Case Report

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Liver support in fulminant liver failure after hemorrhagic shock

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Leberersatzverfahren bei fulminantem Leberversagen nach hämorrhagischem Schock

Zusammenfassung. Fulminantes Leberversagen stellt eine interdisziplinäre medizinische Herausforderung dar. Trotz den Verbesserungen in der Intensivmedizin bleibt die Mortalität mit bis zu 80% aufgrund der Komplikationen wie Hirnödem, Sepsis und Multiorganversagen hoch. Die einzige kurative Therapie für Patienten mit fulminantem Leberversagen, bei denen eine spontane Regeneration nicht möglich ist, stellt die Lebertransplantation dar. Dies ist aber mangels Spenderorganen und der kritischen Gesamtsituation des Patienten nicht immer möglich.

Maschinelle Leberunterstützungsverfahren könnten es ermöglichen, die Zeit bis zur Lebertransplantation oder bis zur Erholung der erkrankten Leber zu überbrücken. Prinzipiell unterscheidet man verschiedene Detoxifikationsverfahren und zellgestützte Bioreaktoren. Einer von den neueren extrakorporalen Detoxifikationssystemen ist das Molecular Adsorbent Recirculating System (MARS). MARS funktioniert auf Basis der Albumindialyse und entfernt albumingebundene und wasserlösliche Toxine aus dem Patientenblut.

Wir berichten über einen jungen Patienten, der sich mit den typischen Symptomen einer ischämischen Hepatitis und konsekutivem Multiorganversagen (APACHE II Score 38 → vorhergesagte Mortalität 87%) nach einem prolongierten hämorrhagischen Schock präsentierte. Eine Lebertransplantation war wegen der Anamnese von Metastasen eines Insulinoms kontraindiziert. Aggressive konservative Therapie und extrakorporale Leberunterstützungstherapie mit MARS war die einzige gegebene Möglichkeit, um das kritische Zustandsbild zu stabilisieren.

Wir haben den Patienten 5 Zyklen der MARS Therapie unterzogen. Während der MARS-Therapie haben wir eine deutliche Verbesserung der Hämodynamik, der Lungenfunktion, des Säure-Basen-Haushaltes und der Laborparametern registriert. Die Plasmaverschwinderate von Indocyaningrün, ein dynamischer Leberfunktionsparameter, hat sich ebenfalls verbessert. Obwohl ein ausgeprägtes Hirnödem im CT mit hochgradig eingeschränktem Blutfluss im transkraniellen Ultraschall diagnoszitiert wurden, hat sich der Patient auch neurologisch völlig erholt. Der Patient hat überlebt und konnte aus dem Spital ohne Folgeschäden entlassen werden. Durch MARS-Therapie konnte die kritischste Periode des Leberversagens bis zur Regeneration erfolgreich überbrückt werden.

Schlüsselwörter: Fulminantes Leberversagen, Molecular Adsorbent Recirculating System, Albumindialyse, Leberersatztherapie.

Summary. Acute liver failure (ALF) is a rare clinical syndrome associated with a mortality of up to 80% and its management remains an interdisciplinary challenge. Despite recent improvements in intensive care management, the mortality of patients with ALF remains high and is related to complications such as cerebral edema, sepsis and multiple organ failure. Emergency orthotopic liver transplantation (OLT) is currently the only effective treatment for those patients who are unlikely to recover spontaneously. Nevertheless, OLT is not always possible because of the shortage of the organs and/or complications related to ALF.

Newly introduced liver-assist devices can temporarily support the patient's liver until native liver recovers or can serve as a bridging device until a liver graft is available. The support devices use both cell-based and non-cell-based techniques. One of the latest non-cell-based extracorporeal hepatic support devices, the molecular adsorbent recycling system (MARS), is based on the concept of albumin dialysis. MARS utilises selective hemodiafiltration with countercurrent albumin dialysis aiming to selectively remove both water-soluble and albumin-bound toxins of the low and middle molecular-weight range.

