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## Desflurane Preconditioning in Hepatectomies



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**Recruitment Status :** Completed  
**First Posted :** February 21, 2019  
**Last Update Posted :** February 21, 2019

### Sponsor:

Aristotle University Of Thessaloniki

### Information provided by (Responsible Party):

Eleni **Koraki**, Aristotle University Of Thessaloniki

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## Study Description

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### Brief Summary:

Hepatectomies are considered as operations of high bleeding risk. The history of massive hemorrhage in liver surgery led to the emergence of techniques to control excessive blood loss. These techniques temporarily occlude the blood vessels that supply liver (the Pringle Maneuver) limiting subsequent losses. However, this leads to the ischemia - reperfusion injury impairing liver function. Research points to methods targeting on tempering reperfusion pathophysiology. Volatile anesthetics have been used for pharmacological preconditioning and proved to protect against organ damage. The aim of this study was to investigate the potential beneficial effect of desflurane on ischemia-reperfusion injury of the liver. Patients presenting for elective hepatectomy were randomized equally into two groups. The Control Group received no pharmacological preconditioning and the Desflurane Group received pharmacological preconditioning with Desflurane before induction of ischemia.

Condition or disease	Intervention/treatment	Phase
Ischemia Reperfusion Injury	Drug: Desflurane	Not Applicable

### Detailed Description:

Hepatectomies are characterized by an elevated risk of severe hemorrhage. The high vascular supply of the liver has historically troubled surgeons who resolved to techniques to control excessive blood loss. The Pringle Maneuver commonly employed in liver surgery is a temporary method to occlude the vascular supply of the liver. As a result, ischemia is developed and a pathophysiologic cascade is initiated. Upon the resolution of ischemia, reperfusion occurs which is linked to further damage and the ischemia-reperfusion injury is developed. Ischemia and reperfusion lead to activation of the innate immune response, which interacts with the adaptive immune response. Result of this interaction is the production of inflammatory cytokines, chemokines, complement products, and the recruitment of neutrophils to the site of injury. Previous studies have shown that animal's livers suffered from ischemia-reperfusion injury had increased neutrophil infiltration and pharmacological agents attenuating neutrophil's activity improved hepatic Ischemia-Reperfusion Injury (IRI). Preconditioning refers to the exposure of an organ to short intervals of ischemia which has been shown to mitigate the aforementioned ischemia-reperfusion injury. Preconditioning can be pharmacological and volatile anesthetics have been successfully used in preconditioning models. Sevoflurane have been proved beneficial for a series of hepatectomies in limiting transaminase levels postoperatively. However, sevoflurane by virtue can be hepatotoxic through Compound A production, elevated free calcium and reactive oxide species activation. On the other hand, desflurane undergoes minimum liver metabolism. In liver ischemia-reperfusion models, desflurane preconditioning led to decreased cell death and inflammatory cytokines inhibition.

The goal of the investigator's study was to investigate the effect of desflurane preconditioning in patients undergoing elective hepatectomy of at least two segments. Patients were randomized 1:1 to receive pharmacological preconditioning (Desflurane Group, Group D) or not (Control Group, Group C). The surgeon and the Intensive Care Unit were blinded as to the intervention. Anesthetic management was the same for all patients. For GroupD thirty minutes before the initiation of ischemia desflurane was delivered and propofol was stopped for the same interval.

## Study Design

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**Study Type :** Interventional (Clinical Trial)  
**Actual Enrollment :** 46 participants  
**Allocation:** Randomized  
**Intervention Model:** Parallel Assignment  
**Masking:** Triple (Participant, Care Provider, Outcomes Assessor)  
**Primary Purpose:** Basic Science  
**Official Title:** Pharmacological Preconditioning With Desflurane in Liver Surgery  
**Actual Study Start Date :** April 1, 2016  
**Actual Primary Completion Date :** June 30, 2018  
**Actual Study Completion Date :** June 30, 2018

### Resource links provided by the National Library of Medicine



[Drug Information](#) available for: [Desflurane](#)

[U.S. FDA Resources](#)

## Arms and Interventions

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Arm	Intervention/treatment
Experimental: Desflurane Group Thirty minutes before initiation of ischemia the surgeon was instructed to notify the anesthesiologist. At this single time point, propofol infusion was stopped and substituted with the volatile anesthetic desflurane to achieve a Minimum Alveolar Concentration of 1. The procedure included a 5-minute induction of desflurane, a 20-minute preconditioning and a 5-minute washout period when propofol was reintroduced and desflurane stopped.	Drug: Desflurane
No Intervention: Control Group No pharmacological preconditioning was implemented	

## Outcome Measures

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### Primary Outcome Measures :

1. Matrix Metalloproteinases (MMPs) 2 and 9 level [ Time Frame: Sample 1: At surgery, before initiation of the procedure , Sample 2: Thirty minutes after reperfusion ]

The levels of Matrix Metalloproteinase 2 and Matrix Metalloproteinase 9 as evaluated by the relative gene expression using RT-PCR. The comparative CT method also referred to as the 2- $\Delta\Delta$ CT method was used to calculate the fold change and then convert it to percentage. Their presence has been linked to hepatic cellular injury so increased levels represent worse injury.

