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Case Report

Hemoadsorption as Bridge to Liver Transplant in A Six-Month Old Patient with Hepatic Failure

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Abstart

Introduction: Progressive familial intrahepatic cholestasis (PFIC) is a group of inherited disorders that result in the impairment of bile flow through the liver that predominantly affects children. Many of these patients will progress to end stage liver disease and require liver transplantation. Acute on chronic liver failure (AoCLF) may occur in these patients, with rapidly progressive evolution and severe prognosis that can lead to death if patients are not transplanted.

Methods: We present a case of a female patient, aged 6 months, hospitalized in our ICU for Acute on Chronic Liver Failure due to Progressive Familial Intrahepatic Cholestasis. The administration of coagulation factors (Provertinum, not activated plasma derived Factor VII, pdFVII), associated with Platelets and Fresh Frozen Plasma, was started to reverse her dramatic hypercoagulable state. The patient underwent a continuous renal replacement therapy because of acute kidney injury, with the addition of hemoadsorption filter (Cytosorb®Cytosorb®), started to limit the severe hyperbilirubinemia and hyperammoniemia.

Results: The efficacy of Provertinum was assessed by better coagulation parameters, stopped bleeding and none thrombotic events. Hemadsorption with Cytosorb resulted in a dramatic reduction of bilirubin and ammonium levels. After three days the patient was transferred to underwent liver transplantation.

Conclusions: This is the first experience with the use of Provertinum and Cytosorb hemoadsorption in a low weight infant as a bridge to liver transplantation. This preliminary experience underlines the role of hemadsorption in the management of severe hepatic failure in pediatric patients before liver transplantation.

Keywords: Pediatric acute liver failure; Hemoadsorption; Progressive familial intrahepatic cholestasis; Cytosorb; CRRT; Coagulation, Provertinum; Liver transplantation

Abbreviations

PFIC: Progressive Familial Intrahepatic Cholestasis; FIC1/2: Familial Intrahepatic Cholestasis, Type 1 / 2; BSEP Gene: Bile Salt Export Pump; BRIC: Benign Recurrent Intrahepatic Cholestasis; ICP: Intrahepatic Cholestasis Of Pregnancy; NICCD: Neonatal Intrahepatic Cholestasis Caused By Citrin Deficiency; AoCLF: Acute on Chronic Liver Failure; MAP: Mean Arterial Pressure; HR: Heart Rate; WBC: White Blood Cell; PLT: Platelets; Hb: Hemoglobin; AKI: Acute Kidney Injury; TEG: Thromboelastogram; CRRT: Continuous Renal Replacement Therapy; ELS: Extracorporeal Liver Support; ICU: Intensive Care Units; ESLD: End-Stage Liver Disease; FFP: Fresh Frozen Plasma

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Introduction

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of inherited disorders related to a defect in bile secretion that predominantly affects children. Two types of PFIC are recognized: PFIC-1, which is due to mutations of the FIC1 (familial intrahepatic cholestasis, type 1) gene and PFIC-2, which results from mutations of the BSEP (bile salt export pump) gene. The accumulation of bile salts leads to progressive liver damage [1], and if left untreated, can end up in end-stage liver disease, multiple organ failure and death. Likewise, Acute On Chronic Liver Failure (AoCLF) may occur in these patients. Neonatal cases with ascites are described, with a rapidly progressive evolution and poor prognosis if patients are not transplanted [2]. These infant patients often present with worsening jaundice and pruritis within their first few years of life and in particular cases, liver transplantation remains the only option. The role and timing of liver transplantation is still debated controversially, but based on various studies, liver transplantation offers an excellent survival benefit for a selected subset of patients [1]. However, the availability of donor organs poses a considerable impediment and patients sometimes have to wait for years until transplantation with a suitable organ can be performed. During this time, the clinical state of the patients is heavily dependent on the potential of the liver to fulfill its task regarding e.g. detoxification, which is most often considerably compromised in PFIC patients. The same holds true for the role of the liver regarding production of coagulation factors. Therefore, therapy options serving

as a bridge-to-transplant are urgently needed. Recently, promising approaches have entered the field in the form of specific coagulation factors as well as hemoadsorption therapies.

