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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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Ischemia-reperfusion injuries (IRI) take place right after the reperfusion of the anoxic, transplanted liver, due to massive production of oxygen radicals and cytokines, toxic for endothelial and parenchymal cells.[1] Prostaglandins E (PGE) have been shown to have a direct and indirect cytoprotective effect on hepatocytes and sinusoidal endothelial cells by preventing IRI after liver transplantation (LT).[2,3] Of particular interest in organ transplantation, PGE have been shown to have an immunomodulatory effect and to enhance regeneration.[3] 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[4]: 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,[5-7] decreasing primary nonfunction,[1,6,8] and avoiding vascular thrombosis,[4] These studies resulted in diverging conclusions.[8-11] There is only 1 small pediatric study that shows no effect on ischemia-reperfusion or on vascular complications.[12]

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 (γGT)[13]), on the recovery of liver function post-LT (factor V levels and international normalized ratio (INR)[7]), 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

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C. L. and B. E. W. designed the study. C. L. collected and analyzed the data and drafted the article; B. E. W. and V. A. M. revised the article. B. E. W. supervised the study; all authors have read and approved the final version to be published.

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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, niprussiate, 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, yGT, 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, yGT, 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 graft survival 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

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 (2)	1	0	
Primary disease				
BA	22 (55)	7	15	0.03
Others	18 (45)	13	5	
Type of graft[a]				
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	ns
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	ns
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 (36)	78 (63)	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 (2.5)	–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
γGT 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, h[b]	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

[a] All of them heart-beating donors.

[b] Defined as the sum of cold and warm ischemia times.

IQR, interquartile range; ns, not significant; n/a, not applicable; PELD, pediatric end-stage liver disease score.

dinoprostone between 0.1 and 0.6 µg/kg per hour, over 5 days, any difference in beneficial or harmful effects of high- or low-dose dinoprostone administered immediately after pediatric LT.

IRI is thought to be one of the etiologic factors of graft primary nonfunction.[13] In 1989, Greig et al were the first to show a significant decrease of mortality in a group of patients with primary nonfunction treated with PGE (10 patients) in comparison with nontreated patients (6 patients), in a cohort of 82 patients (18 children and 64 adults). Yet, later on, the majority of studies did not support a direct effect of PGE on primary nonfunction.[5,6,8,11,12,14,15] In our study, there was no primary nonfunction event; therefore, the effect of dinoprostone could not be evaluated. Greig et al[13] also showed a more rapid decrease of AST and ALT. In 1997, Giostra et al[1] confirmed these findings and also revealed a cytoprotective effect of PGE (significant decrease of transaminases and of bilirubin) in 38 adults. The effect was limited to the first 5 days after LT, and thereafter aminotransferase levels and mortality rates were similar in the treatment and control groups. Another study confirmed that in case of posttransplant elevated hepatic artery resistive index (>0.75), a sign of IRI, the administration of PGE led to a significant reduction of transaminases and a decline of the resistive index.[16] In contrast to these positive studies, Alevizacos et al[5] showed, in a randomized prospective study, the absence of a cytoprotective effect of PGE after administration for 3 days: the control group had lower ischemia reperfusion parameters than the treated group, and no significant difference in prothrombin time was observed between the control and treatment group. Another study failed to show a difference of bilirubin and γGT levels between groups receiving or not PGE during 14 days after LT.[10] These findings are supported by our study, where we observed no significant trend of transaminases, nor bilirubin or γGT with increasing cumulative dose of dinoprostone.

The aim of trying to reduce IRI is to improve hepatic function. Indeed, Greig et al[13] showed a positive effect on liver function with a more rapid rise of coagulation factors (V and VII) and prothrombin time. Kornberg et al[10] confirmed an improved liver function after PGE treatment: factor V was significantly higher in the first 2 days postsurgery in the treatment group (a group that had a high hepatic arterial resistance index (>0.75) and therefore was treated) in comparison to the control group. These results are even more valuable, because the group receiving PGE had indirect signs of severe IRI. In the present 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
γGT, U/L	–0.03	0.85
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.

