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Effect of ursodeoxycholic acid on liver regeneration capacity after living donor hepatectomy: a prospective, randomized, double-blind clinical trial

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Abstract. – OBJECTIVE: Ursodeoxycholic acid (UDCA) has multiple hepatoprotective activities: it modifies the bile acid pool, decreases levels of endogenous, hydrophobic bile acids while increasing the proportion of nontoxic hydrophilic bile acids. It also has cytoprotective, antiapoptotic, and immunomodulatory properties. The aim of this study was to analyze the effect of postoperative administration of UDCA on liver regeneration capacity.

PATIENTS AND METHODS: This is a single-center, prospective, randomized, double-blind study that was carried out in our Liver transplant Institute. Sixty living liver donors (LLDs) who underwent right lobe living donor hepatectomy were divided into two groups using computer-generated random numbers: one group received oral UDCA 500 mg 12 hourly for 7 days (UDCA group; n=30) from the first postoperative day (POD) and the other did not receive UDCA (non-UDCA group; n=30). Both groups were compared in terms of the following parameters: clinical and demographic parameters, liver enzymes (ALT, AST, ALP, GGT, total bilirubin, direct Bilirubin), and INR.

RESULTS: The median ages in the UDCA and non-UDCA were 31 years (95% CI for median: 26-38) and 24 years (95% CI for median: 23-29), respectively. Liver function tests showed significant differences at various times within the first seven PODs. The INR was lower in UDCA group patients on POD3 and POD4. However, GGT was significantly lower on POD6 and POD7 for the UDCA group. Total bilirubin was also significantly lower on POD3 for the UDCA group patients, but ALP was lower all from POD1 to POD7. A significant difference was also observed in AST on POD3, POD5 and POD6.

CONCLUSIONS: Postoperative administration of oral UDCA significantly improves liver function tests and INR among LLDs.

Key Words:
Living donor liver transplantation, Living liver donors, Right lobe living donor hepatectomy, Ursodeoxycholic acid, Regeneration capacity.

Abbreviations

UDCA: Ursodeoxycholic acid; LLD: Living liver donors; POD: Postoperative day; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transferase; INR: International normalized ratio; LT: Liver transplantation; LDLT: Living donor liver transplantation; LDH: Living donor hepatectomy.

Introduction

Liver transplantation (LT) represents the only curative treatment for patients with end-stage liver disease and selected patients with hepatocellular carcinoma[1-5]. With improvements in surgical techniques and advances in immunosuppression, LT has become a routine proce-

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dure. Indications for LT have been expanded with a resultant increase in the need for transplantable organs[6]. The increasing demand meant that deceased donation is not enough for the ever-expanding pool of patients in need of organ donation. Therefore, expanding the donor pool and reducing the waiting list mortality is one of the major concerns of the liver transplant community. Some of the efforts to expand the donor pool included the use of non-heart-beating donors, split liver donation, and living donor liver transplantation (LDLT)[6-9].

LDLT was performed by Raia et al[10] in 1988 in Brazil and in the same year, the first successful LDLT was performed by Strong et al[11] from Australia. Since then, there has been tremendous improvement in LDLT and it is currently the main type of liver transplant in Asia and some parts of Europe[2,7,8,12,13]. LDLT is made possible by the ability of the liver to regenerate: up to 70% of the liver volume can be resected for donation and the remaining 30% is expected to regenerate[14-18]. Living liver donors (LLDs) are typically healthy adults who do not derive any personal medical benefit from the procedure. Therefore, in order to justify exposing LLDs to such an operation, it is imperative to have a broad and clear understanding of the potential effects of LDLT on the LLDs. With increasing numbers of LDLTs being performed, there is an increasing concern about the safety of LLDs; however, no systematic and sufficiently large reports[7,13,17,19,20] on this subject are available. One of the ever-present concerns about LDLT is the danger of post-donation hepatic insufficiency, especially in right donor hepatectomy[19]. To avert this, adequate preoperative donor evaluation is important in LLDs[21-23]. However, even with adequate preoperative radiological assessment, some patients show varied mostly self-limiting liver function and enzyme derangements after donor hepatectomy[24]. This is more pronounced in right donor hepatectomy patients, probably because of the relatively larger volume of the liver resected[5,24]. Therefore, there may be a need for hepatoprotective medications to counter inflammatory processes brought about by regeneration mechanisms and enhance recovery.

