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Efficacy and Safety of Steroid Therapy for Posttransplant Hyperbilirubinemia Caused by Early Allograft Dysfunction: A Randomized Controlled Trial

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Hyperbilirubinemia is a common event that occurs after liver transplantation. Hyperbilirubinemia is usually caused by early allograft dysfunction. Glucocorticoid is widely used for immunosuppression, but few studies have analyzed the effects of steroid therapy on posttransplantation hyperbilirubinemia. The aim of this study was to assess whether glucocorticoid was beneficial in treating hyperbilirubinemia caused by early allograft dysfunction.

Material/Methods: Patients with postoperative hyperbilirubinemia (those with conditions such as biliary complications and rejections were excluded) were randomly assigned, in a 2: 1 ratio, to the steroid and control groups. Patients in the steroid group were treated with glucocorticoid combined with ursodeoxycholic acid, whereas patients in the control group were only treated with ursodeoxycholic acid. The primary endpoint was decrease in bilirubin and the secondary endpoint was safety.

Results: From 1st June 2016 to 30th April 2018, 40 patients were enrolled into the steroid group, and 20 were enrolled into the control group. Donor, recipient, and operative data were similar between the 2 groups. The decrease in bilirubin levels in the steroid group was significantly greater than that in the control group on the first day after the intervention was finished (9.25±1.30 mg/dL *vs.* 3.11±1.45 mg/dL, p=0.005), and after 2 weeks (15.01±1.20 mg/dL *vs.* 8.88±1.98 mg/dL, p=0.007). The steroid group did not have a higher complication rate but it did have a shorter postoperative hospital stay than in the control group.

Conclusions: Low-dose steroid therapy was effective and safe for treating hyperbilirubinemia caused by early graft dysfunction, and it improved liver function.

MeSH Keywords: **Hyperbilirubinemia • Liver Transplantation • Methylprednisolone • Primary Graft Dysfunction**

Abbreviations: **TBIL** – total bilirubin; **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **γ-GGT** – gamma glutamyl transferase; **PA** – prealbumin; **ALP** – alkaline phosphatase; **INR** – international normalized ratio; **DCD** – donation after circulatory death; **UDCA** – ursodeoxycholic acid; **IRI** – ischemia-reperfusion injury; **MELD** – model for end-stage liver disease; **EAD** – early allograft dysfunction; **PNF** – primary non-function; **NAS** – non-anastomotic biliary strictures; **AS** – anastomotic stricture; **MRCP** – magnetic resonance cholangiopancreatography; **ERCP** – endoscopic retrograde cholangiopancreaticography; **FFP** – fresh frozen plasma; **COTRS** – China Organ Transplant Response System; **POD** – postoperative day; **ICU** – Intensive Care Unit; **MP** – methylprednisolone

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Background

Liver transplantation is the only available treatment for end-stage liver disease. However, liver graft dysfunction remains a challenge for patients and clinicians, especially given the trend that expanded-criteria donors and cardiac-death donors are increasingly being utilized [1,2]. Early allograft dysfunction (EAD) reflects poor graft function, manifested as increased transaminase levels, hyperbilirubinemia, and an increased international normalized ratio (INR), during the early period after transplantation [3]. Hyperbilirubinemia on postoperative day (POD)7 is one of the most frequently used diagnostic criteria for EAD [3–5]. Prolonged hyperbilirubinemia is not only indicative of poor graft function, but also impedes recovery of the graft liver, because high levels of bilirubin can be toxic to hepatocytes [6,7]. Postoperative hyperbilirubinemia is also a risk factor for graft loss in liver transplantation [8,9]. Although many studies have reported risk factors [3,10] and prevention strategies [11] for early graft dysfunction, few studies have investigated the treatment of hyperbilirubinemia caused by graft dysfunction [12].

Traditionally, corticosteroids have been widely used for immunosuppression, but with the development of immunosuppression protocols [13] and considering the adverse effects of steroids, more and more transplant centers have adopted steroid-free/avoidance protocols for liver transplantation. However, steroids play many roles in liver transplantation, such as reducing ischemia/reperfusion injury (IRI) [14,15], reducing inflammation, and increasing hepatic clearance of bilirubin [16,17].