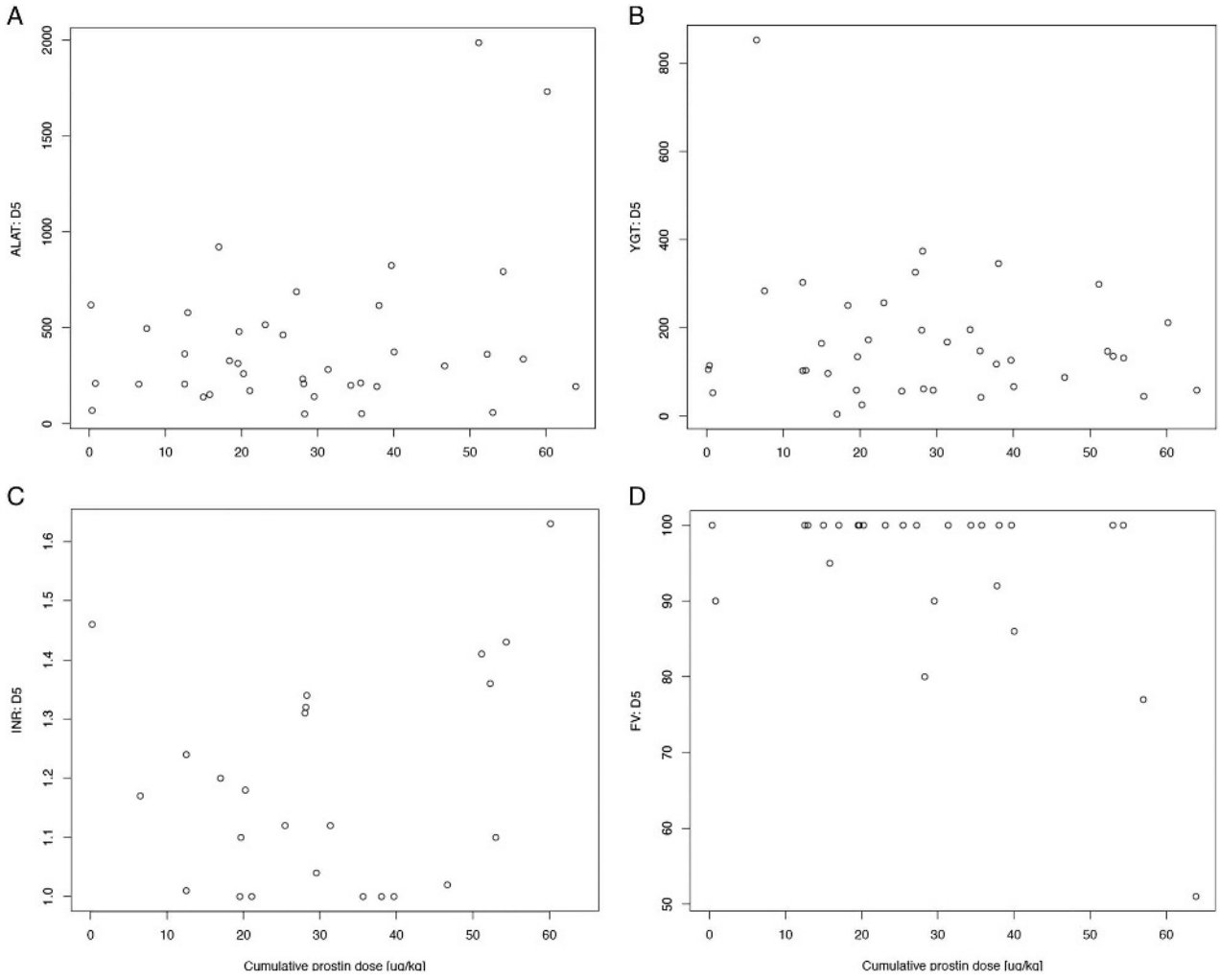

FIGURE 1. Transversal scatterplot analyses of the cumulative dose of dinoprostone on: A, ALT; B, γGT; C, INR; D, Factor V (%) at day 5 after LT. There was no significant correlation with the measured outcome parameters.

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 posttransplant, 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

TABLE 3.

Comparison of outcome parameters 5 days after LT between the 2 patient groups

Analyzed parameters	Group <28 μg/kg[a]	Group >28 μg/kg[a]	*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

[a] Cumulative dinoprostone dose of < or >28 μg/kg body weight.

Outcome variables at day 5 after LT were not statistically different.

TABLE 4.

Longitudinal analysis of the effect of the cumulative dose of dinoprostone after LT on outcome variables over the observation period

	Univariate (dinoprostone and time)		Adjusted for MELD, primary disease, weight z score	
Analyzed parameters	**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
yGT, 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.