2. Tissue Inhibitor Metalloproteinase (TIMPs) 1 and 2 [ Time Frame: Sample 1: At surgery, before initiation of the procedure , Sample 2: Thirty minutes after reperfusion ]

The levels of Tissue Inhibitor Metalloproteinase 1 and Tissue Inhibitor Metalloproteinase 2 as evaluated by the relative gene expression using RT-PCR. The comparative CT method also referred to as the 2- $\Delta\Delta$ CT method was used to calculate the fold change and then convert it to percentage. Their inhibitory effect on Matrix Metalloproteinases has been associated with a limitation of cellular injury. Thus, the higher the levels of Tissue Inhibitor Metalloproteinases the greater their protective activity.

### Secondary Outcome Measures :

1. Histological findings of hepatic parenchyma [ Time Frame: Sample 1: Upon surgical dissection of the liver, before inflow occlusion, Sample: thirty minutes after reperfusion ]

Hematoxylin Eosin, Gomori and Masson staining were used. With Hematoxylin Eosin staining the degree of steatosis was assessed while Gomori and Masson staining was used to determine the level of fibrosis.

Steatosis was characterized (x100 magnification) as mild (10%-30%), moderate (30%-60%), severe (>60%) according to the presence of fat droplets in hepatic cells.

Fibrosis was also graded based on the METAVIR score as absent - F0, portal fibrosis without septa - F1, portal fibrosis with rare septa - F2, numerous septa - F3 and cirrhosis - F4.

## Information from the National Library of Medicine



Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, [Learn About Clinical Studies](#).

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)  
Sexes Eligible for Study: All  
Accepts Healthy Volunteers: No

## Criteria

## Inclusion Criteria:

- hepatectomy of at least two segments

## Exclusion Criteria:

- Hepatitis B, C or HIV infection
- liver cirrhosis
- autoimmune disease, inflammatory bowel disease
- pregnancy
- prior additional ablation therapies (cryosurgery or radiofrequency)
- liver resections without inflow occlusion

## Contacts and Locations

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## Information from the National Library of Medicine



To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT03848780**

## Sponsors and Collaborators

Aristotle University Of Thessaloniki

## Investigators

Principal Investigator: Eleni **Koraki**, Dr Aristotle University Of Thessaloniki

## Study Documents (Full-Text)

Documents provided by Eleni **Koraki**, Aristotle University Of Thessaloniki:

[Study Protocol and Statistical Analysis Plan](#) [PDF] April 30, 2018

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## Publications:

Rosen HR, Martin P, Goss J, Donovan J, Melinek J, Rudich S, Imagawa DK, Kinkhabwala M, Seu P, Busuttil RW, Shackleton CR. Significance of early aminotransferase elevation after liver transplantation. *Transplantation*. 1998 Jan 15;65(1):68-72.

Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Nozawa S, Furukawa K, Mitsuhashi N, Sawada S, Takeuchi D, Ambiru S, Miyazaki M. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. *J Surg Res*. 2006 Jun 15;133(2):102-12. Epub 2006 Jan 4.

Boros P, Bromberg JS. New cellular and molecular immune pathways in ischemia/reperfusion injury. *Am J Transplant*. 2006 Apr;6(4):652-8. Review.

Beck-Schimmer B, Breitenstein S, Urech S, De Conno E, Wittlinger M, Puhon M, Jochum W, Spahn DR, Graf R, Clavien PA. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann Surg*. 2008 Dec;248(6):909-18. doi: 10.1097/SLA.0b013e31818f3dda.

Responsible Party: Eleni **Koraki**, Principal investigator, Anesthesiologist, Aristotle University Of Thessaloniki  
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## Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Keywords provided by Eleni **Koraki**, Aristotle University Of Thessaloniki:

- preconditioning
- hepatectomy
- ischemia reperfusion injury

Additional relevant MeSH terms:

- |                             |                                    |
|-----------------------------|------------------------------------|
| Reperfusion Injury          | Desflurane                         |
| Ischemia                    | Anesthetics, Inhalation            |
| Pathologic Processes        | Anesthetics, General               |
| Vascular Diseases           | Anesthetics                        |
| Cardiovascular Diseases     | Central Nervous System Depressants |
| Postoperative Complications | Physiological Effects of Drugs     |