Controversy exists regarding the effect of steroids on improving graft function in liver transplantation [18]. Katja et al. [19] reported that methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation. A randomized placebo-controlled trial demonstrated that steroid pretreatment of organ donors did not improve graft functions [20]. However, few studies have focused on steroids treatment during the postoperative period of liver transplantation. Therefore, the aim of this study was to assess whether steroids are beneficial in ameliorating hyperbilirubinemia caused by early graft dysfunction.

Material and Methods

This was a single-center randomized controlled trial (RCT) performed between 1 June 1 2016 and 30 April 2018. Informed consent was signed by all patients in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the hospital Ethics Committee.

Surgical procedures and immunosuppression

No organs from executed prisoners were used. All organs were from donation after death and were allocated by the China Organ Transplant Response System based upon the model for end-stage liver disease (MELD) score, medical urgency, and the time of patients on the waiting list. Donor organs were procured using a rapid-procurement technique: rapid cannulation of the aorta and portal vein for perfusion with cold University of Wisconsin solution, followed by flushing the bile duct *in situ* with hypertonic citrate adenine solution. The intraabdominal organs were removed en bloc and placed in UW solution at 4°C for storage. The liver transplantation was performed by experienced transplant surgeons using a bicaval or piggy-back technique.

Immunosuppression therapy was based on tacrolimus with basiliximab induction protocols (steroid-free protocols). Briefly, 20 mg of basiliximab was administered intraoperatively and on POD 4. Tacrolimus was administered from POD 4, and the target FK506 concentration was 8–12 μg/L for the first 3 months. In our center, steroids are used cautiously during the postoperative period and avoided when possible. Generally, steroids are only used in ABO-incompatible transplantations and rejections (confirmed by biopsies).

Study design

This study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. We referenced the most commonly accepted diagnostic criteria for EAD [3] and defined those recipients who presented with TBIL levels greater than 10 mg/dL after POD 7 as having hyperbilirubinemia. Therefore, from POD 7 to POD 14, recipients with serum TBIL levels greater than 10 mg/dL who presented without a decreasing trend were initially included the present study.

This study aimed to evaluate the efficacy of steroid therapy for postoperative functional hyperbilirubinemia caused by graft dysfunction, so we first evaluated the possible causes of hyperbilirubinemia. Postoperative liver function assays were monitored daily until relative normal and stable liver function was achieved. Abdominal ultrasonography of the liver graft was monitored regularly (at least once every other day in the first 2 weeks) for monitoring the parameters of portal vein, hepatic arterial, and bile duct. Suspicious bile duct anastomotic stricture (AS) would be confirmed by magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Biliary leakages were diagnosed by abnormal abdominal drainage or ERCP; graft weight less than 0.8% of recipient weight would be excluded from the study due to possibilities of small-for-size syndrome. Rejections were confirmed by biopsies. Generally, patients with confirmed biliary

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stricture or leakage, hepatic artery thrombosis, portal vein stenosis or thrombosis, small-for-size syndrome, rejections, and ABO-incompatible transplantations were excluded from enrolment and analysis. Patients administered steroids before the POD 7 or intraoperatively were secondarily excluded from the study. Patients with other conditions that made them unsuitable for steroid therapy were also excluded from the study, such as those with serious infections, hepatitis B virus (HBV)-positive donors, or ulcer bleeding.

The included patients were randomly assigned 2: 1 to the steroid or control group based on a computer-generated random number table produced with SAS 9.2 (SAS Institute, Inc., Cary, NC). After assignment, patients in the steroid group received 1 mg/kg of methylprednisolone (MP) intravenously once daily, with 250 mg of oral ursodeoxycholic acid (UDCA) 3 times daily for 5 days. Patients in the control group received 250 mg of oral UDCA 3 times daily for 5 days.

The sample size calculation was based on our historic data from treating postoperative hyperbilirubinemia. With to a ratio of 2: 1, an α error of 0.05 and β error of 0.2 (power of the test=1–β=80%), the intervention group required 40 patients, and the control group required 20 patients. The primary endpoint was the change in TBIL levels within the first 2 weeks after the intervention was finished. The change in alkaline phosphatase (ALP), γ-glutamyltransferase (γ-GGT), and prealbumin (PA) levels within the first 2 weeks after the intervention was finished and adverse events were recorded as secondary endpoints.