We report on a young patient who presented with clinical symptoms of ischemic hepatitis and multi-organ failure (APACHE II score 38 → predicted postoperative mortality 87%) due to prolonged hemorrhagic shock. OLT was contraindicated because of history of pancreas cancer with metastases. It was necessary to use aggressive conservative therapy and an extracorporeal liver-assist device until liver regeneration began and hemodynamic conditions were stable.

The patient underwent five treatments with MARS. During the treatment, there were improvements of hemodynamics, respiratory function, acid-base disturbances

and laboratory parameters. The plasma disappearance rate of indocyanine green, a parameter of dynamic liver function, improved during MARS treatment. Although repeated neurological examination predicted diffuse brain damage (brain oedema, decreased cerebral blood flow), the patient recovered without any neurological deficits. The patient survived and was discharged from the hospital in good condition. In this case MARS treatment was successful in supporting the patient through the most critical period of ALF.

Key words: Fulminant liver failure, molecular adsorbent recirculating system, albumin dialysis, liver-assist device.

Introduction

Fulminant liver failure is diagnosed in patients who develop hepatic encephalopathy within two weeks of the onset of jaundice and is associated with a mortality of up to 80%. [1]. In acute liver failure (ALF), the massive necrosis of hepatocytes leads to elevated levels of inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), resulting in a systemic inflammatory response syndrome (SIRS), manifested by systemic vasodilatation, hyperdynamic cardiac function, marked coagulopathy and hepatic encephalopathy [2]. Failure of the detoxification function of the liver leads to accumulation of multiple water-soluble toxins such as ammonia, phenols and mercaptans and protein-bound toxins such as aromatic amino acids, middle- and short-chain fatty acids, endogenous benzodiazepines, digoxin-like substances, nitric oxide and false neurotransmitters. All these toxins have been implicated in causing hepatic encephalopathy, cerebral edema, coma, pulmonary edema, renal failure and cardiovascular collapse, often leading to progressive multi-organ failure and death [3]. Emergency orthoptic liver transplantation (OLT) is currently the only effective treatment for those patients who are unlikely to recover spontaneously. Nevertheless, liver transplantation is not always possible because of the shortage of donor organs and/or complications related to ALF. It is estimated that in Europe only 11% of ALF patients listed for OLT receive a graft and 20–50% die before an organ becomes available [4, 5].

Various liver-assist devices that bridge patients until a compatible organ is available or the damaged liver regenerates have been studied [6, 7]. Such devices use both cell-based and non-cell based approaches. The molecular adsorbent recirculating system (MARS), initially described by Stange and Mitzner, is a newer non-cell-based liver-support device based on the concept of albumin dialysis [8]. MARS is a modified dialysis method using an albumin-containing dialysate that is recirculated and perfused online through charcoal and an anion-exchange column. The method combines the ability to remove both water-soluble compounds such as ammonia, creatinine, and urea and strongly albumin-bound substances such as aromatic amino acids, bile acids, bilirubin, and short- and middle-chain fatty acids. Moreover, mediators of SIRS such as TNF-α and IL-6 are removed [9].

We report on a young patient who presented with clinical symptoms of multiorgan failure with fulminant hepatic failure after hemorrhagic shock. Because the patient was contraindicated for liver transplantation we used a liver-support system to improve his condition.

