin level. UDCA has greater impact on GGT than in other functional liver parameters.

Declaration

Acknowledgement

The authors acknowledge all colleagues and nurses who provided care to the patients.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

EF performed treatment, designed the study, and wrote the paper. NM was responsible for drafting the manuscript and supervising the study. NJ was a major contributor to the writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by Ethics and Professional Committee at the University Clinical Centre of Kosovo. Informed consent was obtained from all participants.

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Citation: Fekaj E, Matveeva N and Jankulovski N. The Effect of Ursodeoxycholic Acid in Liver Functional Restoration of Patients with Obstructive Jaundice after Endoscopic Treatment: A Randomized Controlled Trial. Austin Dig Syst. 2017; 2(1): 1008.