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

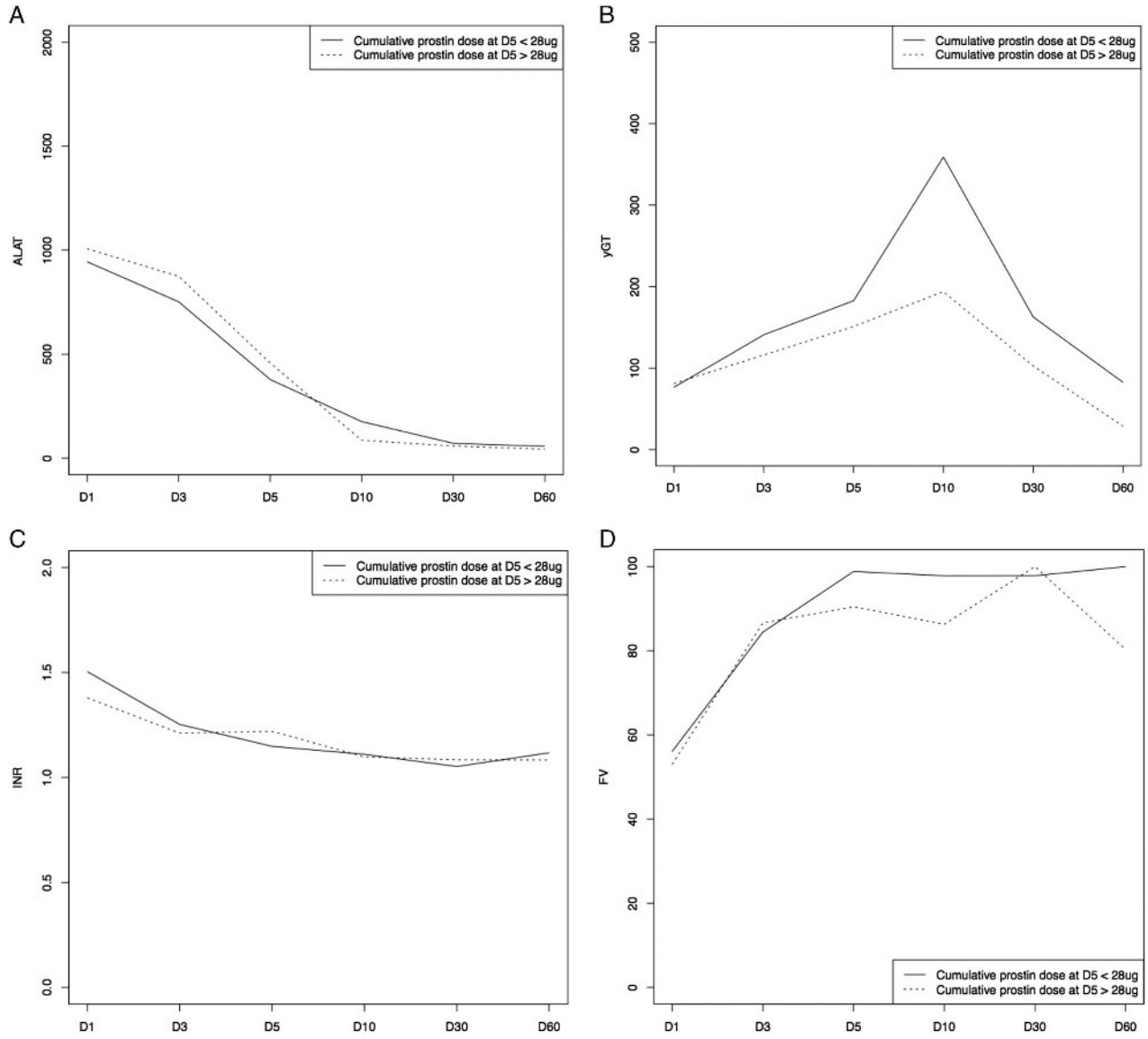

FIGURE 2. Longitudinal analyses of each single dose of dinoprostone on: A, ALT; B, γGT; C, INR; D, Factor V (%) up to 60 days after LT. For easier visualization, patients were stratified into 2 groups of cumulative dose of dinoprostone having received less than and greater than 28 µg/kg body weight.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

TABLE 5.

Detailed analysis of patients with hypotensive episodes

Patient	Moment of hypotension	Cumulative dose of dinoprostone at the moment of hypotension	Cause of hypotension	Treatment
5	D1	3.1 μg/kg per 24 h	Increase of dinoprostone	Reduction of dinoprostone
	D2	5.0 μg/kg per 24 h		
	D4	4.7 μg/kg per 24 h		
7	D5	Stopped 2D before	Undetermined (stop of dinoprostone at day 3)	IV bolus
14	D4	13.8 μg/kg per 24 h	Probably overtreatment with antihypertensive medication	Reduction of antihypertensive medication
17	D1	3.6 μg/kg per 24 h	Hypovolemia due to an important postoperative capillary leakage	IV bolus
30	D1	5.8 μg/kg per 24 h	Probably overtreatment with antihypertensive medication	Stop of antihypertensive treatment + vasopressors
	D2	6.0 μg/kg per 24 h		
35	D1	1.5 μg/kg per 24 h	Septicemia	IV bolus
	D4	6.6 μg/kg per 24 h		
39	D3	9.6 μg/kg per 24 h	Allergic reaction to hydroxyethylamidone (Voluven)	IV bolus + vasopressors
41	D1	1.4 μg/kg per 24 h	Undetermined	IV bolus
	D2	6.5 μg/kg per 24 h		

One of 8 hypotensive episode might have been due to an increase of dinoprostone. Four of 8 patients had a clear reason for their hypotension. Two of 8 remained unclear. Two of 8 received an (over)treatment with antihypertensive drugs.

D, postoperative day; IV, intravenous.

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.[5,8,11,12,14] 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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