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# Intraoperative Low-Dose Dexmedetomidine Administration Associated with Reduced Hepatic Ischemia-Reperfusion Injury in Pediatric Deceased Liver Transplantation: A Retrospective Cohort Study

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Statistical Analysis C  
Data Interpretation D  
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**Background:** Dexmedetomidine (DEX) attenuates hepatic ischemia-reperfusion injury (HIRI) in adult liver transplantation (LT), but its effects on postoperative liver graft function in pediatric LT remain unclear. We sought to investigate whether intraoperative DEX administration was associated with improved liver graft function in pediatric LT recipients. It was hypothesized that DEX administration was associated with reduced HIRI and improved liver graft function.


**Material/Methods:** From November 2015 to May 2020, 54 deceased pediatric LT recipients were categorized into a control group and a DEX group. Intraoperatively, the DEX group received an additional infusion of DEX at 0.4 µg/kg/h from incision to the end of the operation in comparison with the control group. Preoperative, intraoperative, and postoperative data were reviewed. Postoperative liver enzyme levels and HIRI severity were assessed and compared. Independent risk factors for HIRI were determined by multivariate logistic regression analysis using a stepwise forward conditional method.

**Results:** We enrolled 28 and 26 patients in the DEX and control groups, respectively. Patients in the DEX group exhibited a reduced incidence of moderate-to-severe HIRI (88.5% vs 60.7%,  $P=0.020$ ) and decreased level of serum alanine aminotransferase (median [interquartile range]: 407 [230-826] vs 714 [527-1492] IU/L,  $P=0.048$ ) compared with the controls. Binary logistic analysis revealed that longer cold ischemia time (odds ratio [OR]=1.006; 95% confidence interval [CI]=1.000-1.013;  $P=0.044$ ) and intraoperative DEX use (OR=0.198; 95% CI=0.045-0.878;  $P=0.033$ ) were independent predictors for moderate-to-severe HIRI.

**Conclusions:** Intraoperative low-dose DEX administration was associated with a lower incidence of moderate-to-severe HIRI in pediatric deceased LT. However, further studies are needed to confirm our results and elucidate the underlying mechanisms.

**Keywords:** Dexmedetomidine • Liver Transplantation • Pediatrics • Reperfusion Injury

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## Background

Hepatic ischemia-reperfusion injury (HIRI), an inevitable event during liver transplantation (LT), may further trigger early allograft dysfunction or even primary nonfunction [1,2]. Previous studies have found that attenuating HIRI could improve post-LT liver graft function [3,4]. Although numerous strategies to mitigate HIRI have been assessed in animal models [5], current therapeutic opinions are still limited in clinical practice.

Dexmedetomidine (DEX) is a selective alpha-2-adrenoceptor agonist with sedative, analgesic, sympatholytic, and anti-inflammatory properties, widely introduced to pediatric practice [6]. Previous animal experiments have demonstrated that DEX can protect against HIRI in conditions of partial hepatectomy [7,8]. A recent observational study revealed that DEX alleviates HIRI in adult living-donor LT [9]. However, few studies have focused on the association between intraoperative DEX administration and the severity of HIRI in the setting of pediatric LT. Therefore, we hypothesized that intraoperative DEX use is associated with better liver graft function in pediatric deceased LT.

In this retrospective cohort study, we sought to explore the effects of intraoperative low-dose DEX administration on the severity of HIRI and postoperative liver graft function in pediatric deceased LT.

## Material and Methods

### Study Subjects

This retrospective cohort study was performed at Beijing Friendship Hospital, which is one of the 3 largest pediatric LT centers in China. We included all pediatric patients of ages 16 years or younger who were consecutively scheduled to undergo deceased LT under anesthesia care by Dr. Liang Zhang from November 2015 to May 2020. Patients who underwent retransplantation, received anesthesia care from other anesthesiologists, or did not have complete data were excluded. The study protocol was conducted in accordance with the Declaration of Helsinki guidelines and its later amendments. Ethics approval (2020-P2-043-02) was provided by the Institutional Review Board of Beijing Friendship Hospital. Given the retrospective nature of this study, the requirement for patient consent was waived, and Dr. Liang Zhang was not blinded to the study protocol; however, data collectors were blinded, and whether a specific patient had been given DEX or not was also blinded to Dr. Liang Zhang.