Case report

An 18-year-old male patient underwent a pancreas resection, liver wedge resection, cholecystectomy and splenectomy because of metastases of pancreas insulinoma. After surgery severe arterial bleeding occurred and acute relaparotomy followed. However, owing to the massive bleeding, the patient developed hemorrhagic shock with consecutive multi-organ dysfunction syndrome with fulminant hepatic failure. He was transferred to the University hospital and admitted to the transplant intensive care unit. He was intubated, analgosedated and presented with hemodynamic instability, tachycardia (120 b/min), low systemic vascular resistance index ($334\,dyn \cdot s \cdot m^2/cm^5$), high catecholamines (norepinephrine 2.6 µg/kg/min) and crystalloid/colloids usage (+5160 ml), high cardiac output (20 L/min), wide slowly/absent pupillary reaction to light, coma, and respiratory (PaO_2/FiO_2 100), renal and liver failure. The APACHE II score was 38, with a predicted postoperative mortality of 87%. Blood chemistry on the 1st day after admission (DAA) revealed dramatic increase of liver enzymes (AST 4740 U/l, ALT 3640 U/l, LDH 5960 U/l), bilirubin (4.73 mg/dl), lactate (10 mmol/l), creatinine (3.54 mg/dl) and ammonia (120 µmol/l). Prothrombin time reached 39 % and factor V 19% after massive substitution with fresh frozen plasma (FFP) and clotting factors. The King's College criteria could not be applied because of the FFP substitution, but nonetheless listing for urgent OLT was denied because of the history of malign insulinoma. Cranial computer tomography showed brain oedema, and Doppler sonography revealed decreased cerebral blood flow. A femoral artery catheter for hemodynamic monitoring based on pulse-contour analysis was inserted because the right heart catheter presented with a floating thrombus on the tip and could not be repositioned. We immediately started liver-support therapy (MARS) and performed five treatments in the first six days. During this time we could gradually lower the catecholamine usage (norepinephrine $2.6 \rightarrow 0.125$ µg/kg/min from 1st to 7th DAA) and ventilator variables such as fraction of inspired oxygen (FiO_2), maximal inspiratory pressure and positive end-expiratory pressure (PaO_2/FiO_2 $100 \rightarrow 240$ from 1st to 7th DAA). A measurement of dynamic liver function, the plasma disappearance rate of indocyanine green (PDR_{icg}), revealed a massive liver excretory dysfunction (PDR_{icg} 2.3%/min), and although this improved and stabilised after MARS treatment (PDR_{icg} 13%/min at discharge from ICU) it was far from physiological range (PDR_{icg} 18–25%/min). During the MARS therapy we were able to normalize the fluid balance, using intrathoracic blood volume index as a preload parameter. Bilirubin, as a marker of albumin-bound substances cleared by MARS, decreased and kept at a stable level during the MARS treatment (Table 1). Factor V activity increased from 19 to 33% and liver enzymes decreased (GOT $3640 \rightarrow 682$ U/l, GPT $4740 \rightarrow 988$ U/l) from the 1st to 7th DAA during the MARS treatment. This confirmed that the treatment was effective in detoxification, it cleared the blood of albumin-bound toxins and mediators thought to be involved in the development of organ dysfunction. After withdrawal of MARS treatment bilirubin increased rapidly and reached peak levels of 45 mg/dl on the 15th DAA. On the 9th DAA we discontinued the sedation, and on the 11th DAA a neurological examination was performed. The evoked potentials suggested a bilateral dysfunction of cerebral cortex (missing N70-poten-

Table 1. Blood chemistry and hemodynamic parameters before and after MARS treatments

	pre MARS1	MARS 1	MARS 2	MARS 3	MARS 4	MARS 5
T. Bilirubin	4.73	3.19	3.6	5	5.6	6
Ammonia	120	88	51	64	63	75
MAP	60	65	70	72	70	75
Cardiac index	7.9	7.1	6.8	5.9	5.2	6.1
ITBVI	–	902	920	862	936	931
Norepinephrine	1.5	2.6	1.51	1.33	0.51	0.12
PDR_{ICG}	2.3	5.9	6.7	7.1	6	5.9
Body temperature	–	36.9	36.3	37.1	36.5	36.9

T. Bilirubin total bilirubin (mg/dl); *Ammonia* (µmol/l); *MAP* mean arterial blood pressure; *Cardiac index* (l/min.m^2); *ITBVI* intrathoracic blood volume index (ml/m^2); *norepinephrine* (µg/kg/min); *PDR_{ICG}* plasma disappearance rate of indocyanine green (%/min); *Body temperature* central blood temperature measured by femoral artery catheter (°C)

tials) but fair primary somatosensoric evoked potentials. The patient began to communicate on the 18th DAA by moving his head, hands and eyes. He was consecutively mobilised and transferred after seven weeks to a general surgical ward for further treatment and rehabilitation. He survived and was discharged from the hospital without any neurological deficits.