Postoperative liver function assays were monitored daily during the first week and at appropriate time-points. The main liver function parameters included TBIL, aspartate aminotransferase (AST), alanine transaminase (ALT), γ-GGT, ALP, and PA levels and the INR. Donors, intraoperative and postoperative data were prospectively collected by an independent investigator unaware of each patient's group allocation. The Donor Risk Index (DRI) was calculated for all donors according to the formula proposed by Feng [21].

Adverse effects such as peptic ulceration, infections, hyperglycemia, and delayed incision healing were recorded. Peptic ulceration was defined as postoperative gastrointestinal bleeding and was diagnosed by endoscopy. Infections were defined as positive cultures consistent with clinical evidence. Data from a follow-up period of at least 6 months was available for all patients.

Statistical analysis

Continuous parameters were reported as the mean and standard error of the mean (SEM) or as the median and range, as appropriate, in the text or tables, and as the mean ±SEM in figures. Statistical analysis was performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY). Continuous parameters were compared with the *t* test or a 2-tailed Mann-Whitney nonparametric test, while Fisher's exact test was used to compare categorical parameters. A p-value <0.05 was considered to indicate statistical significance.

Results

Patients

Of the 362 consecutive patients who underwent liver transplantation at the First Affiliated Hospital, Sun Yat-sen University between 1 June 1 2016 and 30 April 2018, 297 patients were excluded from the study. A total of 65 eligible patients were randomly assigned to the steroid group (n=43) or the control group (n=22). Of these 65 randomized patients, 5 were excluded because of a diagnosis of biliary complications or cessation of treatment after assignment (see the flowchart in Figure 1). Finally, 60 patients were compared – 40 in the steroid group and 20 in control group.

Clinical and laboratory data from the donors were comparable between the 2 groups, as summarized in Table 1. The recipients included in the analysis included 56 males and 4 females. The baseline patient characteristics were also similar between groups. The operative time, blood loss, and length of postoperative stay in the ICU were also comparable (see Table 2 for more details). In summary, baseline clinical characteristics were balanced between the 2 groups.

Efficacy

The median TBIL peaks were approximately 21–22 mg/dL in both groups. High TBIL levels were mainly caused by the relatively high DRI and long cold storage time. Although both groups finally achieved normal liver function, the steroid groups had a shorter hyperbilirubinemia period. As shown in Figure 2, after 5 days of therapy, the decrease in TBIL in the steroid group was greater than that in the control group (9.25±1.30 mg/dL *vs.* 3.11±1.45 mg/dL, p=0.005). There were also greater decreases of TBIL during the first week after treatment was completed (12.93±1.30 mg/dL *vs.* 6.97±1.96 mg/dL, p=0.012) and 2 weeks after treatment was completed (15.01±1.20 mg/dL *vs.* 8.88±1.98 mg/dL, p=0.007).

During the first and second weeks, the decrease in γ-GGT in the steroid group was greater, but the difference was not statistically significant (Figure 3). ALP, another marker of biliary injury, showed similar results; only on the first day after treatment was finished did ALP exhibit different trends (decrease