### Anesthesia Protocol

All the patients receiving the basic anesthesia protocol from our institution were described previously [10]. However, it was

not until 2017 that the anesthetist-in-charge began to more liberally choose to administer DEX as an anesthetic adjuvant. As a result, patients were divided into one of the following 2 groups: the control group (standardized anesthesia protocol without intraoperative DEX) or the DEX group (standardized anesthesia protocol with intraoperative DEX administration). In the DEX group, DEX was administered by continuous infusion at 0.4 µg/kg/h without a loading dose from incision to the end of the operation to exert anti-inflammatory and sympatholytic effects.

### Surgical Technique

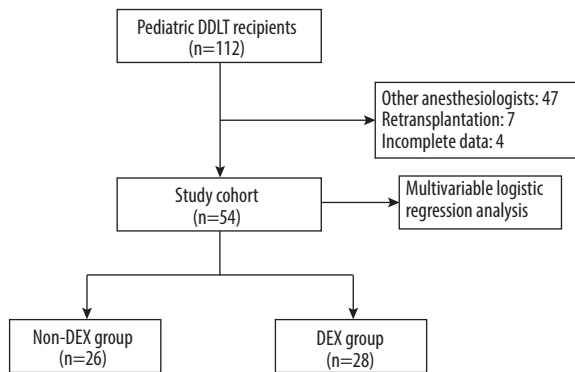
For surgical procedures, a whole liver graft was anastomosed using the conventional technique, whereas a split or reduced-size liver graft was anastomosed following the modified piggy-back technique. During the anhepatic phase, the inferior vena cava was completely clamped in all cases without venovenous bypass or temporary portocaval shunt.

### Outcomes Measures

The primary endpoints were the peak alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic dehydrogenase (LDH) levels during the first week after LT and the severity of HIRI, which was assessed by Rahman's criteria [11] based on the peak AST level within 24 h after LT (Mild HIRI, AST <1000 U/L; Moderate HIRI, AST 1000-5000 U/L; and Severe HIRI, AST >5000 U/L). Secondary outcomes included the peak blood urea nitrogen (BUN) and serum creatinine (Cr) levels during the first week after LT, the incidence of the severe postreperfusion syndrome (PRS) and acute kidney injury (AKI), and the durations of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay. The extent of severe PRS and AKI were evaluated using the Peking criteria [10] and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [12].

### Statistical Analysis

Continuous variables are presented as the mean±standard deviation or median (interquartile range) and were compared using the *t* test or Mann-Whitney *U* test. The categorical variables are described as frequencies and percentages and were compared using the chi-square and/or Fisher's exact test. To identify the independent predictors for moderate-to-severe HIRI, potentially significant variables with *P* values <0.10 in the univariate analysis were further analyzed by stepwise binary logistic regression (forward likelihood ratio). Statistical analyses were performed using SPSS software Version 22.0 (SPSS, Inc., Chicago, IL, USA). *P* values <0.05 were considered to be statistically significant.



**Figure 1.** Patient and analysis flowchart. DEX – dexmedetomidine; DDLT – deceased donor liver transplantation. Adobe Photoshop CS6 (Adobe Systems Software Ireland, Ltd.).

## Results

### Baseline Characteristics of the Study Population

A total of 54 patients who underwent pediatric deceased LT met the inclusion criteria (Figure 1). The patients were divided into 2 groups: the control group (n=26) and the DEX group (n=28). The median age of the entire cohort was 3.0 years (37.0% females), with biliary atresia (61.1%) as the most common indication. The basic characteristics of the 2 groups are listed in Table 1. No statistically significant differences were noted between the control and DEX groups with regard to age, sex, height, weight, graft type, graft weight, graft-to-recipient weight ratio, cold ischemia time (CIT), and the indication for LT (all  $P>0.05$ ). However, the warm ischemia time (WIT) duration was significantly longer in the control group than in the DEX group ( $52\pm 13$  vs  $43\pm 10$  min,  $P=0.004$ ).

### Liver Graft Function Assessment and Other Clinical Outcomes

Postoperative peak serum ALT levels during the first week decreased significantly in the DEX group compared with the control group (median: 407 vs 714 IU/L,  $P=0.048$ ). The peak AST and LDH levels in the DEX group were also reduced compared with the control group, but the differences were not statistically significant (median: 1378 vs 1735 IU/L,  $P=0.107$ ; and median: 1677 vs 2350 IU/L,  $P=0.106$ , respectively). However, cohort analysis revealed that moderate-to-severe HIRI occurred less frequently in the DEX group than in controls (60.7% vs 88.5%,  $P=0.020$ ) (Figure 2). The postoperative peak BUN and Cr levels within 7 days after LT were comparable between the DEX and control groups (median: 6.13 vs 5.33 mmol/L,  $P=0.082$ ; and median: 35.6 vs 37.0  $\mu\text{mol/L}$ ,  $P=0.177$ , respectively).

