The Effect and Safety of Prostaglandin Administration in Pediatric Liver Transplantation

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Background. Prostaglandins are often administered after liver transplantation (LT) to diminish ischemia-reperfusion injury (IRI), to favor liver recovery and to prevent vascular thrombosis. Possible beneficial effects in adult liver recipients are controversial, but the single existing pediatric small case series shows no significant impact of prostaglandin administration after LT. The purpose of this study was to analyze the effect of the prostaglandin dinoprostone in pediatric liver recipients.

Methods. A retrospective analysis of 41 children (<16 years) who underwent LT between March 2008 and December 2013 was performed. Dinoprostone was administered at a rate from 0.1 to a maximum of 0.6 μg/kg per hour immediately after LT and for a maximum of 5 days. Effect of dinoprostone on post-LT IRI and hepatic function up to 60 postoperative days and number of hypotensive episodes were analyzed.

Results. The median cumulative dose of dinoprostone was 28 μg/kg (interquartile range, 23.2). Dinoprostone had no significant effect on post-LT liver function tests and factor V levels at any of the administered dosages. There was no significant association between the total quantity of vasopressor given and the number of hypotensive episodes observed in 8 patients. One patient showed a short-lasting hypotension, possibly related to the administration of dinoprostone.

Conclusions. This study did not show, at any dosage between 0.1 and 0.6 μg/kg per hour, any differences in beneficial or harmful effects of high- or low-dose dinoprostone administered immediately after pediatric LT on markers of IRI, hepatic function, or hypotension.

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PGE further induce vasodilatation and inhibit thrombocyte aggregation, which theoretically might improve hepatic perfusion and portal circulation, and thus decrease the risk of vascular thrombosis: this is the rationale for the use of PGE in LT. Studies in adult patients have examined the benefit of PGE administration in the immediate postoperative period with the aim of improving the recovery of liver function, decreasing primary nonfunction, and avoiding vascular thrombosis.

These studies resulted in diverging conclusions. There is only 1 small pediatric study that shows no effect on ischemia-reperfusion or on vascular complications.

Our center routinely uses dinoprostone during the first 5 days after LT. The aim of this study was to retrospectively analyze the effect of dinoprostone on markers of IRI (an increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyl transferase (yGT)), on the recovery of liver function post-LT (factor V levels and international normalized ratio (INR)) on the rate of vascular complications, and on the prevalence of side effects such as the safety of administration, by monitoring blood pressure, because hypotension is known to be a major side effect.

MATERIALS AND METHODS

Patient Cohort

Children aged 0 to 16 years who underwent LT in our center from March 2008 to December 2013 were included. They were listed for LT, when they met 1 or more of the following criteria: (i) in patients with liver cirrhosis: rising serum bilirubin levels, repetitive episodes of cholangitis, worsening portal...
hypertension, declining synthetic function; (ii) in patients with metabolic disease: failure to thrive, problems in disease management, severe impairment of quality of life.

PGE was administered to have the patients benefit from its cytoprotective and regenerative effect and to help to avoid hepatic artery thrombosis by its effect on vasodilatation and thrombocyte aggregation. PGE was given to any child with the same dosage regimen, without considering the graft type (whole vs split), indication for LT, or severity of pre-LT portal hypertension. Patients received continuous dinoprostone intravenously immediately after surgery, that is, 2 hours after closure of the abdomen, starting at 0.1 μg/kg per hour, increasing the dose every 6 hours as tolerated (ie, no increase if hypotension) to a maximal 0.6 μg/kg per hour, for a duration of 5 days. Treatment was stopped for the following reasons: (a) completion of a 5-day infusion, (b) early discharge to the floor, (c) hypotensive episode temporally related to increase in dinoprostone dose.

This study was approved by the Ethical Committee of the University Hospitals of Geneva (CER 11-10R) and parents of the analyzed patients provided informed written consent before the study.

Outcome Measures

Data were collected from the individual electronic patient charts. The following variables were recorded: demographic data of patients, donors and grafts at time of LT, perioperative data, post-LT laboratory data at days 1, 3, 5, 10, 30, and 60 post-LT, complications, defined as an adverse event arising within 4 weeks post-LT, vasoactive drugs or vasopressors administered in the intensive care unit (cumulative dose during 5 days post-LT for (nor)epinephrine, dobutamine, dopamine, niprusitate, nifedipine, and enalapril). For the purpose of statistical analysis, patients were divided into 2 categories “no drug given” and “1 dose of any drug.” Hypotension was defined as an episode of a mean arterial pressure below the fifth percentile for age; the number of hypotensive episodes during the first 5 days post-LT was recorded.