Ursodeoxycholic acid (UDCA) has multiple hepatoprotective activities: it modifies the bile acid pool, decreases levels of endogenous, hydrophobic toxic bile acids while increasing the proportion of nontoxic hydrophilic bile acids. It also has cytoprotective, antiapoptotic, and immunomodulatory properties[25-30]. In the light of this information, the study aimed at assessing the effect of UDCA on liver function tests during the early regeneration and postoperative inflammatory period after living donor hepatectomy (LDH).

Patients and Methods

Study Design

This is a single-center, prospective, randomized double-blind study that was carried out at the Liver Transplant Institute, Inonu University, Malatya, Turkey from the 1st of September to the 15th of December 2021.

The Outcomes, Sample Size, and Statement

The primary outcomes measured were the liver enzymes and INR levels in the two groups. These outcomes were compared between the groups to see if the administration of UDCA has any protective effects on the remnant liver in the UDCA group. A priori power analysis revealed a minimum of 26 patients per group (52 in total) considering an alpha of 0.05, a beta of 0.20, an effect size of 0.80, an allocation ratio of 1, and a two-tailed hypothesis test[31]. In the current study, 60 patients (30 in each group) were enrolled to perform the assumed analyses. CONSORT (Consolidated Standards of Reporting Trials) checklist was evaluated to address potential issues that arise as a result of insufficient reporting of randomized controlled trials[32].

Study Population

60 LLDs were recruited into the study, and they were grouped into two. One group received oral UDCA 500 mg 12 hourly for 7 days (UDCA group) from the first postoperative day (POD) and the other group did not receive any additional treatment (non-UDCA group).

Inclusion and Exclusion Criteria

All adult LLDs that consented to participate and underwent right living donor liver hepatectomy were included in the study, while the left living donor liver hepatectomy or left lateral hepatectomy patients and patients with steatosis greater than 20% were excluded from the study. LLDs who underwent reoperation due to bleeding or ileus in the first 7 days postoperatively were also excluded from the study.

Randomization Protocol

Randomization was done using computer generated random number. If the number generated is an odd number, then the patient is placed in the UDCA group. If the number generated is even, then the patient is in the non-UDCA group.

Outcome

The primary outcome was the difference in the level of ALP, AST, GGT, TB and ALT measured from day 1 to day 7 after living donor hepatectomy between the two groups. The secondary outcome measured is the difference in the level of INR measured in the two groups from day 1 to day 7 after surgery.

Ethical Considerations

Informed consent was obtained from all the patients included in the study. Verbal and written consent was voluntary and those that chose not to participate were not treated any differently. Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (2021/217).

Intervention

All the participants underwent right lobe LDH which was carried out as described by our liver transplantation team[33,34]. The intervention was commenced for patients in the UDCA group on the first postoperative day (POD1). They received oral UDCA 500 mg 12 hours from POD1 to POD7. Samples for liver enzyme and INR were taken from POD1 to POD7 post-operatively with the first sample taken at least 12 hours after receiving the first dose of UDCA.

Statistical Analysis

The related data were collected from the patients and laboratory reports and entered into Microsoft Excel 2010. The data collected includes patient age, gender, body mass index (BMI), remnant liver volume, preoperative liver enzymes, and INR, type of donation, and post-operative liver enzyme and INR from POD1 to POD7. Quantitative variables were summarized using median and 95% confidence interval (CI) for median, while qualitative variables were summarized using percentages and numbers. The Kolmogorov-Smirnov test was used to assess the normality of the data. Non-normally distributed continuous variables were compared using Mann-Whitney U test, while categorical variables were compared using Chi-square or Fischer's exact test. A p-value <0.05 was considered a statistically significant value. IBM SPSS Statistics v.25 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Sociodemographic, Anthropometric, and Remnant Liver Volume

A total of 60 patients were involved in the study with 30 patients per group. The median age of patients in the UDCA group was 31 years and it was not statistically different from the median age of the non-UDCA group which was 24 years. The male to female ratio was also similar in the two groups. The body mass index of the two groups was also similar. The median remnant liver volume of LLDs in the UDCA group was 34.3% of the total liver volume, while the median remnant volume in the non-UDCA group was 33.7%. Descriptive statistics of the sociodemographic and remnant liver volume characteristics are given in Table I.