Discussion

It is known that 20–30% of patients with ALF survive with medical treatment alone. However, identification of such patients remains difficult as there are multiple variables influencing the outcome [10]. The King's College criteria that have been adopted by most centres fail to identify patients at low risk of dying [11]. Furthermore the coagulation abnormalities often have to be corrected in these patients, and in such cases (including our case report) these criteria, relying basically on prothrombin time in non-paracetamol ALF, cannot be applied. The only proven curative therapy for patients who are unlikely to recover spontaneously is liver transplantation. Because of the shortage of organ donors and contraindications for OLT, the development of liver-support devices has been necessary. Over the years, a variety of liver-support systems have been evaluated, including hemodiafiltration, hemoperfusion over charcoal, plasmapheresis, hybrid bioartificial livers and ex vivo xenotransplant. None of these has proven to be entirely effective. Because of side effects and risks to the patients, and the complexity and resource consumption when using bioartificial liver, attention has been refocused on the use of detoxification systems.

We have used MARS support of the excretory and detoxification functions of liver in our clinical settings. The cut-off level of the hemofilter used is about 60 kDa when loaded with albumin. This enables removal of water-soluble and albumin-bound toxins and drugs in middle molecular range (< 60 kDa). Albumin does not cross the filter because of its 65 kDa molecular weight [3]. Furthermore, additional factors thought to be essential for liver regeneration, such as hepatocyte growth factor, hormones and plasma proteins, are not removed because of their higher molecular weights.

We observed an improvement of the hemodynamic situation during the continuous MARS treatment, with consecutive withdrawal of vasopressor support and increase of Factor V. The decreased blood pressure in patients with ALF, requiring vasopressor support when albumin-bound toxins reach critical levels and occupy all albumin binding sites, may be caused by the limited binding capacity of circulating albumin for nitric oxide. Thus increasing the albumin binding capacity using MARS may lead to improvements of hemodynamics.

After withdrawal of MARS therapy, the rapid increase of bilirubin clearly identified the detoxificating function of MARS. Because the hemodynamic situation was stable at this time, no further MARS treatments were performed, on the basis that this inflammatory-induced cholestasis would resolve with further liver regeneration. We were not concerned about the peak levels of aminotransferases at the time of admission, because it is well known that the magnitude of aminotransferase levels and their rate of decline do not affect the prognosis of ALF.

The neurological status of the patient at admission had no prognostic relevance because the patient was analgosedated. However, cranial CT showed brain oedema and Doppler sonography revealed decreased cerebral blood flow. Further neurological examination suspected cortical damage with missing brain N70-evoked potential; also electroencephalography was pathological. Missing N70-evoked potential is the result of either hypoxaemic brain injury, which is irreversible in most cases, or metabolic coma. Because of the prolonged hemorrhagic shock with consecutive multi-organ failure and low oxygenation that could have additionally worsened the hepatic coma, we admitted the possibility of irreversibility of the brain injury. Fortunately, the patient slowly began to react and communicate, and the next neurological examinations suggested slow progression towards recovery. This confirms the value of quick therapeutic intervention with a support system in the acute phase of liver failure with consecutive shock. MARS can clear toxins and mediators (IL-6, TNF-α) that are involved in shock and organ dysfunction and also increase albumin-binding sites for free unbound fractions of these molecules. This may diminish the progression of remote organ failure or even reverse it. Thus, quick intervention in the early stage may improve both the outcome and the quality of life of the patient after discharge from ICU.

Recently two randomised trials proved MARS to be beneficial in patients with hepatorenal syndrome and patients with cirrhosis with superimposed acute liver injury [12, 13]; however, randomised clinical trials in patients with ALF are still lacking and are needed for validation of this therapy in settings of ALF.

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