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Experience with liver dialysis in acetaminophen induced fulminant hepatic failure: A preliminary report

Asetaminofene bağlı fulminan karaciğer yetersizliğinde karaciğer dializi ile deneyim: Ön rapor

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Background!aims: *Our aim was to assess the efficacy of the liver dialysis unit (LDU) in the treatment of patients with acetaminophen-induced fulminant hepatic failure.* ***Methods:*** *Seventeen patients with acetaminophen-induced fulminant hepatic failure between January 1996 and December 2001 were retrospectively studied. A liver dialysis unit became available in our Unit in July 2000, and as of December 2001, four of these 17 patients had undergone treatment with liver dialysis.* ***Results:*** *Mean age was 29 years (range: 14-47) and 76% were women. Four of 17 patients underwent a total of 12 (range: 1-4) LDU sessions. Ammonia level tended to be lower following the LDU and all four patients recovered without a need for orthotopic liver transplantation (OLT). Prior to July 2000, eight of 13 patients survived with supportive therapy, three expired and two underwent OLT. No major bleeding episodes were observed during the LDU course. A significant difference was found between the three cases who died and the cases that survived with respect to the grade of encephalopathy ($p<0.001$). There was significant difference in the admission serum creatinine among survivors ($p<0.05$).* ***Conclusion:*** *In conclusion, the Liver Dialysis Unit treatment appeared to benefit patients with acetaminophen-induced fulminant hepatic failure by reverse of the encephalopathy and spontaneous recovery of the damaged liver in selected patients.*

Key words: Fulminant hepatic failure, acetaminophen toxicity, liver dialysis unit

Amaç: *Asetaminofene bağlı fulminan karaciğer yetersizliğinde karaciğer dializ ünitesi (KDÜ) tedavisinin etkinliğini değerlendirmek.* ***Yöntem:*** *Ocak 1996 ile Aralık 2001 yılları arasında asetaminofene bağlı fulminan karaciğer yetersizliğ gelişen 17 olgu retrospektif olarak incelendi. Bu olguların 4'üne karaciğer dializ ünitesinde tedavisi uygulandı.* ***Bulgular:*** *Olguların %75'i kadındı ve ortanca yaş 29 (sınırlar; 14-47 yıl)'du. Dört olguya total 12 (sınırlar; 1-4) seans karaciğer dializ ünitesi uygulandı. Amonyak düzeyi karaciğer dializ ünitesi sonrası düştü ve olguların hepside karaciğer transplantasyonu yapılmaksızın iyileşti, karaciğer dializ ünitesinin olmadığı dönemde (Temmuz 2000 öncesi) 13 fulminan karaciğer yetersizlikli olgunun 8'i destek tedavisi ile yaşarken, 3 olgu kaybedildi, 2 olguya ise karaciğer transplantasyonu yapılmak zorunda kalındı. Sağ kalımı etkileyen en önemli faktörler ise ensefalopatinin derecesi ($p<0.001$) ve serum kreatinin düzeyiydi ($p<0.05$).* ***Sonuç:*** *Karaciğer dializ ünitesi tedavisi asetaminofene bağlı fulminan karaciğer yetersizliğinde, seçilmiş hastalarda, ensefalopatiyi düzeltmekte ve karaciğerin spontan iyileşmesine imkan sağlamaktadır.*

Anahtar kelimeler: Fulminant karaciğer yetersizliği, asetaminofen zehirlenmesi, karaciğer diyalizi

INTRODUCTION

Acetaminophen is a universally available and used analgesic/antipyretic drug because of its efficacy and relative safety. However, large doses of acetaminophen might lead to fulminant hepatic failure (FHF) and death (1, 2). In developed countries, FHF most commonly occurs due to acetaminophen-induced hepatotoxicity and carries a grim prognosis with a high mortality rate (3-5). Recent developments in critical care management and early orthotopic liver transplantation (OLT) have improved the survival rate (6, 7). Although transplantation might be the only ultimate therapy for FHF, shortage of suitable donors has been the major obstacle. Other treatment modalities, such as artificial liver support systems, are being investigated to support the patient until a suitable organ is allocated or even better, until enough regeneration of the liver is achieved to sustain life (8, 9).

