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

Jie Yang*  
Lei Yang*  
Linwei Wu  
Qiang Zhao  
Maogen Chen

Corresponding Author: Xiaoshun He, e-mail: gdtrc@163.com
Source of support: This study was supported by the National Natural Science Foundation of China (grant no. 81373156, 81471583, and 81570587)

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 cholangiopancreatography; FFP – fresh frozen plasma; COTRS – China Organ Transplant Response System; POD – postoperative day; ICU – Intensive Care Unit; MP – methylprednisolone

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915128
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.
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 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 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 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
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. 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.

**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
Steroid attenuates posttransplant hyperbilirubinemia

Yang J. et al.: Steroid attenuates posttransplant hyperbilirubinemia © Med Sci Monit, 2019; 25: 1936-1944

Table 1. Donor characteristics.

| Variable                  | Total (n=60) | 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 [6–65]            | 0.832 |
| Donor serum Na (mmol/L)   | 150 [131–187]| 149 [133–180]        | 150 [131–187]        | 1.000 |
| Donor ALP (mg/dL)         | 11.2 [0.4–3.7]| 11.1 [0.4–2.3]      | 11.2 [0.4–3.7]       | 0.465 |
| Donor γ-GT (U/L)          | 79.5 [8–249] | 75.5 [12–249]        | 80.5 [8–232]         | 0.644 |
| Donor AST (U/L)           | 37 [10–300]  | 40 [14–300]          | 35 [10–183]          | 0.505 |
| Donor ALT (U/L)           | 69.5 [17–683]| 64 [17–683]          | 78 [21–662]          | 0.736 |
| Donor DRI                 | 12.5 [1.01–2.87]| 14.7 [1.01–2.83]   | 11.2 [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-GT – 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...

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)
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).
the duration of graft dysfunction. The markers of biliary injury ALP and \(\gamma\)-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 \textit{in 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

### Table 3. Efficacy and safety of steroid therapy.

| Variable                       | Control group (n=20) | Steroid group (n=40) | p  |
|-------------------------------|----------------------|----------------------|----|
| \(\Delta\) TBIL after 1st day (mg/dL) | -3.11±1.45           | -9.25±1.30           | 0.005 |
| \(\Delta\) TBIL after 1st week (mg/dL) | -6.97±1.96           | -12.93±1.30          | 0.012 |
| \(\Delta\) TBIL after 2nd week (mg/dL) | -8.88±1.98           | -15.01±1.20          | 0.007 |
| \(\Delta\) ALP after 1st day (U/L)     | 31.5 [-80–682]       | -1 [-95–297]         | 0.041 |
| \(\Delta\) ALP after 1st week (U/L)    | 10 [-128–430]        | -32 [-380–209]       | 0.093 |
| \(\Delta\) ALP after 2nd week (U/L)    | 27.5 [-177–612]      | -47.5 [-441–167]     | 0.014 |
| \(\Delta\) \(\gamma\)-GGT after 1st day (U/L) | -2.13±33.82       | 41.2±30.3            | 0.382 |
| \(\Delta\) \(\gamma\)-GGT after 1st week (U/L) | -29 [-405–873]    | -110.5 [-553–530]    | 0.335 |
| \(\Delta\) \(\gamma\)-GGT after 2nd week (U/L) | -41 [-528–1525]   | -160 [-543–451]      | 0.100 |
| \(\Delta\) PA after 1st day (mg/dL)    | 14.13±13.72          | 67.43±8.13           | 0.001 |
| \(\Delta\) PA after 1st week (mg/dL)   | 50.10±12.73          | 63.612±8.07          | 0.356 |
| \(\Delta\) PA after 2nd week (mg/dL)   | 96.5 [-74–150]       | 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; \(\gamma\)-GGT – gamma glutamyl transpeptidase; PA – prealbumin; \(\Delta\) means change from the treatment finished day to the day of monitored.
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.

References:

1. Kim WR, Smith JM, Skeans MA et al: OPTN/SRTR 2012 Annual Data Report: liver. Am J Transplant, 2014; 14(Suppl. 1): 69–96

2. Johnson RJ, Bradbury LL, Martin K, Neuberger J, UK Transplant Registry: Organ donation and transplantation in the UK – the last decade: A report from the UK national transplant registry. Transplantation, 2014; 97(Suppl. 1): 51–27

3. Olthoff KM, Kuijk L, Samstein B et al: Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl, 2016; 18(6): 943–49

4. Hudcova J, Scopa C, Rashid J et al: Effect of early allograft dysfunction on outcomes following liver transplantation. Clin Transplant, 2017; 31(2)

5. Croome KP, Wall W, Quan D et al: Evaluation of the updated definition of early allograft dysfunction in donation after brain death and donation after cardiac death liver allografts. Hepatobiliary Pancreat Dis Int, 2012; 11(4): 372–76

6. Perez MJ, Briz O: Bile-acid-induced cell injury and protection. World J Gastroenterol, 2009; 15(14): 1677–89

7. Sokol RJ, Devereaux M, Khandwala R, O’Brien K: Evidence for involvement of oxygen free radicals in bile acid toxicity to isolated rat hepatocytes. Hepatology, 1993; 17(5): 869–81