Furthermore, no statistically significant differences were identified between the 2 groups with respect to the occurrence of severe PRS and AKI, epinephrine requirement for severe PRS, and durations of mechanical ventilation, ICU stay, and hospital stay (all  $P>0.05$ ) (Table 2).

### Association Between Dexmedetomidine Use and Moderate-to-Severe HIRI

Univariate analyses revealed the potential risk factors associated with moderate-to-severe HIRI, including height (odds ratio [OR]=0.978; 95% confidence interval [CI]=0.952-1.004;  $P=0.097$ ), Child score (OR=1.380; 95% CI=1.001-1.901;  $P=0.049$ ), CIT (OR=1.006; 95% CI=1.000-1.013;  $P=0.035$ ), and intraoperative DEX use (OR=0.202; 95% CI=0.049-0.836;  $P=0.027$ ). Multivariate logistic analysis revealed that intraoperative DEX use (OR=0.198; 95% CI=0.045-0.878;  $P=0.033$ ) and CIT (OR=1.006; 95% CI=1.000-1.013;  $P=0.044$ ) were independent predictors of moderate-to-severe HIRI (Table 3). The multiple regression coefficient of determination was 0.255.

## Discussion

This retrospective study demonstrates that intraoperative use of DEX was significantly associated with improved post-LT liver graft function following pediatric deceased LT. Patients who received low-dose DEX treatment exhibit significantly decreased postoperative peak levels of serum ALT and a reduced incidence of moderate-to-severe HIRI. To the best of our knowledge, this study is the first to assess the hepatoprotective effect of DEX in pediatric deceased LT. Finally, our results confirm that DEX exerts protective effects against HIRI in pediatric deceased LT recipients.

As one of the critical challenges during LT, HIRI is strongly associated with increased morbidity and mortality in the post-LT period [5,13]. Generally, the severity of HIRI during LT is assessed by postoperative peak serum transaminase levels [11,14,15]. Despite being the subject of intense study and development efforts over the past 2 decades, current effective therapeutic opinions for HIRI in LT are limited in clinical practice. Currently, pharmacological agents to attenuate HIRI in the setting of clinical LT include N-acetylcysteine [16,17], nitric oxide [18], rifaximin [19], L-alanyl-glutamine [20], prostaglandin E1 [21], and omega-3 fatty acids [22]. However, none of these agents have been shown to reduce HIRI-associated morbidity and mortality in clinical studies.

DEX, an alpha-2-adrenergic agonist with sedative, anxiolytic, sympatholytic, and analgesic properties, has been increasingly used in both pediatric clinical trials and routine clinical practice. Animal experiments and clinical studies have revealed that DEX

**Table 1.** Patients' characteristics.

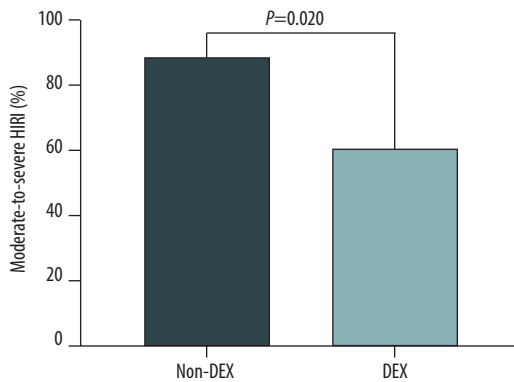
	Entire cohort (n=54)	Control group (n=26)	DEX group (n=28)	P value
Age (y), median (IQR)	3.0 (0.8-5.8)	1.5 (0.8-5.9)	3.5 (1.4-5.8)	0.315
Female gender, n (%)	20 (37.0)	12 (46.2)	8 (28.6)	0.181
Height (cm), median (IQR)	91 (68-110)	79 (67-107)	96 (72-110)	0.416
Weight (kg), median (IQR)	13.8 (7.4-17.6)	10.2 (7.0-18.3)	14.8 (7.9-17.5)	0.416
Child score, median (IQR)	7 (6-10)	8 (6-10)	7 (5-9)	0.293
PELD score, median (IQR)	2 (-5-15)	8 (-3-15)	-2 (-9-17)	0.328
Indication for LT, n (%)				
Biliary atresia	33 (61.1)	17 (65.4)	16 (57.1)	0.535
UCDs	6 (11.1)	3 (11.5)	3 (10.7)	1.000
PFIC	4 (7.4)	2 (7.7)	2 (7.1)	1.000
Hepatoblastoma	2 (3.7)	1 (3.8)	1 (3.6)	1.000
Fulminant hepatic failure	2 (3.7)	1 (3.8)	1 (3.6)	1.000
Methylmalonic acidemia	2 (3.7)	0 (0)	2 (7.1)	0.491
Caroli disease	2 (3.7)	0 (0)	2 (7.1)	0.491
Wilson disease	1 (1.9)	1 (3.8)	0 (0)	0.481
Crigler-Najjar syndrome	1 (1.9)	0 (0)	1 (3.6)	1.000
Congenital hepatic fibrosis	1 (1.9)	1 (3.8)	0 (0)	0.481
Partial liver graft, n (%)	12 (22.2)	4 (15.4)	8 (28.6)	0.244
Graft weight (g), median (IQR)	375 (300-501)	403 (296-500)	364 (309-506)	0.815
GRWR (%), mean±SD	3.31±1.09	3.46±1.10	3.18±1.08	0.346
CIT (min), mean±SD	597±115	605±106	590±125	0.631
WIT (min), mean±SD	47±12	52±13	43±10	0.004