Selection criteria for grafts were maximal accepted donor age not more than 50 years older than the recipient, maximal BMI 25, biological parameters had to show an improving trend from admission to procurement, sodium levels less than 160 μmol/L, and liver steatosis on ultrasound had to be estimated as less than 10%.

Statistics

Cross-Sectional Analysis

Associations between the cumulative doses of dinoprostone at day 5 post-LT and the outcome parameters were examined visually using a scatterplot. These associations were quantified using the Spearman correlation, this analysis being robust to extreme values. We then stratified children into 2 groups, having received more or less than 28 μg/kg of dinoprostone as a cumulative dose. 28 μg/kg was the median of the entire cohort. Results were considered statistically significant if they reached a P value less than 0.05.

Longitudinal Analysis

To evaluate the course of the outcomes according to the cumulative dose of dinoprostone given after LT, we first represented the evolution of each outcome factor over time, in function of each single (noncumulative) dose of dinoprostone. A multivariate analysis using the same model was carried out while adjusting for the effect of dinoprostone on model for end-stage liver disease score (MELD), patient’s weight (z score), primary disease (biliary atresia [BA] vs others) over time. The Spearman correlation coefficient was also used to assess the association between the cumulative dose of dinoprostone and the use of vasopressors (per day and until day 5 post-LT).

RESULTS

One of the 41 patients was excluded because of an aberrant, unreasonable value of cumulative dinoprostone dose, most probably due to an error in data recording. Patient characteristics for each treatment group are summarized in Table 1. The 2 groups differed in the need for emergency for LT, the type of liver graft, and the primary disease. For the latter, statistics were adjusted during further analysis. There was no early vascular complication. Therefore, analysis of this outcome measure was not possible.

Cross-Sectional Analysis

No significant correlation was observed between the cumulative dinoprostone dose and all analyzed outcome variables (AST, ALT, γGT, bilirubin, INR, factor V) up to 60 days after LT (Table 2, Figure 1). There was no difference in outcome 5 days post-LT between the group having received less than 28 μg/kg and that having received greater than 28 μg/kg of cumulative dinoprostone dose (Table 3).

Longitudinal Analysis

No significant correlation was observed between each single dinoprostone dose and all outcome variables analyzed over the entire observed period of 60 days (AST, ALT, γGT, bilirubin, INR, factor V). Results remain nonsignificant when adjusted for the possible confounding factors: pre-LT MELD, primary disease (BA vs others) and weight z score (Table 4, Figure 2).

Patient and Graft Survival

The overall 5-year patient survival was 95%, with 1 death in each group, 1 due to an overwhelming adenovirus infection, and the other patient due to multiple organ failure in a super urgent setting. Overall 5-year graft survival was 92.5%; there was a 90% 5-year graft survival in the group having received less than 28 μg/kg of cumulative dinoprostone dose, and a 95% 5-year survival graft in the group having received greater than 28 μg/kg, with no significant difference.

Adverse Events: Patients With Hypotension

Eight (20%) of 40 patients experienced hypotensive episodes, without measurable sequelae. These patients are summarized in Table 5: 4 of 8 patients had a clear reason for their hypotension, 2 of 8 remained unclear, 2 of 8 had received an antihypertensive drug overdose, and 1 of 8 hypotensive episode might have been due to an increase of dinoprostone. No association was found between the number of hypotensive events and the quantity of administered vasopressors.

DISCUSSION

This study aimed to determine the influence of dinoprostone on markers of IRI, the recovery of liver function after LT, the rate of vascular complications and the side effects of administering dinoprostone in a cohort of pediatric liver transplant recipients. We did not show, at any dosage of
of 82 patients (18 children and 64 adults). Yet, later on, the comparison with nontreated patients (6 patients), in a cohort with primary nonfunction treated with PGE (10 patients) in show a significant decrease of mortality in a group of patients

