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:

THE ROLE OF THE ADVANCED ORGAN SUPPORT (ADVOS) SYSTEM IN CRITICALLY ILL PATIENTS WITH MULTIPLE ORGAN FAILURE.

Acharya M, et al. Artif Organs. 2022 Feb 6. doi: 10.1111/aor.14188

Key Message

This review by Acharya et al. evaluates the scientific literature available regarding the ADVOS system by discussing its strengths, limitations, and future challenges.

In porcine models of acute liver injury (ALI) and in small clinical studies in humans the ADVOS therapy is able to:

- Significantly enhance the elimination of water-soluble and protein-bound toxins and metabolites, including creatinine, ammonia, blood urea nitrogen (BUN), and lactate.
- Improve cardiovascular parameters and renal function.
- Rapidly correct pH abnormalities, achieving normalization of CO_2, and bicarbonate levels.
- Rapidly correct acid-base imbalance and respiratory acidosis in patients with COVID-19.
- Reduce expected mortality in multiple organ failure (MOF).
- Show an adequate safety profile with minimal adverse events.

Background

The mortality rate of patients with MOF is high, despite the improvement in the management of critically ill patients. The term extracorporeal organ support (ECOS) describes all forms of therapies involving blood extraction and further processing in specifically designed circuits and devices. Multiple procedures for the support of individual organs, including those for renal replacement therapy and extracorporeal lung (e.g. ECMO - (extracorporeal membrane oxygenation) and liver support (e.g. SPAD - Single-Pass Albumin Dialysis, MARS - Molecular Adsorbents Recirculation System) are available.

The ADVanced Organ Support (ADVOS) haemodialysis system (ADVOS multi, ADVITOS GmbH, Munich, Germany) is indicated for patients with acute, chronic, and acute-on-chronic liver failure and/or renal failure. ADVOS multi integrates kidney, liver, and lung support in one single device. A recirculating and recyclable albumin enriched solution serves as the primary dialysate fluid and is intended to remove protein-bound toxins from the blood. In contrast to conventional dialysis procedures, the ADVOS therapy eliminates not only water-soluble substances (e.g. creatinine, urea, and ammonia), but also albumin-bound substances (e.g. bilirubin, bile acids, aromatic amino acids, copper) in addition to fluid-based CO_2 removal and acid-base balance correction.

ADVITOS GmbH
Agnes-Pockels-Bogen 1
D-80992 München

Telefon: +49 (89) 4111 842 00
Telefax: +49 (89) 4111 842 09
info@advitos.com
www.advitos.com

Amtsgericht München HRB 150 905
Geschäftsführer: PD Dr. Bernhard Kreymann
Beiratsvorsitzender: Mathias Klingler
USt-Id: DE 235056961

HypoVereinsbank München
IBAN: DE82700202700015487334
BIC: HYVEDEMMXXX

Methods

A literature search was performed using the PubMed database for the terms “Hepa Wash”, “Advanced Organ Support” and “ADVOS” to identify human and animal studies evaluating the ADVOS haemodialysis system. Peer-reviewed publications that have been indexed in PubMed were further discussed throughout this review.

Studies

Preclinical Studies

Study	Goal	Results	Conclusion
Al-Chalabi 2013 / 2017	Evaluation of the safety and efficiency of the ADVOS multi (former Hepa Wash) in a highly standardized porcine model of Acute Liver Failure (ALF) and cholestatic liver injury	Stabilization of cardiovascular, respiratory, and renal parameters Elimination of bilirubin (5.5 vs. 2.3 mg/dl, p = 0.001) and creatinine (1.4 vs. 2.3 mg/dl, p = 0.01)	Promising safety and efficacy profile Improved survival in a sepsis-like animal model with dysfunction of multiple organs
Perez 2019	Ability of the ADVOS therapy to eliminate CO_2 and to correct blood pH was investigated in an ex vivo model of either lactic or hypercapnic acidosis, using porcine blood and a continuous supply of lactic acid and/or CO_2, respectively	61 ml/min (2.7 mmol/min) of CO_2 removed at 400 ml/min blood flow and a dialysate pH of 10 without altering blood pCO_2 (36 mmHg) and HCO_3^- (20 mmol/l) If elevated pCO_2 (117 mmHg) and HCO_3^- (63 mmol/l) were allowed, up to 142 ml/min (6.3 mmol/min) of CO_2 can be removed Up to 3 mmol/min acid load compensated during continuous lactic acid infusion Normalization of pH and bicarbonate within 1 hour when acidosis was triggered. Neither CVVH (Continuous Veno-Venous Haemofiltration) nor CVVHD (Continuous Veno-Venous Haemodialysis) were able to do this.	Proof of concept for CO_2 removal Removal of 50% of the amount of CO_2 typically produced by an adult human