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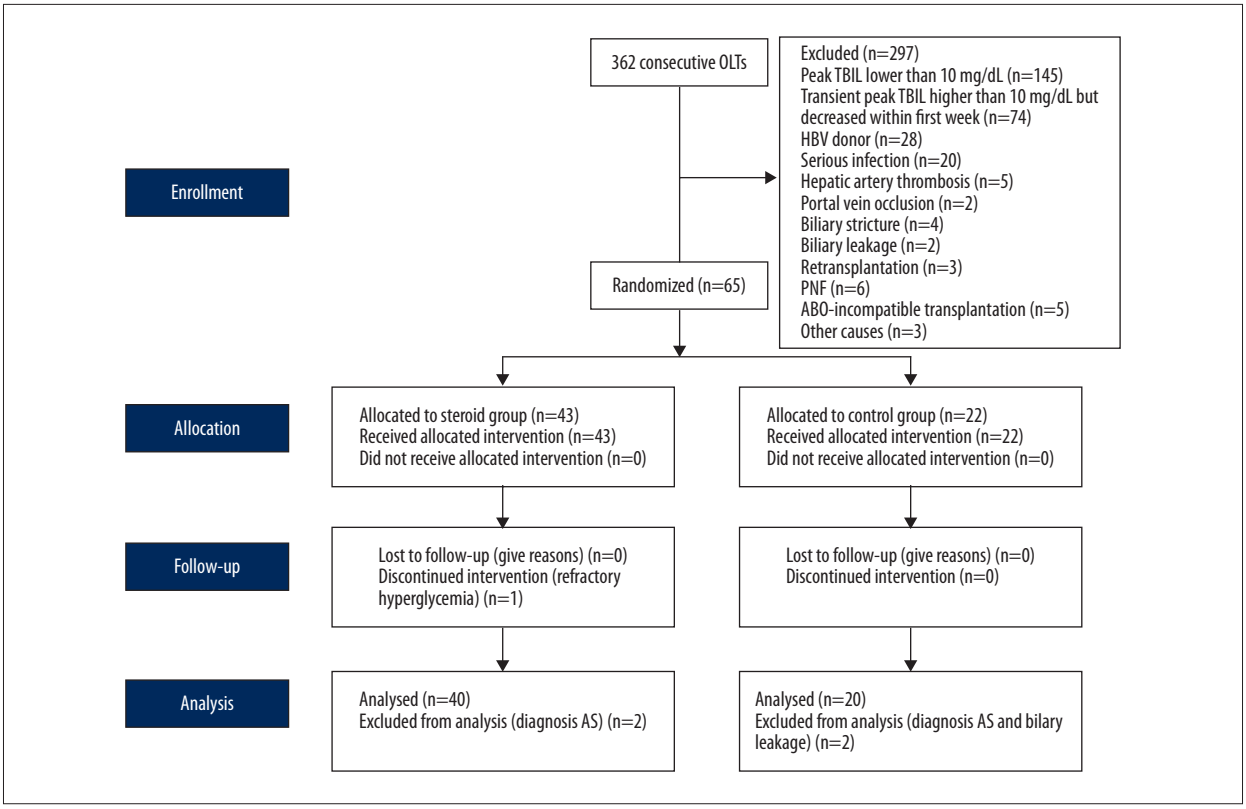

Figure 1. CONSORT flowchart illustrating study enrollment. One hundred and 45 patients were excluded for peak TBIL levels less than 10 mg/dL, 74 for transient peak TBIL levels greater than 10 mg/dL that decreased within the first week, 28 for having HBV donors, 20 for serious infections, 5 for hepatic artery thrombosis, 2 for portal vein occlusions, 4 for biliary strictures, 2 for biliary leakage, 3 for repeated transplantations, 6 for primary non-function (PNF), 5 for ABO-incompatible transplantations, and 3 for other causes. Two patients assigned to the control group were excluded because of subsequently diagnosis biliary leakage and anastomotic stricture (AS). After assignment, 2 patients who developed AS confirmed by endoscopic retrograde cholangiopancreatography (ERCP) on POD 26 and POD 29 were excluded from the steroid group. Treatment was stopped in another patient in the steroid group on the third day of the intervention due to refractory hyperglycemia, and this patient was also excluded from the analysis. OLT – orthotopic liver transplantation; TBIL – total bilirubin; AS – anastomotic stricture.

of 1 U/L *vs.* increase of 31.5 U/L, p=0.041). In addition, after 5 days of treatment, PA levels in the steroid group increased much faster than that in the control group (67.43±8.13 *vs.* 14.13 mg/dL, p=0.003). The postoperative hospital stay in the control group (median, 37.5 days; range, 17–54 days) was much longer than that in the steroid group (median, 28.5 days; range 12–111 days; p=0.043). No patients developed ischemic-type biliary lesions (follow-up range: 6–28 months) in either group (see Table 3 for more details).