| TABLE 1. Patient and group characteristics |
|------------------------------------------|
| Variables                                | All patients, n (%) | Group <28 μg/kg, n | Group >28 μg/kg, n | P  |
|------------------------------------------|---------------------|---------------------|---------------------|----|
| Sex                                      | Male                | 21 (52)             | 13                  | 8  | ns |
|                                          | Female              | 19 (48)             | 7                   | 12 |    |
| Blood group                              | A                   | 39 (98)             | 19                   | 20 | ns |
|                                          | B                   | 0 (0)               | 0                   | 0  |    |
|                                          | O                   | 1 (02)              | 1                   | 0  |    |
| Primary disease                          | BA                  | 22 (55)             | 7                   | 15 | 0.03 |
|                                          | Others              | 18 (45)             | 13                  | 5  |    |
| Type of graft                            | Split liver         | 24 (60)             | 15                  | 9  | 0.005 |
|                                          | Whole liver         | 13 (33)             | 2                   | 11 |    |
|                                          | Living donor        | 3 (7)               | 3                   | 0  |    |
| Blood group compatibility                | Identical           | 26 (65)             | 12                  | 14 |    |
|                                          | Compatible          | 13 (33)             | 7                   | 6  |    |
|                                          | Incompatible        | 1 (3)               | 1                   | 0  |    |
| Type of emergency                        | Elective            | 26 (67)             | 11                  | 15 | 0.02 |
|                                          | Urgent              | 3 (8)               | 8                   | 2  |    |
|                                          | Super-urgent        | 10 (26)             | 0                   | 3  |    |
| Infection post-LT                        | None                | 25 (62)             | 13                  | 12 | ns |
|                                          | Bacterial           | 11 (28)             | 5                   | 6  |    |
|                                          | Viral               | 4 (10)              | 2                   | 2  |    |
|                                          | Acute rejection post-LT (<4 wk) | 11 (28) | 7 | 4 | ns |
|                                          | Primary nonfunction  | 0                   | 0                   | 0  |    |
|                                          | Vascular complications post-LT | 0 (0) | 0 | 0 | n/a |
| Median (IQR):                            | PELD                | 14 (22)             | 16 (27)             | 10 (21) | ns |
|                                          | Age at LT, y        | 1.2 (3.4)           | 1.5 (8.3)           | 1.1 (3.0) | ns |
|                                          | Height at LT, cm    | 76 (30)             | 78 (65)             | 75 (24) | ns |
|                                          | Weight at LT, kg    | 9.8 (10.1)          | 10.0 (17.0)         | 9.8 (6.5) | ns |
|                                          | Weight (z score) at LT | −0.9 (2.1) | −1.3 (2.3) | −0.6 (1.4) | ns |
|                                          | Creatinine before LT, μmol/L | 21 (16) | 23 (19) | 19 (15) | ns |
|                                          | INR before LT       | 1.3 (0.9)           | 1.4 (1.3)           | 1.3 (0.6) | ns |
|                                          | γ GT before LT, U/L | 76 (145)            | 69 (217)            | 86 (126) | ns |
|                                          | Total bilirubin before LT, μmol/L | 79 (340) | 151 (342) | 69 (331) | ns |
|                                          | Donor age, y        | 19 (30)             | 22 (20)             | 16 (32) | ns |
|                                          | Total ischemia time, h8 | 1.3 (5.7) | 1.1 (6.3) | 2.1 (4.2) | ns |
|                                          | Red blood cell transfusion, mL | 680 (924) | 1006 (1633) | 490 (1633) | ns |

In this study, the effect of PGE did not seem to confer an advantage for the recovery of liver function as measured by factor V and INR.

Graft type and type of emergency might have an important influence on outcomes in this cohort. Whole livers displayed more rapid recovery of synthetic hepatic function. A positive cumulative effect of whole liver grafts together with a higher dose of cumulative dinoprostone, as in our study, was probable, but this was not observed. Nonemergent LT are also expected to have better immediate outcome parameters, because the patient usually is in a more stable condition. Emergency LT together with a lower dose of cumulative dinoprostone might come

**TABLE 2. Cross-sectional analysis of the cumulative dose of dinoprostone for each variable**

| Analyzed parameters | Spearman correlation | P   |
|--------------------|----------------------|-----|
| AST, U/L           | −0.09                | 0.57|
| ALT, U/L           | 0.10                 | 0.52|
| γ GT, U/L          | −0.03                | 0.86|
| Bilirubin, μmol/L  | −0.25                | 0.13|
| INR                | 0.12                 | 0.58|
| Factor V, %        | −0.31                | 0.12|

There was no significant correlation between doses of cumulative dinoprostone and all analyzed outcome variables up to 60 days after LT.
together with a worse outcome, but again, no effect was identified in our study.

PGE was given to any child with the same dosage regimen, without considering the graft types or indications for LT, and treatment was only stopped before the 5-day completion of the infusion if hypotensive episodes were recorded and considered to be due to an increase in dinoprostone dose. Thus, the observed statistical differences between the 2 groups, with more BA patients, elective and whole graft recipients receiving higher doses, are not to be seen as related with a deliberate high or low dose PGE dosage.

