Consequences of liver surgery for liver function and cell injury

Published: 14-05-2007
Last updated: 20-05-2024

1 Primary Objective To investigate the effects of 15* liver ischemia versus 30* liver ischemia on liver injury and liver function.To investigate the effect of liver manipulation during mobilisation for a right hemihepatectomy, that can be used as a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON30540

Source
ToetsingOnline

Brief title
Liver surgery

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
liver metastases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ischemia reperfusion, liver function, liver surgery

Outcome measures

Primary outcome

As the primary endpoint, we will look at plasma levels of novel markers of liver damage, such as ophthalmic acid and Liver - Fatty Acid Binding Protein (L-FABP), as well as more traditional markers such as ASAT, ALAT.

We will compare the alanin aminotransferase (ALAT) and aspartate aminotransferase (ASAT) plasma levels between the three groups. ASAT and ALAT are commonly used and accepted as parameters for liver cell injury and will be used as the gold standard in this study. However ASAT and ALAT are crude estimates of liver cell injury because they are gradually and slowly released from injured cells and remain in the circulation for a long period. Esaki (5) et al concluded that there was no clinically relevant difference in the bilirubin ratio and ASAT/ ALAT levels on the second post operative day between two groups of patients that underwent a period of 15* or 30* minutes liver ischemia. In this study the aim is to investigate the effects of 15* liver ischemia versus 30* liver ischemia using more sophisticated markers of liver injury and liver function such as L-FABP and Ophthalmic acid.
L-FABP plasma levels are currently arising as more sensitive and specific plasma markers for hepatic injury. L-FABP*s are small and cystolic proteins which after leakage from injured cells have a short plasma half-life. The L-FABP plasma level is a good liver injury marker because it possesses liver

tissue-specificity and its molecular weight is low by which it can be released from injured liver cells in an early stage and in significant amounts.

During liver surgery (resection, transplantation) the liver is exposed to oxidative stress during the phase of temporary clamping of the portal vein and hepatic artery. Ischemia is typically characterized by ATP depletion and necrotic cell death. Upon reperfusion a multifactorial process leading to apoptotic cell death is initiated that further aggravates cell injury already initiated by plain ischemia. An important factor in this process is the formation of large quantities of reactive oxygen species (ROS) immediately after reperfusion. This so-called oxidative burst may induce per-oxidation of membrane phospholipids and intracellular proteins, triggering a cascade leading to caspase activation and apoptotic cell death. Oxidative injury can be limited by one of the most important intracellular anti-oxidants in human cells in quantitative terms, the antioxidant gluthathione. Glutathione (GSH γ-glutamyl-cysteinyl-glycine) is a tripeptide, which is synthesized from glutamate, glycine, and cysteine. GSH contains a sulfhydryl group which can reduce ROS upon oxidation to glutathione disulfide (GSSG). Information about the glutathione synthesis rate and capacity in the perioperative phase is very important in order to protect a patient against ischemia reperfusion damage (which can also occur during e. g. aorta surgery). In vivo measurements of glutathion synthesis in human are complex and attempts to use stable isotopes in order to clarify this, also our group, have led to data that are difficult to interpret and not easy to reproduce. Recently it has been suggested that tissue and plasma ophthalmic acid can be an *alternative read-out* for hepatic

glutathione synthesis. Ophthalmate is an analog of GSH and has the same pathway of synthesis as GSH. However when GSH levels are decreased during conditions of higher oxidative stress because of a persistent oxidative load which leads to an acceleration of hepatic depletion that is not matched by an equal increase of GSH synthesis, the ophthalmic acid level increases (reciproke *read out* see figure 2). Ophthalmate is not an antioxidant, can not conjugate with free radicals and will be effluxed to the circulation.

Recently Soga et al (8) found that in mice with acetaminophen-induced hepatotoxicity, activation of the ophthalmic acid biosynthesis pathway occurs. The first step is that 2-aminobutyrate is linked to glutamate which is catalyzed by GCS, then glycine is linked to this dipeptide via GS. The only difference between glutathione and ophthalmic acid is that 2-aminobutyraat is replaced by cystein. Glutathione has a normally negative feedback on GCS. In a situation of ischemia (for example acetaminophen-induced hepatotoxicity) this negative feedback mechanism disappears and because all the cystein is depleted by oxidation, the alternative pathway will be activated leading to excessive generation of ophthalmic acid via the same pathway. The increase of the ophthalmic acid is just as high as the decrease of gluthathion is. See figure 2.