Safety

One patient in the control group died on POD 50 due to graft failure. There were no postoperative deaths or graft failures in the steroid group. No patients in the steroid group developed gastrointestinal bleeding, and only 1 patient in the control group had gastrointestinal bleeding caused by gastric ulceration. Four patients in the control group and 3 in the steroid group experienced postoperative infections, but there was no significant difference between groups. Two patients in the steroid group and 1 in the control group had delayed wound healing, likely due to delayed recovery of liver function. An enrolled patient in the steroid group developed refractory hyperglycemia after use of MP and was excluded from the analysis due to cessation of treatment. Thus, low-dose steroid therapy did not increase the postoperative complication rate.

Discussion

Many cases of postoperative functional hyperbilirubinemia do not need intervention, and waiting for the liver graft to recover is sufficient by itself. However, in some cases, prolonged hyperbilirubinemia increases the length of postoperative hospital stay and costs, and these patients should be treated more actively to achieve quick recovery of graft function. Based on clinical practice, steroids have been shown to attenuate hyperbilirubinemia, but clinical studies of steroid therapy for

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Table 1. Donor characteristics.

Variable	Total	Control Group (n=20)	Steroid Group (n=40)	p
Donor gender (M/F)	44/16	13/7	31/9	0.302
Donor age (years)	42 [6–65]	42.5 [8–65]	42 [6–59]	0.832
Donor serum Na (mmol/L)	150 [131–187]	149 [133–180]	150 [131–187]	1.000
Donor TBIL (mg/dL)	1.2 [0.4–3.7]	1.1 [0.4–2.3]	1.2 [0.4–3.7]	0.465
Donor ALP (U/L)	79.5 [8–249]	75.5 [12–249]	80.5 [8–232]	0.644
Donor γ-GGT (U/L)	37 [10–300]	40 [14–300]	35 [10–183]	0.505
Donor AST (U/L)	69.5 [17–683]	64 [17–683]	78 [21–662]	0.736
Donor ALT (U/L)	47.5 [13–1067]	45.4 [13–1067]	49.5 [16–507]	0.748
DRI	1.54 [1.01–2.87]	1.47 [1.01–2.85]	1.56 [1.02–2.87]	0.900
DCD (Yes/No)	15/45	3/17	12/28	0.206
Cold ischemic time (h)	7.5±0.3	7.6±2.2	7.5±1.9	0.920
Hepatic Steatosis (Yes/No)	24/36	11/9	13/27	0.094

TBIL – total bilirubin; ALP – alkaline phosphatase; γ-GGT – gamma glutamyl transpeptidase; AST – aspartate transaminase; ALT – alanine transaminase; DRI – donor risk index; DCD – donation after cardiac death.

Table 2. Recipient and operation characteristics.

Variable	Total (n=60)	Control Group (n=20)	Steroid Group (n=40)	p
Recipient gender (M/F)	56/4	20/0	36/4	0.291
Recipient age (years)	49.27±1.45	49.6±2.5	48.9±1.8	0.778
MELD score	18 [7–44]	20.5 [7–44]	17 [7–41]	0.604
Diagnosis				0.944
Cirrhosis	17.00	6	11	
Cirrhosis+HCC	25.00	9	16	
Liver failure	15.00	4	11	
Other	3.00	1	2	
Operation time (min)	477.8±12.133	458±20.9	487.7±14.8	0.252
Blood loss (ml)	2200 [500–15000]	2250 [1000–6500]	2200 [500–15000]	0.544
FFP transfusion (unit)	9.75 [0–31]	9.2 [2–19.8]	11 [0–31]	0.53
RBC transfusion (unit)	6.95 [0–60.1]	8 [3–17.8]	6.45 [0–60.1]	0.47
Peak serum ALT (U/L)	826.5 [127–7539]	920 [127–7539]	826 [146–3792]	0.838
Peak serum AST (U/L)	2528 [138–14426]	3397 [215–9360]	2061 [138–14426]	0.196
Peak TBIL (mg/dL)	22.15 [8.5–43.4]	21.2 [12.5–37]	22.2 [8.5–43.4]	0.748

MELD – model for end-stage liver disease; HCC – hepatocellular carcinoma; FP – fresh frozen plasma; RBC – red blood cells; ALT – alanine transaminase; AST – aspartate transaminase; TBIL – total bilirubin.

posttransplant hyperbilirubinemia are lacking. To evaluate whether steroid therapy can ameliorate hyperbilirubinemia caused by graft dysfunction during the early period after liver transplantation, we designed a prospective RCT involving consecutive recipients. In this study, low-dose MP therapy (1 mg/kg) significantly accelerated the clearance of bilirubin in posttransplant patients with functional hyperbilirubinemia.

