Trial Description

Title

ECLS-Therapy in HIT II patients – safety of Argatroban- vs Heparine therapy: ECMO-SAvHE - Study

Trial Acronym

ECMOSAvHe

URL of the trial

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Brief Summary in Lay Language

The ECMOSAvHe trial observes patients that need artificial organ assist for their lung (veno-venous extra corporal live support, vv-ECLS) or their heart and lung (veno-arterial extra corporal live support, va-ECLS) during their courses on intensive care units. Both ECLS systems provide a wide contact between an artificial surface and the blood oft he patient. Coagulation therefore is strongly induced and each patient needs anticoagulation therapy to prevent coagualtion and ECLS-failure.In patients that do not suffer from heparin allergy heparin therapy is initiated. Patients who show an allergic reaction towards heparin (heparin induced thrombocytopenia, HIT II) receive Argatroban. Both therapeutic strategys are standardized on intensive care units. During this trial we observe 200 patients during their therapeutic course without and trial-associated intervention regarding non inferiority of Heparin therapy versus Argatroban therapy in respect of coagulation, bleeding, patient survival and therapeutic controllability of both agents.

Brief Summary in Scientific Language

Pulmonary, cardiac, and hemodynamic failure may induce shock. Some patients require veno-venous or veno-arterial extra corporal life support (ECLS) for stabilization. These patients represent a group of high risk individuals with accelerated risk of SIRS, sepsis, organ and multi-organ failure and overall high mortality. The intensified contact of the blood with external surfaces within the ECMO and, in particular, the integrated oxygenator makes anticoagulation indispensable in these patients. Common therapeutic regimes use administration of heparin with control of PTT and / or ACT. During mechanical ECLS support and medical therapy, loss of thrombocytes is frequently evident. Heparin-induced thrombocytopenia type II (HIT II) is common in this group of patients which has been treated with heparin before in almost 100% of cases Antibodies to heparin platelet factor 4 (PF4) bind complexes and lead to disseminated coagulopathy accordingly. Mortality of this complication is described is described in as many as 10-30% of cases.
In the case of clinical suspicion, conversion of heparin therapy into a direct thrombin antagonist, Argatroban, is performed in clinical routine. Complete termination of anticoagulation would lead to thrombosis in 40-50% of patients who are not ECLS-treated but almost 100% of ECLS-treated patients. A short

elimination half-life of 45 min and a hepatic metabolism makes Argatroban therapy feasible for patients with renal dysfunction. Argatroban positively influences the outcome of patients with suspected or confirmed HIT II, but there are currently only individual case reports and meta-analyzes of these on the therapy of patients on ECLS support. Argatroban itself is permitted in the intensive medical treatment of critically ill patients and especially in patients undergoing heart surgery. For this purpose, special dosage recommendations are given in the specialist information, which are implemented in daily intensive medical regimens. The aim of this project is to investigate the safety of Argatroban therapy in ECLS patients with regard to effectiveness of anticoagulation on the one hand and bleeding complications on the other hand. The data required for this purpose are to be collected in a non-interventional observational study in a multi-centered prospective manner over a period of at least 2 years. Recruitment of participants relies on an all-comers-design. The therapeutic course according to the clinical routine decision is documented. Therapeutic decisions are not taken (non-interventional). A daily study visit for documentation will be established. ECLS patients of the participating study centers are regularly treated with heparin. If HIT II is suspected, Argatroban therapy is routinely implemented according to the specialist information for critically ill patients after heart surgery. The therapy is controlled by means of PTT measurements and bedside ACT measurements, in which the aPTT is to be raised to 1.5-3.0, but not more than 100 seconds. Each ECLS patient is included in the observation. Discrimination in the study arms with / without heparin / Argatroban is based solely on the clinical decision of the treating physicians. Since regular therapy in all patients is treatment with heparin, initially all patients belong to study arm 1: "ECLS-heparin". If treatment is switched to Argatroban, the study arm for this corresponding patient will be transferred to study arm 2: ECLS-Argatroban. Analysis of study arm 2 will be performed post-hoc in groups 2a: "ECLS-Argatroban - HIT II detected", and 2b: "ECLS-Argatroban - HIT II suspected but not detected". In participating study centers, patients are treated with veno venous as well as with veno-arterial support. Since both systems address different diagnoses and patient groups, both ECLS system arms should be observed separately with respective study arms 1 and 2. Patients are screened for parameters of coagulation, bleeding complications, metabolic situation, therapy control and system integrity (demanded oxygenator exchange, ECLS system change or change of dialysis membranes), system functionality (oxygenation / decarboxylation properties, pressure behavior). For this purpose, routine laboratory examinations and medical measuring points are documented during the clinical course. Data on patient survival is collected at the time of discharge and 1 year after therapy by means of telephone interviews. The measurements of the pressure conditions at the oxygenators of the respective ECLS give indirect indication of a possible degree of thrombosis and possibly an indication for the change of the oxygenators. For the morphological quantification, we are planning a radiological examination of the oxygenators after flushing with contrast media in order to determine the proportion of thrombus volume / total volume. In addition to this examination, a volume determination of the total oxygenator volume is carried out by means of a recirculation measurement. The course data of this study, the radiological-morphological data and the pressure examinations are to be investigated with regard to a correlation.
The aim of this study therefore is:
1) Proof of safety of anti-coagulation therapy by direct thrombin inhibition and/or heparin on ECLS support
2) Non-inferiority analysis Argatroban vs. Heparin during ECLS support (coagulation / bleeding)
3) Proof of principal for technical safety during Argatroban therapy (oxygen-thrombosis, pressure conditions as non-inferiority design)