Case Presentation

We present the case of a 6-month-old female patient (8 kg, 55 cm), who was admitted to our hospital due to severe hyperbilirubinemia. She was a known case of PFIC undergoing a genetic work-up. On admission the patient was awake and breathing spontaneously. Continuously measured Mean Arterial Pressure (MAP) was 60 mmHg, Heart Rate (HR) 110 bpm, and SpO2 100%. She exhibited signs of jaundice and a painful abdomen. Laboratory data showed a White Blood Cell (WBC) count of 23.520/mm3; Platelets (PLT) 231,000/ mm3; Hemoglobin (Hb) 11 g/dl; C-Reactive Protein (CRP) 5.6 ng/l; lipase 175 U/L; amylase 3.04 U/L; ammonia 219 µg/dl; Lactate Dehydrogenase (LDH) 381 mU/ml; total bilirubin 29.42 mg/dl (indirect 9.36 mg/dl, direct 20.06 mg/dl); Creatinine Phosphokinase (CPK) 252 mU/ml; creatinine 0.11mg/dl; lactate 6.1 mmol/L, international normalized ration (INR) 3.52, Activated Partial Thromboplastin Time (aPTT) 3.05, and Anthrombin (AT)III 17%. Peripheral venous access was obtained for the administration of fluids (NaCl 0.9 % with 10 ml/h), HPC (300UI) and Vitamin K (10 mg). Ten hours after admission, the patient developed tachypnea, anuria and her neurological status deteriorated severely. Despite the initial therapies, laboratory data indicated a rapid worsening of coagulation parameters: INR and aPTT ratio were not measurable, PLT 68,000/ mm3, Hb 7.6 g/dl, ATIII 7 %. Simultaneously, she developed Acute Kidney Injury (AKI). Following transfer to the Intensive Care Unit (ICU) with subsequent sedation and curarization, the patient was intubated and mechanically ventilated in pressure control mode. Additionally, immediate transfusion with Red Blood Cells (RBC) was performed. Chest radiograph indicated pulmonary thickenings. Blood gas analysis showed a pH of 7,44, PaCO2 23 mmHg, PaO2 287 mmHg, lactate 2.4mmol/L, and Base Excess (BE) of -7.5 mmol/L. Two peripheral intravenous catheters, one central venous catheter (left femoral vein) and a right femoral arterial catheter for continuous pressure monitoring were inserted. A bilumen catheter for hemodialysis was placed into the right femoral vein. Of note, a notable amount of bleeding occurred when the catheters and a nasogastric tube were inserted resulting in the immediate start of blood transfusions. The Thromboelastogram (TEG) showed an "R" of 73 minutes, followed by administration of RBC 240 ml, Fresh Frozen Plasma (FFP) 130 ml, PLT 100 ml, Fibrinogen 150 mg, non activated plasma derived Factor VII (pdFVII, Provertinum® 400 UI) (max dosage is 50 UI/KG for massive bleeding) and human prothrombin complex (HPC, Prothromplex 400 UI). After this initial (coagulation-focused) treatment (with RBC, FFP, fibrinogen, pdFVII and HPC), laboratory data showed a slight improvement in coagulation parameters: INR 4.27, PLT 13,000, fibrinogen 112 mg/dl, ATIII 13%, Hb 12.4 g/dl, Hct 34%, although aPTT was still not measurable. Due to the development of AKI, Continuous Renal Replacement Therapy (CRRT, Prismaflex System, Baxter, Germany) was initiated and run in Continuous Veno-Venous Hemodiafiltration (CVVHDF) mode (dose between 20-30 ml/kg/h). Ultrafiltration rate was variable with hemodynamics and regional citrate anticoagulation (RCA) was used to avoid systemic anticoagulation with heparin, as citrate works by chelating ionized calcium, a cofactor in multiple steps in the coagulation cascade [3-4]. Informed consent was obtained from patient's parents, including an accurate description of the severity of the clinical picture and the hitherto ineffectiveness of standard therapies: for all other procedures a prior authorization remains valid (ETHICAL COMMITTEES 53891- 2017). With the rationale to reduce circulating bilirubin and ammonia plasma levels, and after a hemoadsorber cartridge (CytoSorb, CytoSorbents, Monmouth Junction, NJ, USA) was integrated post-hemofilter. The priming procedure included (Blood Cell, 100 ml). After 3 hours of combined therapy, the decision was made to stop the RCA due to a rapid increase in lactate levels. During the treatment, the patient received a total of 1200 UI pdFVII (three times), representing the maximum dosage for cases with massive bleeding, as well as 20 mg Vitamin K, 1500 UI HPC, 1.5 g Fibrinogen, and 500UI ATIII. After 18 hours of combined CRRT and CytoSorb hemoadsorption treatment, we witnessed a massive reduction in bilirubin plasma concentrations (from 29.42 to 2.91 mg/dL) while urea levels decreased simultaneously (Table 1). Furthermore, there was a considerable improvement in PRISM III and SOFA Score (PRISM III from 21 to 17; SOFA from 13 to 7). Importantly, during CVVHDF and CytoSorb treatment, the same dosage of amines was administered without any worsening of hemodynamic conditions. After three days, the patient could be transferred to the national transplant for liver transplantation which she received, and was discharged home after a further four months.