8. Lee DD, Singh A, Burns JM et al: Early allograft dysfunction in liver transplantation with donation after cardiac death donors results in inferior survival. Liver Transpl, 2014; 20(12): 1447–53

9. Marubashi S, Dono K, Nagano H et al: Postoperative hyperbilirubinemia and graft outcome in living donor liver transplantation. Liver Transpl, 2007; 13(11): 1538–44

10. Hoyer DP, Paul A, Gallinat A et al: Donor information-based prediction of early allograft dysfunction and outcome in liver transplantation. Liver Int, 2015; 35(1): 156–63

11. Martini S, Tandol F, Terzi di Bergamo L et al: Negativization of viremia prior to liver transplant reduces early allograft dysfunction in hepatitis C-positive recipients. Liver Transpl, 2017; 23(7): 915–24

12. Choe W, Kwon SW, Kim SS et al: Effects of therapeutic plasma exchange on early allograft dysfunction after liver transplantation. J Clin Apher, 2017; 32(3): 147–53

13. Uldao L, Xiol X, Figueras J et al: Immunosuppression without steroids in liver transplantation is safe and reduces infection and metabolic complications: Results from a prospective multicenter randomized study. J Hepatol, 2006; 44(4): 710–16

14. Aldrighetti L, Pultano C, Arru M et al: Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: A prospective randomized study. Liver Transpl, 2006; 12(6): 941–49

15. Saidi RF, Chang J, Verb S et al: The effect of methylprednisolone on warm ischemia-reperfusion injury in the liver. Am J Surg, 2007; 193(3): 345–47; discussion 347–48

16. Okuhbo K, Okuda K, lida S: Effects of corticosteroids on bilirubin metabolism in patients with Gilbert’s syndrome. Hepatology, 1981; 1(2): 168–72

17. Aach RD: Corticosteroids and bilirubin metabolism. Gastroenterology, 1969; 56(2): 363–68

18. D’Aragon F, Bellely-Cote E, Agarwal A et al: Effect of corticosteroid administration on neurologically deceased organ donors and transplant recipients: A systematic review and meta-analysis. BMI Open, 2017; 7(6): e014436

19. Kotsch K, Ulrich F, Reutzel-Selke A et al: Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: A prospective randomized controlled trial. Ann Surg, 2008; 248(6): 1042–50

20. Amatschek S, Willflingseder J, Pones M et al: The effect of steroid pretreatment of deceased organ donors on liver allograft function: A blinded randomized placebo-controlled trial. J Hepatol, 2012; 56(6): 1305–09

21. Feng S, Goodrich NP, Bragg-Gresham JL et al: Characteristics associated with liver graft failure: The concept of a donor risk index. Am J Transplant, 2006; 6(4): 783–90

22. Davenport M, Parsons C, Tizzard S, Hadzic N: Steroids in biliary atresia: Single surgeon, single centre, prospective study. J Hepatol, 2013; 59(5): 1054–58

23. Pakarinen MP, Johansen LS, Svensson JF et al: Outcomes of biliary atresia in the Nordic countries – a multicenter study of 158 patients during 2005–2016. J Pediatr Surg, 2018; 53(8): 1509–15

24. Daker C, Daminhorn EH, Patel S et al: Beneficial effect of intra-operative methylprednisolone on immediate post liver transplant intensive care course. Ann Transplant, 2015; 20: 76–84

25. Turner S, Dhamarajah S, Bosomworth M, Bellamy MC, Leeds Liver Transplant Group: Effect of perioperative steroids on renal function after liver transplantation. Anaesthesia, 2006; 61(3): 253–59

26. Martens A, Boada M, Vanaudenaerde BM et al: Steroids can reduce warm ischemic reperfusion injury in a porcine donation after circulatory death model with ex vivo lung perfusion evaluation. Transpl Int, 2016; 29(11): 1237–46

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.

Acknowledgements

Thanks for Shanzhou Huang and Zhebin Zhu for critical advice.

Conflict of interest

None.

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)
27. Wei Q, Xu X, Wang C et al: Efficacy and safety of a steroid-free immunosuppressive regimen after liver transplantation for hepatocellular carcinoma. Gut Liver, 2016; 10(4): 604–10
28. Segev DL, Sozio SM, Shin EJ et al: Steroid avoidance in liver transplantation: Meta-analysis and meta-regression of randomized trials. Liver Transpl, 2008; 14(4): 512–25
29. Fardel O, Payen L, Courtois A et al: Regulation of biliary drug efflux pump expression by hormones and xenobiotics. Toxicology, 2001; 167(1): 37–46
30. Jeon J, Watkins A, Wagener G et al: Complex hepatectomy under total vascular exclusion of the liver: Impact of ischemic preconditioning on clinical outcomes. World J Surg, 2013; 37(4): 838–46
31. Abua-Mara M, Gurusamy KS, Glantzounis G et al: Pharmacological interventions for ischaemia reperfusion injury in liver resection surgery performed under vascular control. Cochrane Database Syst Rev, 2009; (4): CD008154