Trial Description

Title

Remote Ischemic Preconditioning (RIPC) versus sham-control for reduction of ischemia-reperfusion injury of the Liver after liver surgery in patients with pre-damaged liver: a prospective, randomized controlled, triple-blind, clinical phase III monocenter trial

Trial Acronym

RIPL

URL of the trial

http://no website available

Brief Summary in Lay Language

Ischemia-reperfusion injury of the liver is a dreaded complication after liver surgery. For example, ischemia (reduced perfusion of an organ or tissue) occurs when, during the surgical removal of liver tissue, the blood supply to the liver is temporarily stopped in order to reduce blood loss (the so-called Pringle maneuver). Once the blood supply is restored and the liver is reperfused, this can also lead to liver damage. There is still an urgent need for methods to minimize organ damage through ischemia-reperfusion injury. "Remote ischemic preconditioning" (RIPC) is a novel approach in which a short amount of hypoperfusion is given away from the target organ (e.g., intestine or liver) e.g. by inflating a blood pressure cuff on an arm for 5 minutes). As a result, bodily substances, which mediate a complex control loop that protects against damage from reduced blood flow to the target organ. Numerous studies have demonstrated this protective effect for RIPC in various organs (e.g., brain, heart, kidney, liver).
Pre-damaged liver parenchyma (in fibrosis, steatosis, cirrhosis, or after chemotherapy) is particularly vulnerable to injury from intraoperative ischemia. The fact that RIPC has a protective effect on ischemic liver damage is already known: relevant reduction rates of transaminase levels, in particular AST (aspartate aminotransferase), have been described in the literature. The transaminases are liver enzymes and markers for liver cell injury and accordingly increase in ischemic liver damage. The extent to which RIPC has a protective effect, especially in patients with pre-existing liver damage, is still unclear. On the basis of the existing evidence, the present study was designed, based on the assumption that the protective effect of RIPC in patients with a pre-damaged liver reduces the postoperative transaminase values at least by 10% compared to the control group.

During the 30-day follow-up period, the following outcomes will be assessed: surgical complications, reinterventions, hospital stay, readmission. A positive study outcome would be of high patient and clinical relevance due to the serious effects of liver damage.

Brief Summary in Scientific Language

"Remote ischemic preconditioning" (RIPC) is an innovative approach that differs from other preconditioning strategies in that the ischemic stimulus (by inflating a blood pressure cuff on one extremity) is performed remotely from the target organ. As a result, several cytokines, are released, which protect the target organ against ischemic damage via a complex control loop. RIPC induces the release of serotonin from platelets, which stimulates VEGF secretion, which in turn up-regulates the release of IL10 and Mmp8 in the target organs. Pre-damaged liver parenchyma (in fibrosis, steatosis, cirrhosis, or after chemotherapy) is particularly vulnerable to injury from intraoperative ischemia (i.e. by temporarily stopping the blood supply to the liver during the Pringle maneuver). The fact that RIPC has a protective effect on ischemic liver damage is already known: in the literature, reduction rates of transaminase values on postoperative day 1, in particular AST (aspartate aminotransferase), of 50% compared to the control group without RIPC have been described. ALAT (alanine-aminotransferase) values were similarly reduced by 41% (e.g. Kanoria S et al. (2017) Effect of Remote Ischaemic Preconditioning on Liver Injury in Patients Undergoing Major Hepatectomy for Colorectal Liver Metastasis: A Pilot Randomised Controlled Feasibility Trial. World J Surg 41 (5):1322-1330.). The extent to which RIPC has a protective effect, especially in patients with liver damage, is still unclear. However, in a study by Clavien et al. in which ischemic preconditioning was performed by clamping the portal triad (portal vein, hepatic artery, bile duct) (thus no "remote" character of the intervention), a subgroup analysis of only 7 patients with hepatic steatosis showed an even greater protective effect of IPC with regard to the prevention of liver damage: in patients with hepatic steatosis, the ASAT level on postoperative day 1 was even reduced by 73% compared to the control group without IPC (Clavien PA et al. (2000) Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans Ann Surg 232 (2): 155-162). On the basis of the above cited data, the present study was designed, based on the assumption that the protective effect of RIPC in patients with a pre-damaged liver reduces the postoperative transaminase values at least by 10% compared to the control group.

Do you plan to share individual participant data with other researchers?

No

Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00018931**
- Date of Registration in DRKS: **2019/11/22**
- 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.: **2019-729N , Medizinische Ethik-Kommission II Medizinische Fakultät Mannheim der Universität Heidelberg**

Secondary IDs

Health condition or Problem studied

- ICD10: **K74.6 - Other and unspecified cirrhosis of liver**
- ICD10: **K72.0 - Acute and subacute hepatic failure**

Interventions/Observational Groups

- Arm 1: **Experimental Arm/ Study Intervention: In RIPC, a blood pressure cuff is placed around an arm immediately prior to surgery (after induction of anesthesia and before/ during incision/dissection) and inflated to 200 mmHg or a pressure ≥50 mmHg above systolic pressure for 5 minutes (= limb ischemia). This corresponds to the ischemic stimulus distant from the target organ and is followed by a 5-min break (= limb reperfusion). The whole schedule is performed three times for a total of three 10-min cycles (= 30 min/patient).**
- Arm 2: **Control Arm/ "sham"-RIPC: In "sham"-RIPC, a blood pressure cuff is placed around an arm immediately prior to surgery (after induction of anesthesia and before/ during incision/dissection), but NOT inflated. This is followed by a 5-min break. The whole schedule is performed three times for a total of three 10-min cycles (= 30 min/patient).**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, investigator/therapist, assessor, data analyst**
- Control: **Placebo**
- Purpose: **Prevention**
- Assignment: **Parallel**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

The primary endpoint is the level of the serum transaminases (alanine aminotransferase, ALAT, and aspartate aminotransferase, ASAT) on the first postoperative day (= POD 1). These blood samples are all routinely taken, as predetermined in the clinic's own pathway for liver resections, and therefore do not constitute study-related measures.

Secondary Outcome

Secondary endpoints are: complications according to Clavien Dindo, reinterventions, hospital stay, and readmission. Moreover, effects of RIPC on biomarkers of ischemia-reperfusion injury (serotonin, VEGF) and necrotic cell death (Hmgb1) will be measured in plasma before RIPC (t0), immediately after RIPC (t1), and at 3 hours after RIPC (t2) using ELISA.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Chirurgische Klinik, Mannheim**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2019/12/02**
- Target Sample Size: **102**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Persons meeting the following criteria may be included in the study:
• Known pre-damage to the liver (e.g. liver cirrhosis (Child Pugh A and B), steatosis, fibrosis, s/p chemotherapy, other pathologies leading to liver damage)
• Planned elective liver resection or dissection of the liver tissue (so-called "in situ split") with subsequent resection
• Signed informed consent
• Age ≥18 years

Exclusion criteria

Persons meeting any of the following criteria cannot be included in the study:
• Patients not able to give informed consent

• Liver cirrhosis Child Pugh C
• Patients presenting with the following contraindications to the study intervention (RIPC): arterial occlusive disease (AOD), infections or wounds on the upper extremity, poorly controlled diabetes mellitus, or deep vein thrombosis of the upper extremity
• Patients in whom a Pringle maneuver is unlikely due to the type of procedure or extent of resection (e.g. very small and/or peripheral resections)

Addresses

■ **Primary Sponsor**

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■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

- **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.*