Dear ladies and gentlemen, dear ADVOS users and interested parties,
we are pleased to present you another issue of our ADVOS Literature Service. We regularly select one or more papers from international journals which might be of interest to you in connection with our ADVOS procedure. This month we have selected the following:

APPLICABILITY AND SAFETY OF DISCONTINUOUS ADVANCED ORGAN SUPPORT (ADVOS) IN THE TREATMENT OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) OUTSIDE OF INTENSIVE CARE.

Kaps et al.

Key message

The current study explored the applicability and safety of the ADVOS multi as discontinuous treatment in a regular dialysis unit and compared the outcome of the ADVOS treatment in a case-control study with intermittent hemodialysis (HD) with matched ACLF patients.

The analyses support the results of previous publications showing the ADVOS treatment as a feasible and safe therapy in patients with multiple organ failure even in a discontinuous manner in a peripheral unit.

All treatments were well tolerated, and no therapy-related adverse events were recorded during ADVOS multi treatments.

Using a matched cohort with ACLF treated with hemodialysis, the ADVOS treatment achieved a stronger decrease in bilirubin ($p = 0.01$), while detoxification of water-soluble substances including creatinine and BUN was comparable.

Looking at the 28-day mortality, treatment with the ADVOS multi showed a lower (44% (11/25)) mortality compared to a treatment with HD (60% (15/25)). A trend for improved long-term survival was also observed.

Background

In acute-on-chronic liver failure (ACLF), additional (multi) organ failure occurs on top to acute decompensation of pre-existing chronic liver disease. It is a life-threatening condition (characterized by a high 28-day mortality) which might occur in patients with liver cirrhosis. It appears in up to 40% of the patients with decompensation and is more frequent in young patients. Liver transplantation remains the definitive treatment with a good outcome but is frequently not an option when e.g., alcohol abuse is continuing. Extracorporeal liver support systems help to remove toxins and metabolites and serve as a bridge therapy before liver transplantation.

The ADVanced Organ Support (ADVOS) therapy was developed to support liver function and recovery of patients with ACLF, in addition to lung, kidney, CO2 elimination and acid-base balance correction. Until now, only data from continuous ADVOS treatment in the intensive care unit (ICU) have been reported. Data related to the applicability and safety as discontinuous treatment outside of the ICU is not available. This is the first study to show this.

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Methods

A retrospective study evaluating the ADVOS multi as discontinuous treatment for patients suffering from ACLF outside of an intensive care unit was performed. From July 2018 to November 2020, patients were treated with the ADVOS multi on a normal ward at the Cirrhosis Center Mainz, University Medical Center Mainz, Germany. By chart review or from the local laboratory system, the medical history, dialysis parameter and laboratory data were collected.

Endpoints of the study were:

1. Applicability of the ADVOS multi as discontinuous treatment regarding patient safety in patients with ACLF in non-intensive care
2. The effect of the ADVOS treatment on standard laboratory parameters after cumulative 16 h of dialysis
3. Comparison of detoxification effect of ADVOS multi vs. HD
4. Comparison of 28-days mortality in the matched cohort

The detoxification effect between the ADVOS multi and regular HD was compared by using the markers creatinine, bilirubin and BUN (blood urea nitrogen). Laboratory data of the matched HD patients were gained from a local ACLF registry (136 patients).

The study was approved by the local ethics committee.

Results

Patients

Twenty-six patients with ACLF who received the ADVOS treatment were retrospectively studied. Main etiology of cirrhosis was excessive alcohol consumption (88%), while only 3 patients (12%) had a mixed etiology (HBV, alcohol or NASH). Infections (96%) were identified as the main trigger for decompensation. Baseline data are summarized in the table below. Since coagulation was compromised mirrored by median platelet count of 83 (IQR 60; 132) and median prothrombin time-INR of 2 (IQR 1.7; 2.4), citrate instead of heparin for anticoagulation was regularly applied during the ADVOS treatment.