The focus of this study will be to asses the effects of different ischemia times on the ophthalmic acid plasma levels. By measuring Ophthalmate concentration in hepatic serum several times in both groups we are able to compare the level of hepatic GSH depletion and thus oxidative stress in order to make an accurate estimation of possible differences in liver function and

injury.

Secondary outcome

Concentrations of different inflammatory and intestinal damage markers will be measured in blood.

Inflammatory markers

- Soluble TNF-receptor (n75/ n55)
- IL-6
- IL-8
- Interferon-γ
- MPO
- IL-10

Intestinal damage markers:

- Intestinal Fatty Acid Binding Protein (I-FABP)
- Ileal Lipid Binding Protein (I-LBP)

Study description

Background summary

Colorectal cancer is the second commonest malignancy in Europe. Approximately 50 % of all patients diagnosed with CRC will develop liver metastases at some stage of their disease. For these patients the only potentially curative treatment option is an operation in which the part of the liver that contains metastases is removed. Patients that have undergone a liver resection can develop postoperative complications due to extensive intraoperative blood loss (1, 2). To make an attempt to avoid blood loss during transection a Pringle manoeuvre can be performed. This implies a temporary clamping of the portal

vein and hepatic artery in order to reduce hepatic inflow (3). The advantage of this manoeuvre is that surgery can be performed in a *blood free* liver. This could reduce intraoperative blood loss and consequently the risk of complications.
To prevent ischemic damage the Pringle manoeuvre is applied intermittently which means that every 15 minutes the inflow to the liver is re-established by releasing the clamp to allow reperfusion for a period of 5 minutes. However, the transection of the liver takes in general longer than 15 minutes and therefore several cycles of 15 minutes inflow occlusion and reperfusion are necessary. The safe upper limit of cumulative hepatic ischemia in a normal liver can be extended to 325 minutes (4). Unfortunately, during each reperfusion phase a possibility exists of hemorrhage which is a significant prognostic indicator for postoperative complications.
A possible solution for this problem could be prolonging the interval of ischemia from 15 to 30 minutes. Fewer cycles of inflow occlusion and reperfusion will be necessary, while the safe upper limit of cumulative hepatic ischemia will not be exceeded. Because there are less phases of portal pedicle declamping, cumulative blood loss will probably be reduced. Recent data show that routine application of a prolonged period of 30 minutes will also reduce operation time and even cumulative ischemia time, because the transection can be performed more efficiently (5). A reduced operation time will lower the risk of postoperative infection. A possible disadvantage of a period of 30 minutes liver ischemia is that it might cause more ischemic damage to the functional parenchyma of the remnant liver, than a period of 15 minutes. Recent literature data suggest that a period of 30 minutes liver ischemia can be endured without any clinically relevant effect on remnant liver function (5). However, in that particular study only crude estimates of liver function were applied. Our aim is to investigate the effects of 15* liver ischemia versus 30* liver ischemia using more sophisticated markers of liver injury and liver function.
Our group recently showed that even during liver manipulation at the beginning of surgery for colorectal liver metastases and before application of the Pringle manoeuvre, plasma levels of markers for liver damage (ASAT, GSTα and L-FABP) and inflammation (Il-6) increased significantly in humans. A possible explanation might be that manipulation of the liver induces microcirculatory derangements and oxidative stress followed by Kupffer cell activation and cell death. This damage might even be aggravated in livers suffering from pre-existent liver diseases like steatosis, chemotherapy-associated hepatotoxicity or cirrhosis. After mobilisation of the liver, transection of the extremely perfused liver parenchyma takes place.