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Hemotherapies liver dialysis unit (LDU), an extracorporeal charcoal system, has been recently approved by the FDA to be used in cases with acetaminophen overdose. Outcomes of acetaminophen-induced FHF cases referred to our Liver Unit before and after LDU approval were evaluated.

MATERIALS AND METHODS

Seventeen patients with acetaminophen-induced FHF between January 1996-December 2001 were admitted to the Liver Intensive Care Unit, Nazih Zuhdi Transplantation Institute, Integris Baptist Medical Center, Oklahoma City, OK. Fulminant hepatic failure was defined according to the criteria of O'Grady et al[11]. Grade of encephalopathy at the time of admission was classified on a scale of 1 to 4[11]. Initial laboratory parameters studied on admission included complete blood cells (CBC), prothrombin time (PT) with INR, serum acetaminophen, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), pH and factor V levels.

All patients were managed with protein restriction in total parenteral nutrition (TPN) (40 gr/day), bowel decontamination, lactulose, and intravenous Ha-RA or proton pump inhibitors. N-acetylcysteine was given at a dose of 70 gr/kg (IV or via nasogastric tube) in all cases regardless of the time of initial ingestion, to complete a total of 14 doses. Prophylactic broad-spectrum anti-microbial agents were given intravenously until culture results became available. In cases with progression to grade III-IV encephalopathy, intracranial pressure (ICP) monitor was placed by the neurosurgeon. Cerebral perfusion pressure (GPP) was maintained above the 60-70mmHg range. Hyperventilation (pC02<30mmHg), total sedation with phenobarbital and/or propofol, mannitol 20% IV administration, and vasoconstrictive agents for the management of mean arterial pressure were used to maintain the CPP at the recommended range.

Total plasma exchange (TPE) was done to stabilize the coagulation profile and also to avoid the toxic effects of hyperbilirubinemia.

Liver dialysis was performed with Hemotherapies (San Diego, California) LDU, extracorporeal charcoal hemoperfusion system. It became available in the Liver Unit in July 2000 following its FDA approval during the previous year. It was used for four patients between July 2000 and December 2001, in an attempt to correct hyperammonemia as well as to remove toxic drugs (i.e. acetaminophen or its end products) in a timely fashion in order to be able to promote native liver regeneration. All had evidence of grade III-IV encephalopathy. LDU was performed with the addition of 50 grams of 25 % albumin into D5W prime and heparin protocol for anticoagulation with every 30 minutes ACT (activated clotting time) determination applied for the latter two cases. Orthotopic liver transplantation was offered to cases with biopsy demonstrated massive necrosis, in the absence of active extrahepatic infection and psychosocial contraindications. Preservation of neurological activity was documented by serial EEG studies and/or nuclear cerebral blood flow scans in indicated cases.

Written informed consent was given by LDU-treated patient's family, and details of the therapy were approved by the Ethical Committee of our hospital.

T test was used for statistical analysis.

RESULTS

Seventeen patients with acetaminophen-induced FHF (13 female, 4 male, mean age 29 ± 9.6, range: 14-47 years) were studied. The causes of acetaminophen overdose were suicidal attempts in nine, accidental in eight. Four l|ad, a history of alcoholism. Six of 17 had evidence of advanced encephalopathy (grade III-IV) on admission, while three patients with milder encephalopathy (grade II) progressed to grade III-IV during the hospitalization. Four of these patients with grade III-IV encephalopathy had undergone liver dialysis; a total of nine sessions lasting four to five hours per day, were completed. Range varied between one to four sessions depending on the clinical response. All four LDU patients had recovered without a need for OLT. Two of the other five patients with advanced encephalopathy between January 1996 and July 2000, survived with OLT, while three patients expired. Eight of 17 with grade II encephalopathy recovered with supportive treatment. No significant bleeding episodes were observed during the course of LDU, but patients had required plasma and platelet infusions to correct coagulopathy following treatment sessions. Ammonia level decreased following the LDU treatment ($p>0.05$). Although the difference did not reach statistical significance, neurologic sta-