Changes in INR in the Two Groups

The INR changes observed from POD1 to POD7 showed some differences in the two groups. We observed that patients in the UDCA group had statistically significant differences in INR from those in the non-UDCA group at POD3 and POD4 after right lobe LDH. The INR in the UDCA group was significantly lower than that in the non-UDCA group on the mentioned days with a p=0.007 and p=0.018, respectively.

Table I. Descriptive statistics of the sociodemographic and remnant liver volume characteristics.

Variable	UDCA group	non-UDCA group	p
Age (median [95% CI])	31 [26-38]	24 [23-29]	0.100
Gender (male/female)	17/13	24/6	0.052
Remnant liver volume (median [95% CI])	34 [33.7-35.1]	33.7 [33.3-34.7]	0.574
BMI (median [95% CI])	25.3 [22.9-25.9]	23.4 [21.7-26.6]	0.745

BMI: Body mass index.

Changes in Liver Enzymes in the Two Groups

Five of the liver enzymes showed significant variation between the two groups for the duration of observation. At the POD1, only ALP of LLDs in the UDCA group showed a significant difference as we observed that it was lower than those in the non-UDCA group with a p=0.013. The difference in the ALP value was maintained up to the POD7. On the second postoperative day, we observed that in addition to ALP, ALT values were significantly lower in the UDCA group compared to the non-UDCA group with a p=0.022 and p=0.024, respectively. On the third postoperative day, the difference in ALP and ALT was sustained, we noticed that AST also showed significant variations between the two groups on POD3 with the AST in UDCA group lower than that of non-UDCA group with a p=0.010. Additionally, on the same day, the serum total bilirubin of patients in UDCA group was observed to be lower than that of the non-UDCA group. The difference was statistically significant with a p=0.013. On the POD4, the difference in the values of ALP and ALT was sustained, but there was no statistically significant difference in the values of AST and total bilirubin between the two groups. On the POD5, we observed that the AST of the LLDs in the non-UDCA group had risen compared to LLDs in the UDCA group and the difference was statistically significant. However, there was no statistically significant difference in the ALT values between the groups on POD5. On the POD6 and POD7, the GGT, AST, ALT, and ALP were all significantly lower in patients in UDCA group compared to patients in the non-UDCA group with p=0.014, p=0.002, p<0.001, and p=0.021, respectively. These results are presented in Table II.

Discussion

LT as a treatment for patients with end-stage liver disease and selected patients with hepatocellular carcinoma has undergone significant improvements in surgical techniques and immunosuppressive therapy[35]. It is now considered a routine procedure. Expanding the donor pool and reducing waiting list mortality is one of the major concerns of the liver transplant community[6]. Efforts to expand the donor pool included the use of non-heart-beating donors, split liver donation, and LDLT[6-9,13]. LDLT is based on the main principles of minimizing LLDs morbidity and mortality, and maximal graft survival[2,6-9,13,20,36].