Clinical Trials and Case Series

Study	Goal	Results	Conclusion
Huber 2017	Evaluation of feasibility, efficacy, and safety of the ADVOS therapy	32% bilirubin removal (26.0 vs. 17.7 mg/dl, p = 0.001) 27% creatinine removal (2,2 vs. 1.6 mg/dl, p = 0.005) 37% BUN removal (49.4 vs. 31.1 mg/dl, p = 0.003)	Feasibility of the therapy in critically ill patients proved Removal of water-soluble and albumin-bound substances
Fuhrmann 2020	First clinical data of patients with multiple organ failure treated with the ADVOS device	Significant reductions in bilirubin (-17.0%), creatinine (-7.1%), BUN (-17.6%) and ammonia (-16.4%) Significant improvements in blood pH, HCO_3^-, and $PaCO_2$ in six patients with severe metabolic acidosis refractory to renal replacement therapy and progressive MOF Normalization of blood pH in a median of 6 h	Removal of water-soluble and albumin-bound substances Correction of acid-base imbalances Removal of CO_2 Improvement of haemodynamic status in patients with liver failure, septic shock, or ARDS in need of extracorporeal support
Kaps 2021	Applicability and safety of ADVOS multi as discontinuous treatment in a regular dialysis unit Matched cohort analysis comparing ADVOS multi with intermittent haemodialysis (HD) in ACLF (Acute-on-chronic liver failure) patients (case-control study)	Reduction of BUN (-16.5%), bilirubin (-14.5%) and creatinine (-11.8%) Improvement in 28-days mortality rate (ADVOS 44% vs. Haemodialysis 60%)	Feasibility and safety of ADVOS therapy as discontinuous treatment in patients with ACLF outside an intensive care unit Comparable detoxification effect of ADVOS multi as discontinuous vs. continuous dialysis Improved 28-day mortality compared to regular haemodialysis in patients with ACLF

Fuhrmann 2021	Collection of data on real-life treatment conditions for patients for whom multiple organ dialysis with ADVOS is indicated.	Significant reduction in creatinine (1.5 vs. 1.2mg/dl), BUN (24 vs. 17mg/dl) and bilirubin (6.9 vs 6.5mg/dl) Blood pH, HCO_3^- and base excess returned to the physiological range 28- and 90-day mortality were 60% and 65%, respectively, compared to an expected ICU-mortality rate of 80%	Elimination of water-soluble and albumin-bound substances No major adverse events associated with the ADVOS treatments were observed

COVID-19 Studies

Study	Goal	Results	Conclusion
Allescher 2021	Evaluation of the ADVOS system as treatment option in predominantly old-age-COVID-19 patients with multi-organ failure and CO_2 removal	Rapid correction of acid-base balance and a continuous CO_2 removal Significant removal of water-soluble substances (i.e. creatinine 1.5 vs. 0.8 mg/dl and BUN 30 vs. 11 mg/dl) Significant improvement in blood pH (7.26 vs. 7.41), serum bicarbonate and base excess Median continuous CO_2 removal of 49.2 ml/min with some treatments achieving up to 160 ml/min CO_2 removal correlated with blood flow (Pearson 0.421; $p < 0.001$), $PaCO_2$ (0.341, $p < 0.001$) and HCO_3- levels (0.568, $p < 0.001$)	Feasibility to remove CO_2 in COVID-19 patients with ARDS and MOF Efficient removal of CO_2 at low blood flows up to 300 ml/min using a conventional haemodialysis catheter and without a membrane lung or a gas phase Acid-base balance correction and creatinine and BUN levels decrease within the first treatment

Non-Powered Comparative Retrospective Cohorts

Study	Goal	Results	Conclusion
Falkensteiner 2021	Comparison of MARS and ADVOS therapy in 49 critically ill patients with liver failure undergoing 75 MARS and 58 ADVOS cycles	Similar clearance rates of bilirubin (MARS: -13% vs. ADVOS: -15%) Similar removal rates of creatinine (MARS: -18% vs. ADVOS: -18%) Greater relative reduction in urea with ADVOS (MARS: -6%; ADVOS: -21%, p = 0.01)	Comparable detoxification capabilities in regard of water-soluble and protein-bound substances of MARS and ADVOS therapy in critically ill patients with liver dysfunction
Scharf 2021	Effectiveness of ADVOS therapy and CytoSorb (CS), particularly with respect to total bilirubin elimination was evaluated and compared	Similar clearance rates of bilirubin (CS: 22:5% vs. ADVOS: 22.8%) In-hospital mortality CS: 84.8% (28/33) vs. ADVOS: 66.7% (4/6)	The use of ADVOS therapy and CytoSorb led to a significant and comparable decrease in bilirubin in critically ill patients Further conclusions are subject to bias due to the low number of patients

Commentary

- The studies mentioned above show the feasibility and safety of the ADVOS therapy as a treatment option for patients with MOF as well as patients with COVID-19.
- Integration of multiple organ support systems into one single device
- Efficient detoxification characteristics: Elimination of water-soluble and protein-bound toxins and metabolites, at least at the same level as the state-of-the-art therapies, such as RRT (Renal Replacement Therapy) or MARS.
- Important clinical advantage: Possibility to correct metabolic and respiratory acidosis through the fluid-based direct removal of acid and CO_2
- Less invasive supportive strategy
- Well-tolerated with a minimized side effect profile.
- Significant improvements in haemodynamic and biochemical parameters.
- Tendency towards reduced mortality rates compared to those expected in critically ill populations.
- Larger randomized trials are necessary to further validate the encouraging results.
- Future work should focus on concretising the surrogate markers where the ADVOS therapy could be beneficial, especially in the target groups of patients for the therapy. The ADVOS procedure has been mainly applied in patients with liver failure needing dialysis in German university hospitals. The reimbursement of healthcare institutions utilizing the ADVOS therapy as a liver support system could enhance its adoption across more widespread geographical locations.

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

ADVITOS GmbH
Agnes-Pockels-Bogen 1
D-80992 München

Telefon: +49 (89) 4111 842 00
Telefax: +49 (89) 4111 842 09
info@advitos.com
www.advitos.com

Amtsgericht München HRB 150 905
Geschäftsführer: PD Dr. Bernhard Kreymann
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HypoVereinsbank München
IBAN: DE82700202700015487334
BIC: HYVEDEMMXXX