Baseline characteristics of included patients with ACLF and HRS-AKI:

Patients, n	26*
Male, n (%)	17 (65.3)
Age (years), median (IQR)	53.5 (49; 57.75)
CLIF-C ACLF Score, median (IQR)	56.5 (51; 60), Grad I: 1, II: 14, III: 11
CLIF Organ Failure Score, median (IQR)	12 (11; 12)
Expected 28-days mortality according to CLIF C ACLF Score, median % (IQR)	44 (30; 59)

*In total, 25 matches were found based on the defined criteria, while statistical testing between the matched cohorts revealed no significant difference, indicating successful matching.

ADVOS treatments

As discontinuous treatment, patients received a median of 8 (IQR 7.25; 9.75) ADVOS cycles over the median period of 12 days (IQR 8.25; 17) on a peripheral ward. Median duration of the first two treatment cycles was 8 h (IQR 7; 8), adapted to the specific needs of each patient after the initial treatment cycles. The median blood flow rate was 150 ml/min (IQR 150; 150) and the median ultrafiltration rate was 150 ml/h (IQR 110; 250). No adverse events or alarming changes in laboratory parameter were documented at all.

Performance of the ADVOS therapy

BUN (-16.5, IQR -37.8; -3.5; p≤0.0001) was significantly reduced after cumulative 16 h of ADVOS dialysis, also bilirubin (-14.5%, IQR 8.3; 29.1) and creatinine (-11.8%, IQR -25.4;4.2).

Elimination of water- and protein-bound toxins after ADVOS treatment (cumulative 16 h):

	Before the ADVOS treatment	After the ADVOS treatment	p-value
Serum bilirubin (mg/dL)	23.4 (15.5; 30.75)	17.1 (11.75; 24.5)	0.034
Serum creatinine (mg/dL)	4.7 (3.9; 5.3)	3.4 (-6.7; 1.95)	0.04
BUN (mg/dL)	49 (44.3; 74)	33.5 (29.3; 42.3)	0.00012

Safety

Treatments were well tolerated, and no treatment related adverse events were documented during the ADVOS therapy. No bleeding events were observed despite primary and secondary hemostasis which were severely compromised (low platelet count and high prothrombin time-INR).

Outcome

The 28-days mortality of the matched cohort was analyzed between ADVOS multi vs. HD treated patients. In the ADVOS multi treated cohort 11 of 25 (44%) patients died, while 15 of 25 (60%) patients in the HD treated cohort did not survive (Figure 1). A trend towards an improved long-term mortality was also observed (Figure 2).

Figure 1:

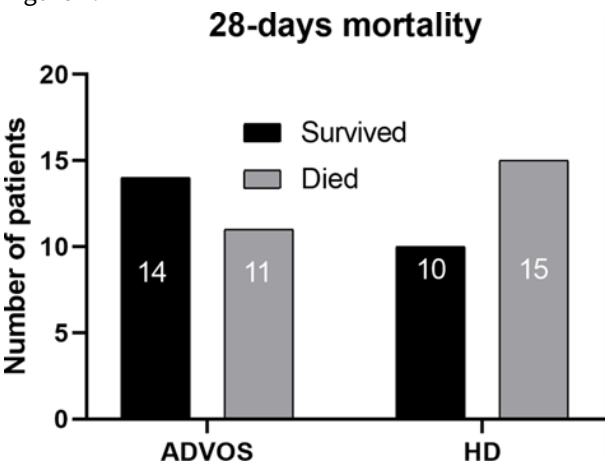
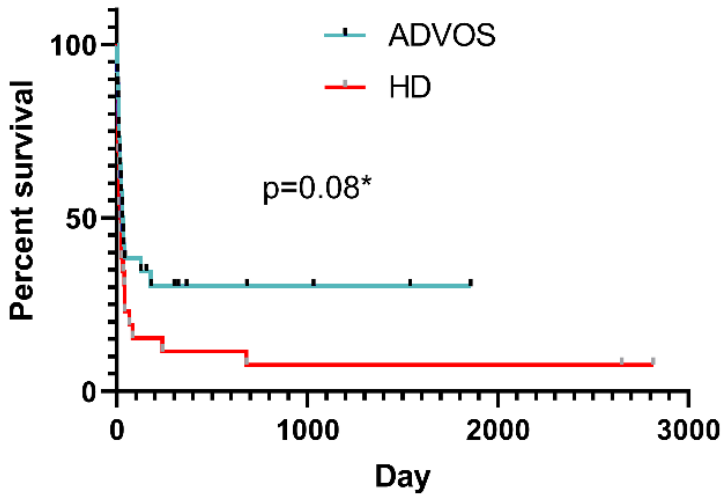


