Reperfusion-induced self-antigen excretion (RISE) following major liver resection

Published: 25-10-2012
Last updated: 26-04-2024

To investigate the release of damage-associated molecular patterns (DAMPs) following major hepatic resection with or without VIO and to correlate the outcomes to the acute inflammatory response and clinical parameters for hepatocellular damage.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON39718

Source
ToetsingOnline

Brief title
RISE study

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
Hepatic ischemia-reperfusion injury, postoperative liver injury

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Damage-associated molecular patterns, Ischemia-reperfusion injury, Sterile inflammation

Outcome measures

Primary outcome

The primary endpoint of this study is defined as the effect of I/R on the

release of DAMPs (i.e., High mobility group protein B1, mitochondrial DNA, and

histones), measured in the systemic circulation.

Secondary outcome

Secondary parameters constitute the expression of acute inflammatory response

genes, AST, ALT, total bilirubin, and INR.

Study description

Background summary

Major liver surgery often requires the surgeon to temporarily halt the afferent blood flow in order to prevent excessive blood loss. Vascular inflow occlusion (VIO) however predisposes the liver to a detrimental inflammatory response once the circulation is restored. Altogether, the ramifications that result from this temporary withdrawal of oxygen supply are known as ischemia and reperfusion (I/R) injury, and the extent to which this occurs determines the functional outcome of the liver after surgery. Recently, it has become clear that (over)activation of the immune system forms the mainstay of hepatic I/R injury. More importantly, it has been shown in animal models that endogenous self-antigens, known as damage-associated molecular patterns (DAMPs), are released from stressed liver cells in the earliest stages of reperfusion and, as such, form the most proximal triggers of hepatic I/R injury. Clinical data on DAMP release following hepatic I/R are however scarce to date. Therefore, the aim of this study is to investigate DAMP release in patients that undergo a major liver resection with or without VIO and to correlate the results to the expression of acute-phase inflammatory response genes and routine clinical parameters for hepatocellular damage.

Study objective

To investigate the release of damage-associated molecular patterns (DAMPs) following major hepatic resection with or without VIO and to correlate the outcomes to the acute inflammatory response and clinical parameters for hepatocellular damage.

Study design

The study is designed as an observational study. Because the decision to apply VIO is often made during surgery, patients will be allocated to a group postoperatively. Therefore, the inclusion of subjects in this study will continue until the calculated sample size of n=30 patients has been reached for the VIO group and n=15 patients for the control group. As approximately 65% of all major liver resections are performed under VIO, this distribution of subjects is in accordance with the clinical practice. However, since about 40% of patients are diagnosed with irresectable disease at the time of surgery we estimate that a maximum of 75 patients will need to be included in this study.

Blood will be drawn preoperatively as well as at 1 and 6 hours of reperfusion/post resection. At all time points, samples will be derived from the central venous line that is in place in all patients undergoing a liver resection. Also, two biopsies will be taken from the future remnant liver during the operation (i.e. one biopsy before resection and one biopsy at 30 min of reperfusion/post resection). A third biopsy from the part of the liver that is to be resected is taken as part of the side-study.
Furthermore, clinical parameters for hepatocellular damage (i.e., AST and ALT) and liver function (i.e., total bilirubin and INR) that are determined as part of the standard perioperative care will be used for this study.

Study burden and risks

Considering that all blood samples are derived from the central venous line that is in place in all patients undergoing a liver resection, this will carry no additional risk. Moreover, the first two samples will be taken in the operating room when patients are under general anesthesia. The biopsies, however, carry a risk of bleeding, albeit this procedure is carried out under direct vision of the surgeon, which means that any bleeding site can be immediately controlled.
Notably, the potential benefits of this study are substantial. Currently, DAMP release is considered to be a cardinal early event in I/R injury as well as a possible target for future interventions. However, systemic concentrations of DAMPs as well as their correlation to clinical outcomes have not yet been determined in a clinical setting of warm hepatic I/R.
In addition, the side study will supply novel information regarding gene expression profiles in cholestatic versus non-cholestatic liver tissue. The outcomes thereof could shed new light on the pathophysiology of cholestasis, which is expected to be of relevance for the surgical as well as hepatological

field of practice.
Lastly, both studies aims to do obtain data in a minimally invasive setting that will impose no significant burden on patients participating in this study.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Malignant or benign hepatic tumor, scheduled for major liver resection (i.e., 3 or more liver segments), ASA I-III, minimum age 18 years

Exclusion criteria

Vascular inflow occlusion less than 20 minutes, age under 18 years, emergency operation, pregnancy or breast feeding

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-01-2013
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	25-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2014
Application type:	Amendment

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01700660
CCMO	NL41737.018.12