THE EFFECTS OF PROPOFOL OR SEVOFLURANE ANAESTHESIA ON POSTOPERATIVE BIOCHEMICAL MARKERS OF LIVERFUNCTION IN ORTHOTOPIC LIVERTRANSPLANTATION

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Dissertation presented in the 2nd Master year in the programme of

Master of Medicine in Medicine
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Abstract

BACKGROUND

Pharmacological conditioning with volatile anaesthesia such as sevoflurane has proven to be organ protective in the heart system. There are studies indicating that anaesthetic preconditioning might be extended to other organs as well in order to protect them from ischemia/reperfusion injury. Because of the shortage of donor organs and extended donor criteria for donor grafts research to improve liver graft function after reperfusion is needed. In this observational study the effects of sevoflurane anaesthesia and propofol anaesthesia on post reperfusion graft function are compared. Expected is a possible liver protective effect of sevoflurane.

METHODS

During the period of 1 January 2010 until 31 September 2013, 186 patients underwent liver transplantation in Ghent University Hospital. Twenty-three patients had missing anaesthesia records and 20 patients were re-transplantations during the same period. In total 143 patients were analysed. Thirty patients received propofol anaesthesia and 113 patients were given sevoflurane anaesthesia. The primary endpoint was postoperative liver function defined by peak alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels over 3 postoperative days. Additional end points were peak values of white cells, PT, fibrinogen, bilirubin, urea levels, creatinine levels, albumin levels, lactate, gamma-glutamyl transferase and alkaline phosphatase. All outcomes were measured 1 day before and 1, 2 and 3 days after reperfusion.

RESULTS

No statistically significant differences between both groups were found for transaminases. P-value was 0.957 for AST and 0.833 for ALT. Additionally no significant differences were found for white blood cells, prothrombin time, fibrinogen, glycaemia, lactate, gamma-glutamyl transferase and alkaline phosphatase. The DRI score and instability during surgery was not different between groups.

Statistically significant differences between groups were detected for peak bilirubin (P=0.006), peak urea (P=0.007), peak creatinin (P=0.006), peak albumin (P< 0.001).
CONCLUSIONS

The results from this limited retrospective observational study could not demonstrate any differences in the primary endpoints (ALT and AST). Peak values for bilirubin, urea, creatinin and albumin were significantly lower in the sevoflurane group compared to the propofol group. Further research with RCT is necessary to elucidate the anaesthetic preconditioning properties of sevoflurane on liver graft function.
Abstract Nederlands

ACHTERGROND

Farmacologische conditionering met dampvormige anesthesie zoals sevofluraan is bewezen orgaan protectief te zijn in het hart. Er zijn studies waaruit blijkt dat anesthesische preconditionering ook in andere organen kan toegepast worden om deze te beschermen tegen ischemie/reperfusie schade. Door een tekort aan donoren en uitgebreide donor criteria voor donororganen is onderzoek nodig om de functie van het levertransplant na reperfusie te verbeteren. In deze observationele studie worden de effecten van sevofluraan anesthesie en propofol anesthesie op de getransplanteerde lever na reperfusie vergeleken. Verwacht wordt een mogelijk lever protectief effect van sevofluraan te zien.

METHODEN

In de periode van 1 januari 2010 tot 30 september 2013, ondergingen 186 patiënten een levertransplantatie in het Universitair Ziekenhuis van Gent. Bij 23 patiënten ontbraken de anesthesiefiches en 20 patiënten werden opnieuw getransplanteerd in de geobserveerde periode. In totaal werden 143 patiënten onderzocht. Dertig patiënten kregen propofol anesthesie en 113 patiënten kregen sevofluraan anesthesie. Het primaire eindpunt was de postoperatieve leverfunctie bepaald door piek transaminases, alanine aminotransferase (ALT) en aspartaat aminotransferase (AST) niveaus, gedurende 3 dagen postoperatief. Bijkomende eindpunten waren piekwaarden van witte bloedcellen, protrombine tijd, fibrinogeen, bilirubine, ureum, creatinine, albumine, lactaat, gamma-glutamyl transferase (γGT) en alkalische fosfatase. Alle resultaten werden gemeten 1 dag vóór en 1, 2 en 3 dagen na reperfusie.

RESULTATEN

Er werden geen statistisch significant verschillen aangetoond voor de piek transaminasen in beide groepen. De P-waarde was 0,957 voor AST en 0,833 voor ALT. Er werden ook geen significante verschillen gevonden voor de piekwaarden van witte bloedcellen, protrombine tijd, fibrinogeen, glycémie, lactaat, γGT en alkalisch fosfatase. De DRI score en instabiliteit tijdens de operatie waren eveneens niet significant verschillend tussen beide groepen.