The inflammatory response following surgery or trauma is essentially favourable, as defense mechanisms are needed to trace and combat pathogens. However, under circumstances the inflammatory response can derail, leading to systemic inflammatory response syndrome (SIRS) and sepsis. Patients suffering from these syndromes are prone to develop organ damage that can be lethal. Our group has shown that high fat nutrition administered before hemorrhagic shock reduces inflammation and preserves gut integrity. The presence of fat in

the proximal small intestine leads to release of neuropeptide cholecystokinin (CCK) that activates the autonomous nervous system. Hence, activation of the efferent vagus nerve inhibits the inflammatory actions of macrophages via binding to nicotinic receptors (figure 1).6
In order to translate this protective mechanism to the human setting, the optimal composition and volume of nutrition is determined in a separate protocol (METC number 06-1-076) In protocol 07-4-016, parameters of inflammation and tissue damage are determined in patients undergoing surgery of the colon and femur fractures. In this study, inflammation and tissue damage are determined during and after liver surgery.7 The results of this study will be used for future intervention studies.

Study objective

1 Primary Objective
To investigate the effects of 15* liver ischemia versus 30* liver ischemia on liver injury and liver function.

To investigate the effect of liver manipulation during mobilisation for a right hemihepatectomy, that can be used as a standardized model in future studies.

To identify markers of inflammation and tissue damage during and after liver surgery, that can be used in future intervention studies.

2 Secondary Objectives
To investigate mechanisms leading to cell injury, liver dysfunction and cellular protective processes during ischemia of the liver in humans.

Study design

Groups:
A Pringle manoeuvre will be necessary in approximately 50% of the patients. This necessity becomes clear not until during surgery. In that case randomisation will take place between a continuous period of 15 (group A) or 30 min (group B) minutes liver ischemia. In 50% of all patients undergoing liver surgery a Pringle manoeuvre is not necessary. This group C will be used as a control group to study the relation between remnant liver volume and postoperative liver function. For a schematic representation of al the time schedule in each group see figure 1.

In all patients (group A, B and C) arterial and renal, portal and hepatic venous blood will be sampled and liver biopsies will be taken according to the schedules below. Blood samples will be taken from the artery line (routinely placed by the anaesthetist) and also from the liver vein, portal vein and renal vein by direct puncture. By measuring concentration differences between the artery, portal vein and the liver vein, the uptake and production of substances

(e.g. proteins, cytokines) can be quantified. The measurement of concentration differences between the renal vein and the artery are necessary to study renal metabolism. Renal metabolism is worthwhile measuring because the kidney is able to compensate important liver functions when the liver is failing, for example clearance of ammonia and urea (1, 6). Markers of liver injury and liver function will be measured and compared between group A and B in order to investigate the effects of 15* liver ischemia versus 30* liver ischemia. In group C the blood flow through the liver will be determined with the use of an indocyanine green infusion. The post operative liver volume will be calculated in group C with a specially developed computer method (7). Liver biopsies will be taken from the part of the liver that will be removed. The methods applied (intraabdominal blood sampling, liver biopsies, ICG infusion) have been used before without any problems for the surgical procedure or the patient (MEC 02-045 and MEC 03-032).

Study burden and risks

There are no additional risks on top of the normal risks of undergoing liver surgery. At present, it is unclear whether prolonging the interval of ischemia from 15 to 30 minutes will cause more liver cell injury. The literature indicates that this is probably not the case, or at least not clinically relevant (5). This is in agreement with our own observations, when the interval of ischemia is longer than 15 minutes as a consequence of the situation. The chance that liver biopsies during surgery will cause an important bleeding is very small because biopsies will be taken from the part of the liver that will be removed. The amount of blood loss due to a biopsy or puncturing the liver, portal and kidney vein is very small compared to the amount of blood loss due to the liver resection (± 0.5-3 litre).The methods applied (intraabdominal blood sampling, liver biopsies, ICG infusion) have been used before without any problems for the surgical procedure or the patient (MEC 02-045 and MEC 03-032) and have been published in peer reviewed journals (9, 10).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with resectable liver tumors (mostly colorectal cancer liver metastases) who undergo a liver resection at the University Hospital Maastricht. Patients should be older than 18 years and younger than 75 years.

Exclusion criteria

Parenchymal liver disease, inflammatory liver disease, inborn errors of metabolism (liver enzyme deficiencies), steroid hormone medication, n-acetyl cystein medication

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-09-2007
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	14-05-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-12-2007
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL13089.068.06