4) Examination of the thrombus load of ECLS oxygenators (CT scan after expansion)
5) Analysis of the peri-procedural and long-term outcome of the patients

Organizational Data

- DRKS-ID: **DRKS00011416**
- Date of Registration in DRKS: **2018/01/08**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **192/16 , Ethik-Kommission des Fachbereichs Medizin der Justus-Liebig-Universität Gießen**

Secondary IDs

Health condition or Problem studied

- ICD10: **R57.0 - Cardiogenic shock**
- ICD10: **J80 - Adult respiratory distress syndrome**

Interventions/Observational Groups

- Arm 1: **standard Therapy (state of the art) . Each patient starts with Heparine ACT (goal:180 -200 sec) or PTT (60-80 sec) while patient on ECLS support**
- Arm 2: **Patients (started with Heparine) in case of suspected or proven HIT change to Argatroban therapy ACT (goal:180 -200 sec) or PTT (60-80 sec) while patient on ECLS support**

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Other**
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**
- Purpose: **Basic research/physiological study**

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Blinding: **[---]***

Who is blinded: **[---]***

Control: **Active control (effective treament of control group)**

Purpose: **Basic research/physiological study**

- Assignment: **Other**
- Phase: **IV**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **No**

Primary Outcome

The primary endpoint of the study is the non-sublimity of Argatroban therapy for anticoagulation and bleeding complications and thromboses.

Hypothesis:
Heparin and Argatroban therapy does not result in a significantly different number of thrombosis + bleeding complications.

Thrombus : any observed thrombus or thrombembolic event during the therapeutic course (echocardiography, caranial/thoracic/abdomonal/CT-Scans), angiographic diagnosis, neurological ischemic events, thrombembolic events, ECLS tubing /oxygenator thrombosis, CT-analysis post oxygenator change / post ECLS-support

Bleeding: every bleeding complication leading to therapeutic medical intervention , re-operation, each morphological evidence of hematoma associated compartment syndrome, all bleeding associated neurological deficits, need of transfusion of red blood cells / and or thrombocytes greater than Mean + 1.5 SD.

Secondary Outcome

1) Both therapies show no variances in coagulation, bleeding, embolization or controllability (combined endpoint)
2) The number and function of thrombocytes is recovered in ECLS-HIT II patients with direct thrombin inhibition (combined endpoint)
3) The therapeutic range is achieved by argatroban and heparin in a comparable time
4) The pressure ratios and gradients on the oxygenators of the ECMO are not differently influenced by heparin or thrombin inhibition (combined endpoint)
5) The pressure relationships show a correlation to morphologic thrombus volume (CT scans).
6) The mortality of the patients is not influenced by the type of anticoagulation. Times: discharge, 1 year postoperatively
7) The frequency of the filter change does not differ between the two groups when hemodialysis / haemofiltration is added to the ECLS.
8) The thrombus load of changed oxygenators is not different in the groups (CT

scans, pilot examination)
9) No accumulation of multi-organ failure occurs in any of the groups.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Universitätsklinikum Giessen und Marburg, Klinik für Herz-, Kinderherz- und Gefäßchirurgie,, Giessen**
- University Medical Center **Klinik für Thorax-, Herz- und Thorakale Gefäßchirurgie, Frankfurt a.M.**
- University Medical Center **Klinik für Herz-, Thorax- und Gefäßchirurgie, Mainz**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/01/03**
- Target Sample Size: **200**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **120 Years**

Additional Inclusion Criteria

1) all patients on veno-venous ECLS support (app. 30 % of patients)
2) all patients on veno-arterial ECLS support (app. 70 % of patients)

Exclusion criteria

non adult patients
pregnancy
hepatic insufficiency CHILD B/C
non-consent
severe cognitive deficite
foreign language / translation problem (telephone interview)

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

■ **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

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Willstätter Strasse 30
40549 Düsseldorf
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■ **Institutional budget, no external funding (budget of sponsor/PI)**

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Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*