After 5 days of intervention, TBIL levels in the steroid group decreased more rapidly than those in the control group, reducing

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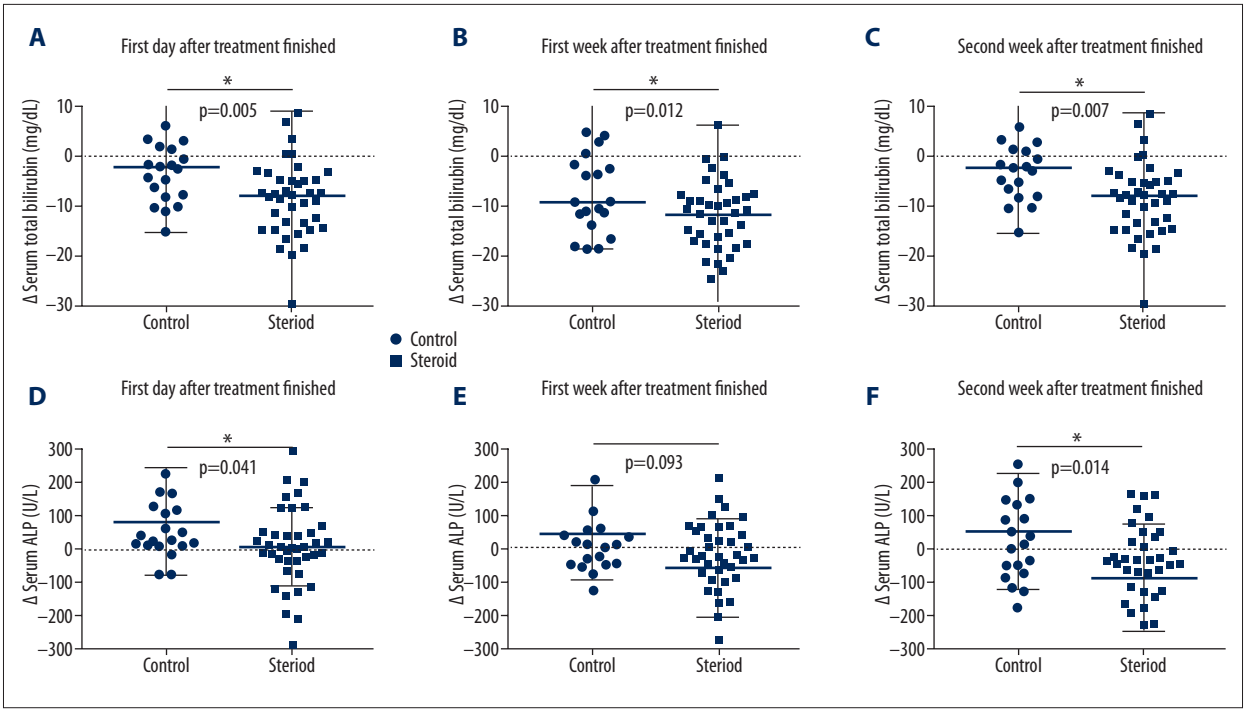

Figure 2. Change of total bilirubin and ALP in 2 groups. (**A–C**) Steroid group was much greater than control group at the reduction of bilirubin levels (p<0.005). (**D–F**) The ALP decreased levels in steroid group was significantly greater than control group on the first day (p=0.041) and second weeks (p=0.014) after treatment was finished.