The overall age range of our study population was 18-50 years. This is narrower than the range among LLDs in a study conducted by Wang et al[37] in Taiwan where an age range of 18- 62 years was observed among LLDs. The range was however wider than the age range reported by El-Mehteni et al[38] in Egypt and Shimada et al[18] in Japan, both of which reported age ranges of 18-45 years and 46-49, respectively. The difference between our age ranges is due to the expansion of our donor criteria to include the elderly (up to 65 years) which in turn expanded our donor pool. The mean BMI in our patients is 25.3 kg/m^2 in UDCA and 23.4 kg/m^2 in the non-UDCA group. This is similar to the BMI reported among LLDs by Urrunaga et al[39], from the John Hopkins University, Maryland, USA, and Donmez et al[15] in Istanbul, Turkey. They reported a BMI of 26.0 kg/m2 and 25.1 kg/m^2 respectively. Pagano et al[20] reported a BMI of 23.8 kg/m^2 among LLDs in Italy and this is also no different from our findings. The similarities in the BMI may be as a result of similarities in the patient studied as all the studies we mentioned were conducted in Europe/ America where the predominant population is Caucasians. The remnant liver volume in our study was 34.3% and 33.7% in UDCA and non-UDCA groups respectively. This is slightly lower than the findings of Donmez and Andaçoğlu[15] in Turkey, where they found a remnant volume of 36.2% among LLDs. It is also lower than what was reported by Pagano and Gruttadauria[20], where a remnant volume of 37.16% was reported among LLDs. This slight difference may be due to patients' selection in the respective studies. We only included LLDs that donated the right lobe of the liver, while the two mentioned studies included all LLDs, including left lobe LLDs and those that donated segments 2 and 3 or less.

There have been numerous reports about alterations in laboratory tests among LLDs after LDH. Trotter et al[9] reported changes in hematological parameters and liver enzymes after donation but most of these changes resolved spontaneously within weeks and revert back to normal. These changes were attributed to the surgical injury to the liver during resection and the enzymes revert to normal once the liver regenerates enough.

One of the dreaded complications of LDH of the liver is the risk of post-donation hepatic insufficiency, especially in right lobe LDH[16,18].

Table II. Comparison of both groups in terms of liver function tests using median [95 % CI for median] values.

LFT	Groups	PreOP	POD1	POD2	POD3	POD4	POD5	POD6	POD7
INR	UDCA Non-UDCA *p*	1.0 [1-1.1] 1.0 [1-1.2] 0.854	1.1 [1.1-1.2] 1.2 [1.2-1.4] 0.155	1.30 [1.2-1.4] 1.37 [1.3-1.5] 0.128	1.2 [1.2-1.4] 1.4 [1.3-1.5] **0.007**	1.1 [1.1-1.2] 1.2 [1.2-1.4] **0.018**	1.1 [1.1-1.2] 1.2 [1.2-1.4] 0.236	1.1 [1-1.13] 1.1 [1.1-1.2] 0.876	1.0 [1-1.1] 1.1 [1-1.1] 0.075
AST	UDCA Non-UDCA *p*	31 [28-37] 22 [18-29] **0.001**	201 [156-167] 203 [147-264] 0.641	167 [133-231] 225 [162-335] 0.074	131 [88-171] 186 [149-211] **0.010**	87 [63-119] 106 [95-135] 0.088	56 [48-70] 78 [67-93] **0.021**	45 [39-60] 64 [49-91] **0.033**	36 [30-45] 51 [46-63] **0.002**
ALT	UDCA Non-UDCA *p*	38 [35-42] 35 [29-38] 0.058	171 [131-217] 202 [177-256] 0.308	213 [163-262] 283 [219-441] **0.024**	185 [125-244] 298 [228-344] **0.001**	146 [115-190] 199 [146-270] **0.030**	111 [89-145] 141 [120-168] 0.095	72 [64-98] 113 [97-139] **0.007**	52 [37-70] 95 [77-122] < **0.001**
ALP	UDCA Non-UDCA *p*	53 [45-60] 52 [45-66] 0.947	55 [44-58] 61 [56-68] **0.013**	59 [52-61] 64 [57-84] **0.010**	58 [54-69] 66 [57-77] **0.022**	63 [52-68] 71 [58-92] **0.019**	67 [60-77] 72 [63-102] **0.029**	70 [63-79] 95 [74-107] **0.001**	74 [70-82] 99 [78-109] **0.021**
GGT	UDCA Non-UDCA *p*	32 [25-39] 30 [21-35] 0.459	22 [15-29] 20 [16-24] 0.912	25 [23-33] 24 [20-32] 0.923	30 [24-39] 26 [19-38] 0.525	37 [19-56] 40 [25-82] 0.367	50 [35-67] 58 [46-133] 0.110	48 [38-69] 88 [57-149] **0.003**	59 [45-89] 98 [66-149] **0.014**
TBil	UDCA Non-UDCA *p*	0.90 [0.7-1] 0.75 [0.6-1] 0.121	1.20 [1.1-2.0] 1.55 [1.3-1.9] 0.115	1.70 [1.5-2.8] 2.25 [1.9-2.6] 0.322	1.35 [1.0-1.6] 2.25 [1.9-3.0] **0.013**	1.10 [1.0-1.6] 1.80 [1.4-2.2] **0.052**	1.0 [0.8-1.3] 1.0 [0.8-1.6] 0.982	0.8 [0.7-1.4] 0.9 [0.8- 1.7] 0.369	0.6 [0.5-0.8] 0.8 [0.6-1.0] 0.174