Discussions and Conclusions

This is, to our knowledge, the first report describing the combined use of pdFVII and CytoSorb hemoadsorption therapy to bridge a low weight infant to liver transplantation. Administration of pdFVII resulted in improved coagulation with no thrombotic events noticed. Subsequent initiation of hemadsorption therapy was associated with a significant reduction in bilirubin and ammonia levels. The patient could subsequently undergo successful liver transplantation. Artificial Extracorporeal Liver Support (ELS) devices are designed to improve the survival of patients with Acute Liver Failure (ALF) by assisting in the detoxification function, but certainly also other processes, acting mainly as a form of a bridging therapy, while awaiting transplantation [5]. Data about ELS in the pediatric population remains scarce. The largest study in the pediatric population thus far comes from a hospital with ten years of experience with the Molecular Adsorbent Recirculating System (MARS) method. In a study performed by Lexmond MARS was employed as ELS in 20 pediatric patients suffering from ALF listed for high urgent liver transplantation. MARS was applied for eight consecutive hours daily until transplantation [6]. All patients were mechanically ventilated and on vasopressor therapy, as was the case in our patient. Application of the MARS method decreased serum ammonia and bilirubin levels. The only encountered adverse effect from the therapy in this study was thrombocytopenia with bleeding requiring blood and platelet mass transfusions in five children, with one case that finally died. CytoSorb has been primarily been studied and marketed for cytokine adsorption in the treatment of septic shock [7-9] and other inflammatory syndromes such as hyperinflammation post cardiac surgery, endocarditis, pancreatitis and burns in adult patients. However, it is has been shown to reduce other endogenous and exogenous compounds from blood such as myoglobin, bilirubin, and others, resulting in the CE mark for treatment of associated diseases with increased plasma levels of these substances [10]. We performed hemadsorption in a six-month-old female infant affected by AoCLF due to PFIC as a rescue procedure, obtaining favorable results in terms of reduction in bilirubin and ammonia levels. In the literature we found only another PEDIATRIC case in which CytoSorb was used to remove bilirubin [11] but, this is the first experience in which CytoSorb was used in low weight infant

Table 1: Data trend before, pre and post treatment.