CIT – cold ischemia time; DEX – dexmedetomidine; GRWR – graft-to-recipient weight ratio; IQR – interquartile range; PELD – Pediatric End-stage Liver Disease; PFIC – progressive familial intrahepatic cholestasis; SD – standard deviation; UCD – urea cycle disorder; WIT – warm ischemia time.

has protective effects against heart [23], lung [24], brain [25], and kidney [26] ischemia-reperfusion injuries. In accordance with our present findings, previous studies demonstrated the hepatoprotective effect of DEX in hepatectomy and LT. In the setting of hepatectomy, Zhang et al [27] and Wang et al [28] indicated that pre-pump administration of DEX exerted a protective effect against HIRI in their randomized controlled trials, while Fayed and colleagues [9] reported that an intraoperative infusion of DEX at 0.8 µg/kg/h exerted hepatoprotective effects against HIRI in adult living-donor LT.

The identification of independent predictors associated with moderate-to-severe HIRI could provide insight into

postoperative liver graft function recovery. Similar to the present results, CIT was typically the most frequent risk factor for developing delayed graft function following deceased LT [29-31]. The possible reason for the association of CIT and postoperative liver graft function recovery involved cell damage in the cold ischemic phase of HIRI [5]. It has been previously reported that the pathophysiology of HIRI in this ischemic phase is due to oxidative stress damage, lipid metabolism disorders, inflammation response, and intracellular calcium overload [5,13]. Therefore, normothermic machine perfusion focusing on the shortening of CIT in clinical LT had the potential to emerge as one of the most promising approaches to alleviate HIRI in LT using marginal liver grafts [32].



**Figure 2.** Intraoperative use of dexmedetomidine is associated with a reduced incidence of moderate-to-severe hepatic ischemia-reperfusion injury in pediatric deceased liver transplantation. DEX – dexmedetomidine; HIRI – hepatic ischemia-reperfusion injury. GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA).

The exact mechanism of the protective effects of DEX against HIRI following LT is still unclear. In animal models of partial hepatectomy and LT, both Wang et al [8] and Lv et al [7] indicated that DEX treatment ameliorated HIRI via suppression of the TLR4/NF- $\kappa$ B pathway. In contrast, Chen and colleagues [33] demonstrated that the acceleration of HIRI in NLRC5 knockout mice could be inhibited by DEX pretreatment through NF- $\kappa$ B suppression, Nrf2 promotion, and Caspase-3 suppression. In clinical studies, both Wang et al [27] and Zhang et al [28] attributed the liver and intestinal protection of DEX after hepatectomy to its anti-inflammatory effects. In contrast, Fayed et al [9] emphasized that DEX exerted protective effects against HIRI during adult living-donor LT by suppressing ICAM-1. Given that inflammation is a key process during the reperfusion phase, the hepatoprotective effects of DEX are possibly related to its anti-inflammatory properties.

Evidence regarding the safety of the off-label use of DEX in children [6] and LT recipients [34,35] remains limited. Potential adverse effects include bradycardia, hypertension, hypotension, elevated blood glucose, decreased serum potassium concentration, interaction with tacrolimus, and drug accumulation [6,35-37]. Although there were concerns of potential risks