This can be prevented by adequate preoperative donor evaluation to calculate the standard liver volume and the proposed remnant liver volume[21]. The remnant liver volume regenerates rapidly after the LDH; however, in patients that developed post-donation hepatic insufficiency, there is a deficiency in this regeneration[2,19,20,40]. The risk of post-donation hepatic insufficiency is low, but to further reduce the risk, efforts at encouraging hepatic regeneration are considered.

Findings that UDCA improves liver function tests in patients with chronic hepatitis were demonstrated by Ichida[41] in 1961, and these findings were supported by other researchers[42]. Since then, it has been used for the treatment of many hepatobiliary diseases including cholesterol gallstones, primary biliary cirrhosis and primary sclerosing cholangitis[43]. It has also been used by Friman et al[1] to prevent acute rejection in recipients of liver transplants with good results. It is believed to act through numerous mechanisms. UDCA improves biliary secretion of bile acids, may improve bile flow, and it has immunomodulatory properties that may reduce immune-mediated liver damage[44,45]. UDCA also reduces the expression of class I antigens on hepatocytes in several cholestatic liver diseases[27,44]. It is also possible that UDCA reduces the antigenic stimulus for T cells that target hepatocytes with altered MHC class I antigen expression[44]. At the molecular level, it directly scavenges reactive oxygen species (ROS), increases the transcription of antioxidant defense genes and stabilization of the plasma membrane against cytolysis which reduces apoptosis[25,46,47]. *In vivo* and *in vitro* studies have shown that UDCA significantly stimulates hepatic regeneration[48,49]. Therefore, post-donation insufficiency in LLDs may be reduced by administration of UDCA to encourage hepatic regeneration. Among the indicators, for post-donation hepatic insufficiency include the persistent abnormalities of hepatic enzymes weeks after LDH.

Our study revealed that LLDs that received post-operative UDCA after living donor hepatectomy has better laboratory values of ALP, ALT, AST, INR, total bilirubin, and GGT at various times within the first 7 postoperative days of surgery compared to those that did not receive UDCA. This is consistent with the findings of Wang et al[30], who found the reduction of the laboratory values of ALT, AST, and GGT reduces among 112 recipients of OLT within 4 weeks of administration of UDCA. Kim et al[29] in South Korea also noticed a reduction of the ALT, AST, and GGT by 40.3%, 33.9%, and 23.0%, respectively, in patients with liver dysfunction after administration of UDCA. Parés et al[50] noticed similar reductions in serum ALP, GGT, and ALT in patients with primary biliary cirrhosis and primary sclerosing cholangitis after treatment with UDCA for 3 months. This was also supported by the findings of Van de Meeberg et al[51].

Conclusions

In this study, we observed that post-operative administration of UDCA to LLDs remarkably improved liver function and enzymes levels after LDH. However, this study was low powered due to limited number of participants and larger, multi-centric studies will be needed to investigate and validate the role of UDCA in post-hepatectomy patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contribution
Aloun A, Akbulut S, Gonultas F and Baskiran A collected data; Akbulut S and Colak C analyzed statistical; Akbulut S, Aloun A, Garzai IU and Hargura AS wrote the manuscript; Akbulut S and Yilmaz S projected the development and reviewed the final version.

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Informed Consent Statement
Informed consent was obtained from all the patients.

Data Availability Statement
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval
Ethics committee approval was obtained from the Malatya Clinical Research Ethics Committee.

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