Table I. Demographics of patients treated with liver dialysis unit (LDU) and outcomes

Patient	Age (yr)	Sex	Reason	pH	INR	Creatinine (mg/dl)	Encephalopathyt	LDU sessions	Outcome
1	26	F	suicidal	7.26	2.02	1	III	4	Spontaneous Recovery
2	41	F	accidental	7.32	2.2	1.4	IV	1	Spontaneous Recovery
3	34	M	suicidal	7.3	1.55	0.7	III	1	Spontaneous Recovery
4	22	F	suicidal	7.3	2.04	0.9	IV		Spontaneous Recovery

*creatinine, PH and INR level on admission t Grade of encephalopathy before LDU treatment

tus of all patients improved. At the same time, because of the small patient sample size, no correlation between survival and LDU treatment can yet be postulated. Demographics of patients treated with LDU and outcomes are shown in (Table 1).

A significant difference was found between the deceased and the cases that survived with respect to the grade of encephalopathy ($p<0.001$). All but one patient with grade IV encephalopathy expired. Creatinine level of more than 1.7 mg/dl was shown to be a poor prognostic indicator ($p=0.003$). There was no corresponding difference in the admission INR, serum ALT, AST, total bilirubin, pH and factor V among survivors (Table 2).

Table 2. Prognostic factors on admission in patients with acetaminophen-induced fulminant hepatic failure.

Parameters	Survivors n=14	Non-survivors n=3	I
Age (yr)	28.5	33.7	NS
Sex (F/M)	10/4	3/0	NS
Creatinine (<1.7 mg/dl)	14	3	<0.05
T. Bilirubin (mg/dl)	5	7.3	NS
Prothrombin time (INR)	3	5.4	NS
ALT (U/L)	5456	3300	NS
AST (U/L)	6330	4484	NS
Encephalopathy			
Grade II	11	-	<0.05
Grade III or IV	3	3	
TPE	14	2	NS
LDU	4	-	NS
Transplantation	2	-	NS

DISCUSSION

Acetaminophen overdose is a leading cause of FHF in developed countries (3). Spontaneous recovery is certainly the preferable outcome in FHF, thus avoiding the risk and expense of the transplantation itself and the lifelong requirement of immunosuppressive therapy. However, in the presence of poor prognostic signs, urgent OLT is the only option for successful treatment of FHF (6, 7). Because of universal shortage of donated organs, over 60% of such patients listed for OLT will expire while waiting for a donor organ. Several bridging techniques, such as artificial liver support devices, have been proposed to sustain patients until an organ becomes available or liver functions recovery naturally (9, 10).

Hemotherapies liver dialysis unit has been shown to provide metabolic and synthetic support, decrease serum ammonia levels and reverse neurologic dysfunctions (13-15). Four of 17 patients underwent treatment with LDU. Tendency for a subsequent decrease in serum ammonia level was found. The patients with LDU treatment demonstrated neurological improvement and clinical stabilization. Furthermore, all survived without a need for OLT. Eight of 13 patients without LDU treatment recovered naturally with only supportive treatment while three patients expired due to lack of organ allocation or other contraindications for OLT. The other two patients who underwent OLT survived.

The degree of encephalopathy was found to be a strong predictor of outcome. Among patients who presented with only grade II encephalopathy, spontaneous recovery was 73 %. Three patients with grade III or IV encephalopathy upon admission survived following LDU treatment while another three patients expired. Liver dialysis in patients with grade III or IV encephalopathy carried a positive effect on their neurological status and survival. Arterial pH, serum creatinine, PT and grade III or IV encephalopathy in aceta-

minophen-induced FHF were found to be the most important predictors for survival (10, 16).

Based on our results, the LDU appeared to serve as a bridge to OLT, as well as to remove toxic drugs in a timely fashion and therefore promote liver regeneration. However, no meaningful conclusion could be drawn regarding the effect of the LDU because of the small patient sample size. A controlled study of more patients is still needed.

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