**Table 2.** Comparison of study outcomes between the control group and the DEX group.

	Entire cohort (n=54)	Control group (n=26)	DEX group (n=28)	P value
<b>Primary outcomes</b>				
Peak ALT (IU/L), median (IQR)	670 (265-1018)	714 (527-1492)	407 (230-826)	0.048
Peak AST (IU/L), median (IQR)	1503 (905-2936)	1735 (1255-3068)	1378 (559-2947)	0.107
Peak LDH (IU/L), median (IQR)	1951 (1132-3284)	2350 (1652-3078)	1677 (757-3506)	0.106
Moderate-to-Severe HIRI, n (%)	40 (74.1)	23 (88.5)	17 (60.7)	0.020
<b>Other outcomes</b>				
Severe PRS, n (%)	8 (14.8)	3 (11.5)	5 (17.9)	0.706
AD dosage for PRS ( $\mu$ g/kg), median (IQR)	0.22 (0.11-0.42)	0.24 (0.12-0.44)	0.21 (0.10-0.40)	0.897
Peak BUN (mmol/L), median (IQR)	5.76 (4.38-8.61)	5.33 (4.26-6.49)	6.13 (4.61-9.93)	0.082
Peak Cr ( $\mu$ mol/L), median (IQR)	36.0 (32.2-46.2)	37.0 (34.0-50.1)	35.6 (28.6-42.3)	0.177
AKI, n (%)	6 (11.1)	2 (7.7)	4 (14.3)	0.670
Ventilation time (hours), median (IQR)	2.5 (1.7-3.6)	2.1 (1.5-2.8)	3.0 (2.0-4.5)	0.064
ICU stay (days), mean $\pm$ SD	3.6 $\pm$ 1.4	3.6 $\pm$ 1.5	3.5 $\pm$ 1.3	0.871
Hospital stay (days), median (IQR)	21.0 (15.0-30.0)	21.5 (17.8-33.0)	19.0 (14.0-28.0)	0.135

AD – adrenaline; AKI – acute kidney injury; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BUN – blood urea nitrogen; Cr – creatinine; DEX – dexmedetomidine; HIRI – hepatic ischemia-reperfusion injury; ICU – Intensive Care Unit; IQR – interquartile range; LDH – lactic dehydrogenase; PRS – post-reperfusion syndrome; SD – standard deviation.



**Table 3.** Risk factors of moderate-to-severe HIRI in pediatric deceased donor liver transplantation.

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.827	0.659-1.037	0.100			
Gender (Female)	2.710	0.654-11.237	0.169			
Height	0.978	0.952-1.004	0.097			
Weight	0.937	0.856-1.026	0.159			
Child score	1.380	1.001-1.901	0.049			
PELD score	1.028	0.978-1.082	0.280			
Graft type (partial)	2.000	0.381-10.511	0.413			
Graft weight	0.997	0.993-1.001	0.158			
GRWR	1.035	0.974-1.100	0.271			
CIT	1.006	1.000-1.013	0.035	1.006	1.000-1.013	0.044
WIT	1.051	0.989-1.117	0.106			
Intraoperative DEX use	0.202	0.049-0.836	0.027	0.198	0.045-0.878	0.033

CI – confidence interval; CIT – cold ischemia time; DEX – dexmedetomidine; GRWR – graft-to-recipient weight ratio; HIRI – hepatic ischemia-reperfusion injury; OR – odds ratio; PELD – Pediatric End-stage Liver Disease; WIT – warm ischemia time.

of delayed awakening and extubation due to the accumulation of DEX in patients with impaired liver function, no studies [9,38], including ours, have demonstrated any increase in the durations of mechanical ventilation, ICU stay, and hospital stay. This could be because the infusion rate and total dose of DEX in our study were lower than those of previous reports [9,27,28,35,38,39]. We used a dose of 0.4 µg/kg/h for approximately 8 h without a loading dose, and DEX infusion was well tolerated by the patients, without noticeable adverse effects attributable to the infusion. Whether a higher dose of DEX infusion could exert a better hepatoprotective effect or delay the awakening and extubation following pediatric LT remains a focus of future research.

The present study has several limitations. First, this was a retrospective study with a relatively small sample size; thus, a potential inherent difference in WIT existed between the 2 groups, making the study prone to possible selection bias. Second, the generalizability of the results is subject to the fact that all the participants were from a single institution and were treated by the same surgical and anesthesia team. Third, we did not

note any serious adverse drug reactions due to DEX administration. Nevertheless, further studies are needed to assess the potential adverse effects of DEX in the pediatric population. Finally, the dose-dependent effects of DEX on HIRI and the underlying mechanisms should be elucidated in future studies.

## Conclusions

Our study revealed 2 independent predictors of moderate-to-severe HIRI in pediatric deceased LT: the duration of CIT and intraoperative use of DEX. Moreover, intraoperative low-dose DEX administration exerted a protective effect against HIRI. Further studies are needed to further elucidate the underlying mechanisms.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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