Figure 2:



The authors conclude:

For the first time, the authors show the feasibility and safety of the ADVOS therapy as a discontinuous treatment in patients with ACLF outside of an intensive care unit. Furthermore, Kaps and colleagues found a comparable detoxification effect of the ADVOS therapy as discontinuous dialysis compared to previous data, where the ADVOS treatment was performed in a continuous dialysis setting. They found that the ADVOS treatment was not inferior in 28-days morality compared to regular hemodialysis in patients with ACLF. Future randomized trials are needed to investigate its prognostic effect compared to regular HD.

We think that

First of all, we thank the authors for their great, valuable study supporting the efficacy and safety of the ADVOS multi.

After publication, the authors noticed some typing errors and sent a commentary to the journal including the corrections.
For the first time, they documented the application of the ADVOS multi in a discontinuous manner on a peripheral unit.

In their study, Kaps et al. included patients suffering from ACLF, HRS, AKI, multi organ failure (liver and kidney) and sepsis. ADVOS multi significantly reduced BUN (49 vs 33.5 mg/dl), creatinine (4.7 vs 3.4 mg/dl) and bilirubin (23.4 vs. 17.1 mg/dl). The reduction was even higher at higher bilirubin levels (>20 mg/dl).

Comparing the two matched cohorts (ADVOS treatment vs. hemodialysis), the ADVOS therapy achieved a greater decline in bilirubin ($p = 0.01$), while detoxification of water-soluble substances including BUN and creatinine were comparable. In addition, ADVOS multi was safe and feasible. No adverse events, even no bleeding, despite primary and secondary hemostasis, were severely compromised (low platelet count and high prothrombin time-INR).

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These results confirm previous studies from Huber and Fuhrmann. On the one hand, Huber et al. had a comparable study cohort as the authors from this study: mean MELD score of 34 (SD±7), age of 54 (SD±13) and 57% of men. Huber and his colleagues found that the ADVOS therapy reduced significantly mean bilirubin (-8.3 mg/dl SD±6.5), creatinine (-0.6 mg/dl SD±0.6) and BUN (-18 mg/dl SD±16) after a mean time of dialysis of 9.6 h (SD±3.2). On the other hand, Fuhrmann et al. reported a median removal rate with the ADVOS treatment of 17.0% for bilirubin, 7.1% for creatinine, 17.6% for BUN and 16.4% for ammonia. The reduction rate was concentration dependent and was higher during the first treatment.

The comparison of the ADVOS multi vs. HD showed a trend to a long-term survival benefit for patients treated with the ADVOS multi.

The authors showed no statistical significance due to the small number of patients. To detect a significant difference with enough power between ADVOS multi and HD a higher number of patients is necessary.

In conclusion, these results show that the ADVOS treatment is a versatile therapy that can be safely used in a continuous manner or as an intermittent therapy either in the ICU or a peripheral ward. The last generated evidence, including data from this study, data from Huber and Fuhrmann or the recently published EMOS-Registry shows a trend to improved mortality, which should be tested in upcoming studies.

If you have further questions or suggestions - please contact us at marketing@advitos.com.

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