PARAMETERS	ADMISSION	PRE CytoSorb	Post CytoSorb
BLOOD COUNT			
WBC	23,52	23,46	14,7
PCR	5,6	8	4,1
PRESEPSINE	232	217	591
HCT	31,65	35,78	21,59
HB	11	12,4	7,6
PLT	231	13	9
KIDNEY / LIVER DATA			
AZOTEMIA	17	29	4,26
CREATININE	0,11	0,11	0,42
BILIRUBIN TOT	29,42	22,98	2,91
BILIRUBIN IND	9,36	11,92	1,96
BILIRUBIN DIR	20,06	11,06	0,95
ALBUMIN	21	24,6	8
GGT	31	16	15
AST	393	223	183
ALT	161	97	70
AMYLASE	3,04	-	4,27
LIPASE	175	257	653
MYOGLOBIN	-	-	-
LDH	381	357	600
CPK	252	1559	310
BLOOD GAS			
PH	7,43	7,41	7,32
PCO2	16,8	28	31
PO2	93,7	226	113
LACT	6,1	2	9,7
K+	4,7	3,9	2,6
Na+	124	128	144
BE	-11	-9,3	-10,1
AMMONIUM	219	-	-
HEMODYNAC DATA			
SAP	90	98	86
DAP	40	48	40
MAP	65	73	63
HR	110	130	140
DRUGS			
ADRENA mcg/kg/min	0	0,06	0,1
NORA mcg/kg/min	0	0,2	0,23
COAGULATION			
INR	3,52	4,27	4,26
PTT	3,05	*Out of Range*	*Out of Range*
FIB	44	*Out of Range*	69
DD	1,32	73	*Out of Range*
ATIII	17	13	11

as bridge to liver transplantation. Using CytoSorb hemoadsorption, the patient could successfully undergo liver transplantation with low plasma levels of bilirubin, ammonia and transaminases, no neurological damage (that might have contraindicated the transplant), and – particularly – without an increase in interleukins and cytokines. Regarding the management of coagulation, we know that coagulation impairment is an essential diagnostic component of AoCLF. Rapid PT or INR changes are characteristic; thrombocytopenia, reduced circulating pro- and anticoagulant proteins and increased PAI-1 (favoring fibrinolysis) are all commonly reported in these patients. There are only two situations that require active management of coagulation and platelets [11]. Firstly, insertion of Intrahepatic Cholestasis of Pregnancy (ICP) monitors requires infusion of (FFP, cryoprecipitate and platelets depending on the initial assessment of coagulation, as guided by neurosurgical specialist societies. Second, significant active hemorrhage necessitates correction of coagulation and thrombocytopenia [12,13], as in our case. Concerning the pdFVII, this is the first experience with the use of this drug in a six-month old patient before liver transplant. pdFVII is a lyophilic coagulation VII Factor derived from "Human Plasma". It works as zymogen of active serine – proteasis (Factor VIIa) and initiates the extrinsic coagulation pathway, increases thrombin production and thus the transformation of fibrinogen in fibrin [14,15]. In this way Tissue Factor Pathway Inhibitor stops the activation between FVII – TF, with a contextually better condition. The efficacy of pdFVII is assessed by an amelioration in coagulation parameters, by stopping bleeding and by the absence of thrombotic events, which occurred in our patient. Regional Citrate Anticoagulation (RCA) for continuous renal replacement therapy is widely used in ICUs worldwide [16]. The lengthening of the INR even above 3 does not produce an extension of the average circuit life for CRRT; indeed, if the treatment is conducted without anticoagulant, the circuit life turns out to be quite short and generally much less than 24 hours. As these observations highlight, there is a need to use an anticoagulant even in patients with liver disease; however, due to increased hemorrhagic risk, a systemic anticoagulant such as heparin is not adequate [17]. This preliminary experience shows how the combination of medical therapies to control coagulation, as well as CVVHDF in combination with CytoSorb hemadsorption, can reduce morbidity and mortality, helping to stabilize a very low weight pediatric patient with AoCLF post PFIC, and to bridge her to liver transplantation. This experience continuous to confirm in our opinion that Cytosorb application in neonate and pediatrics is very useful in many pathological conditions [18,19].

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