The side effects associated with the administration of dinoprostone were evaluated by monitoring for hypotension. We only identified a single patient, who seemed to have hypotensive episodes linked to a dose increase, which responded to dose reduction. The evaluation, if hypotensive events were camouflaged by the administration of vasopressors, revealed no correlation. We conclude that administration of dinoprostone in children with doses of no more than 0.6 μg/kg per hour appears to be safe.

To our knowledge, only 1 exclusively pediatric study exists on the preventive administration of PGE after LT: Bucuvalas et al,12 in 2001, combined PGE and N-acetylcysteine with the aim to reduce IRI. Their study did not show any significant difference in patient and graft survivals, allograft rejection within the first 90 days after LT, peak concentration of serum ALT postransplant, post-LT length of hospitalization, postoperative complications, as well as no adverse events of PGE between the treated group (12 patients) and the control group (13 patients). In our present study, where all study

![Figure 1](image.png)

**TABLE 3.** Comparison of outcome parameters 5 days after LT between the 2 patient groups

| Analyzed parameters | Group <28 μg/kg | Group >28 μg/kg | P   |
|---------------------|-----------------|-----------------|-----|
| AST, U/L            | 119.5           | 92.2            | 0.25|
| ALT, U/L            | 378.1           | 457.5           | 0.54|
| γGT, U/L            | 182.7           | 151.1           | 0.52|
| Bilirubin, μmol/L   | 112.2           | 69.7            | 0.13|
| INR                 | 1.1             | 1.2             | 0.32|
| Factor V, %         | 98.8            | 90.5            | 0.06|

*Cumulative dinoprostone dose of < or >28 μg/kg body weight. Outcome variables at day 5 after LT were not statistically different.
patients have got PGE, we found that with any dosage of dinoprostone between 0.1 and 0.6 μg/kg per hour, there was no observable trend of impact on IRI, hepatic function or hypotensive episodes. Because it is not known what is the best dose of PGE in pediatric patients, it could be that the best dose would be even lower or higher.

Although the cohort is measurably larger than in the previous study, it is small and the following weaknesses should be

| Analyzed parameters | Univariate (dinoprostone and time) | Adjusted for MELD, primary disease, weight z score |
|---------------------|-----------------------------------|-----------------------------------------------|
|                     | Coefficient | P    | Coefficient | P    |
| AST, U/L            | −6.5        | 0.50 | −5.1        | 0.61 |
| ALT, U/L            | −4.6        | 0.30 | −4.9        | 0.29 |
| γGT, U/L            | −1.3        | 0.14 | −0.9        | 0.29 |
| Bilirubin, μmol/L   | −0.2        | 0.77 | −0.5        | 0.43 |
| INR                 | 0.0         | 0.68 | 0.0         | 0.46 |
| Factor V, %         | −0.05       | 0.79 | −0.05       | 0.77 |

With and without adjustment for confounders there was no significant correlation.

**FIGURE 2.** Longitudinal analyses of each single dose of dinoprostone on: A, ALT; B, γGT; C, INR; D, Factor V (%) up to 60 days after LT. For easier visualization, patients were stratified into 2 groups of cumulative dose of dinoprostone having received less than and greater than 28 μg/kg body weight. There was no significant correlation with the measured outcome parameters up to day 60.

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considered in examining the findings. The 2 groups (cumulative dose of dinoprostone of <28 and >28 μg/kg) are not identical, and notably show significant differences as to the primary disease (more BA patients in the group with >28 μg/kg), the type of emergency (more emergent LT in the group with <28 μg/kg) and graft type (more whole liver grafts in the group >28 μg/kg). Although these differences were accounted for in a post hoc analysis, there was no significant difference in the effect of dinoprostone on graft outcomes. A control group is necessary to conclusively analyze effects of PGE. This study is clearly of observational character and only gives a preliminary insight into the topic.

In summary, the present pediatric analysis, in agreement with other studies, failed to demonstrate a significant cytoprotective effect of dinoprostone and no effect on recovery of liver function during the immediate postoperative period after LT at dosages between 0.1 and 0.6 μg/kg per hour.1,2,8,11,12,14 A 2011 Cochrane analysis reported an important risk of bias in most trials reviewed.15 An expensive multicenter controlled study should be carried out, yet on a drug that has fairly consistently failed to show benefit, and thus is highly unlikely to be realized.

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