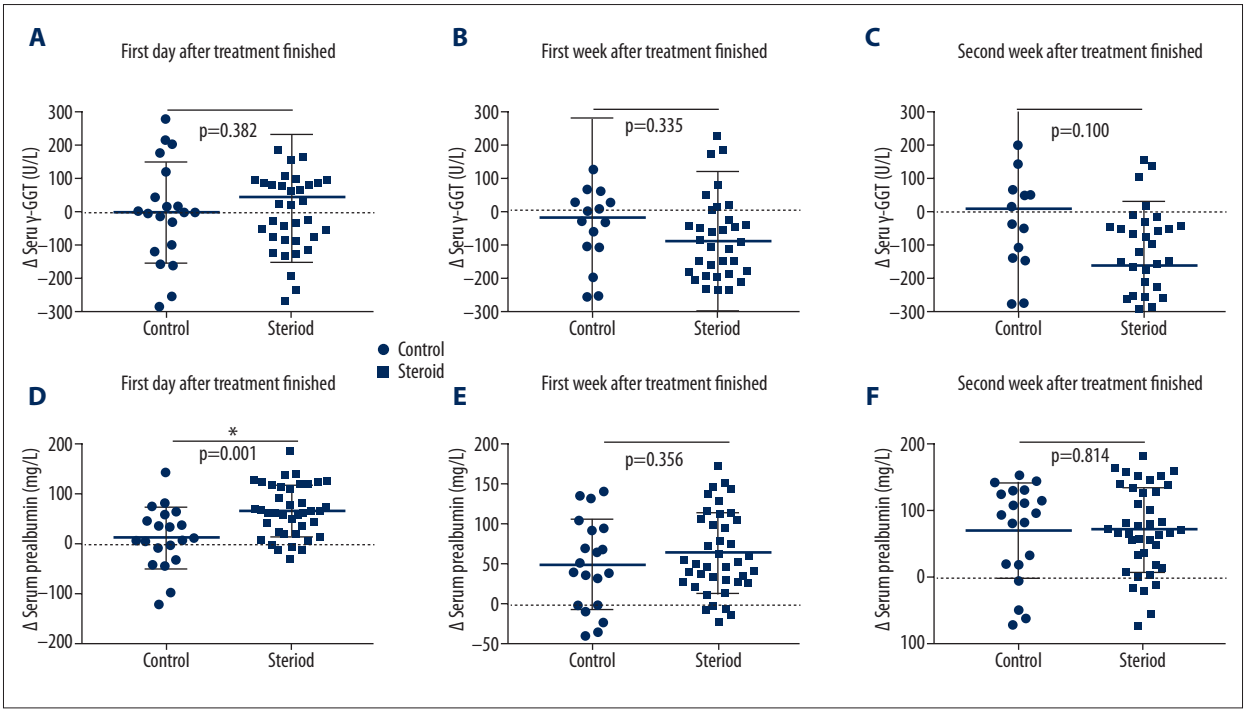

Figure 3. Change of γ-GGT and PA in 2 groups. (**A–C**) The changes in γ-GGT in 2 groups from the start of treatment to the first day, first week, and second week after treatment was finished. (**D–F**) The increase in PA levels in the steroid group was significantly greater at the first day after treatment was finished (p<0.005).

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Table 3. Efficacy and safety of steroid therapy.

Variable	Control group (n=20)	Steroid group (n=40)	p
Δ TBIL after 1st day (mg/dL)	–3.11±1.45	–9.25±1.30	0.005
Δ TBIL after 1st week (mg/dL)	–6.97±1.96	–12.93±1.30	0.012
Δ TBIL after 2nd week (mg/dL)	–8.88±1.98	–15.01±1.20	0.007
Δ ALP after 1st day (U/L)	31.5 [–80~682]	–1 [–95~297]	0.041
Δ ALP after 1st week (U/L)	10 [–128~430]	–32 [–380~209]	0.093
Δ ALP after 2nd week ((U/L)	27.5 [–177~612]	–47.5 [–441~167]	0.014
Δ γ-GGT after 1st day (U/L)	–2.13±33.82	41.2±30.3	0.382
Δ γ-GGT after 1st week (U/L)	–29 [–405–873]	–110.5 [–553~530]	0.335
Δ γ-GGT after 2nd week (U/L)	–41 [–528~1525]	–160 [–543~451]	0.100
Δ PA after 1st day (mg/dL)	14.13±13.72	67.43±8.13	0.001
Δ PA after 1st week (mg/dL)	50.10±12.73	63.6125±8.07	0.356
Δ PA after 2nd week (mg/dL)	96.5 [–74~156]	70 [–75~185]	0.814
Postoperative hospital stay (days)	37.5 [17~54]	28.5 [12–111]	0.043
Ischemic-type biliary lesion (Yes/No)	0/20	0/40	–
Delayed wound healing (Yes/No)	1/19	2/38	1.000
Gastrointestinal bleeding (Yes/No)	1/19	0/40	0.333
Infection (Yes/No)	4/16	3/37	0.208

TBIL – total bilirubin; ALP – alkaline phosphatase; γ-GGT – gamma glutamyl transpeptidase; PA – prealbumin; Δ means change from the treatment finished day to the day of monitored.

the duration of graft dysfunction. The markers of biliary injury ALP and γ-GGT also exhibited a rapid decrease after steroid treatment. The trend in TBIL levels showed that the steroid effect was more pronounced early after treatment. Another interesting finding of this study is that PA levels increased rapidly in the steroid treatment group. The abovementioned results suggest that steroid therapy may be helpful for recovering liver function and may decrease postoperative hospital stay.

Studies of the treatment of hyperbilirubinemia after liver transplantation are limited. Choe et al. [12] reported that therapeutic plasma exchange effectively removed plasma bilirubin and improved survival. Steroids are used to ameliorate hyperbilirubinemia in biliary atresia before and after transplantation [22,23], but studies are lacking to confirm its effect on hyperbilirubinemia after adult liver transplantation.

MP therapy studies have mainly focused on pretreatment of organ donors, but distinct results have been presented in several studies. Katja et al. [19] reported that MP treatment significantly ameliorated IRI during the posttransplant course. However, another RCT demonstrated that systemic administration of 1000 mg of MP to the deceased organ donor did not significantly ameliorate liver allograft dysfunction, mortality, or rejection within the first weeks after engraftment. Recent clinical trials that characterize the benefits or risks of corticosteroid therapy for deceased organ donors are limited [18].

Intraoperative MP can alter the immediate posttransplant course of liver transplantation either by attenuating reperfusion induced by inflammation or by addressing previously unrecognized adrenal insufficiency [24]. An RCT also reported that perioperative use of MP protects against renal and hepatic dysfunction [25]. Martens et al. [26] reported that warm ischemic injury in DCD donation could be attenuated with steroid administration prior to warm ischemia and during *ex vivo* lung perfusion. Taken together, the results of these studies demonstrate the potential benefits of steroid therapy in liver transplantation.

Although the safety and benefits of steroid-free protocols have been confirmed by many studies [13,27,28], the protective effect of steroids against IRI and their role in modulating biliary organic anion transporters should be considered. An important mechanism that induces impaired bilirubin metabolism is IRI, and livers from ECDs and DCD donors promote increased

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vulnerability to IRI. Glucocorticoids can upregulate the expression of both multidrug resistance-associated protein 2 (MRP2) and bile salt export pump (BSEP) in rat hepatocytes, which increases the clearance of bilirubin [29].

Hyperbilirubinemia is also a common complication in hepatic resection surgery with inflow control (the Pringle maneuver) because the remaining liver also undergoes warm IRI. Some studies [30,31] have reported that perioperative steroid administration improves liver function and postoperative outcomes after liver resection with the Pringle maneuver. Considering the protective role of steroids against IRI injury, administration of MP during the perioperative period of OLT may also help to improve liver graft function.

The present study has several limitations. First, this was a single-center study, and few eligible patients were included. Further multicenter randomized clinical trials should be performed to show the effectiveness of steroid therapy. Second, in this study, the dose of MP was relatively low, and the optimal dose and duration of treatment should be considered. Third, the best time-point for intervention is controversial and should be investigated in future studies.

Conclusions

Methylprednisolone is a safe and effective therapy to accelerate recovery from hyperbilirubinemia caused by EAD after liver transplantation.

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Conflict of interest

None.

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