Statistisch significante verschillen tussen de groepen werden waargenomen voor de piek bilirubine (P = 0,006), piek ureum (P = 0,007), piek creatinine (p = 0,006), piek albumine (P <0,001).
CONCLUSIES

De resultaten van deze beperkte retrospectieve observationele studie konden geen verschillen in de primaire eindpunten (ALT en AST) aantonen. De piekwaarden voor bilirubine, ureum, creatinine en albumine waren significant lager in de sevofluraan groep in vergelijking met de propofol groep. Verder onderzoek met RCT moet de effecten op de functie van de getransplanteerde lever door anesthesiologische preconditionering met sevofluraan ophelderen.
### Abbreviations list

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>DRI</td>
<td>Donor Risk Index</td>
</tr>
<tr>
<td>ECD</td>
<td>Extended Criteria Donor</td>
</tr>
<tr>
<td>ESLD</td>
<td>End-Stage Liver Disease</td>
</tr>
<tr>
<td>ET-DRI</td>
<td>European Transplant Donor Risk Index</td>
</tr>
<tr>
<td>FHF</td>
<td>Fulminant Hepatic Failure</td>
</tr>
<tr>
<td>GABA-A receptor</td>
<td>Gamma-Aminobutyric Acid A receptor</td>
</tr>
<tr>
<td>γGT</td>
<td>Gamma-Glutamyl Transferase</td>
</tr>
<tr>
<td>GRWR</td>
<td>Graft Recipient Weight Ratio</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
</tr>
<tr>
<td>I/Rp injury</td>
<td>Ischemia and Reperfusion injury</td>
</tr>
<tr>
<td>MELD</td>
<td>Model for End-stage Liver Disease</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>N-methyl-D-aspartate receptor</td>
</tr>
<tr>
<td>OLT</td>
<td>Orthotopic Liver Transplantation</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin Time</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cells</td>
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</table>
1. Introduction

1.1 Liver transplantation

Liver transplantation is an established therapy and, to date, the only curative treatment of acute and chronic liver disease such as fulminant hepatic failure (FHF), chronic hepatitis B, autoimmune hepatitis, primary biliary cirrhosis, end stage liver disease and hepatocellular carcinoma (HCC) (1, 2).

The most commonly used technique (of liver transplantation) is orthotopic liver transplantation (OLT), in which the native liver is removed and replaced by the donor organ in the same anatomic location as the original liver. Patients can receive a cadaveric liver transplantation (mostly from heart-beating donor), split graft transplantation or living related liver donor-split transplantation. Because the number of patients who could benefit from liver transplantation significantly exceeds the number of available donors, there is a huge shortage of donors. This (and increasing waiting list mortality rates) forms a major problem in all developed countries. In some countries living related donors form the majority of transplant operations (2). To avoid excessive waiting time on the transplantation list extended criteria donor (ECD) livers are used to enlarge the liver donor pool (3-6). No thorough definition for ECD has been established. In table 1 the extended donor criteria as described by Alkofer et al. (6) are shown.

Table 1 Extended donor criteria

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>age &gt;65 years</td>
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<tr>
<td>macro vesicular steatosis &gt;40%</td>
</tr>
<tr>
<td>donation after cardiac death (DCD)</td>
</tr>
<tr>
<td>donor serum sodium &gt;155 mEq/dL</td>
</tr>
<tr>
<td>split-liver transplantation</td>
</tr>
<tr>
<td>cold ischemia time exceeding 12 hours</td>
</tr>
</tbody>
</table>

Also hypotension or inotropic support, biochemical abnormalities, gender mismatch, previous malignancy in the donor, hepatitis C virus (HCV) infection, human T-cell lymphotrophic virus type I/II (HTLV-I/II) infection, other active infections, Centers for Disease Control and Prevention (CDC) high-risk donors or a higher risk of transmission of disease can be extended donor criteria (4, 5, 7, 8).
These donor characteristics are associated with a higher risk of delayed graft function, primary non-function and possible a higher risk of physiologic dysfunction. These liver grafts are also called “marginal donors”.

Orthotopic liver transplantation currently has a 5-year survival of 70-80% and generally provides a good quality of life (9, 10). The most life-threatening complications with OLT occur within the first year and include primary graft dysfunction, acute rejection episodes, severe infections and technical complications such as hepatic artery thrombosis or biliary leaks. Late morbidity and mortality after OLT are caused mainly from the adverse effects of the immunosuppressive medications prescribed to prevent graft rejection. Malignancy and disease recurrence are the major causes of the long term mortality (11). In long-term management of OLT recipients not only preservation of graft function is important, but also prevention and treatment of the metabolic complications that result from the use of immunosuppressive drugs, as well as regular screening for malignancy (12).

1.2 Donor and recipient specific factors

1.2.1 MELD score

Model for End-stage Liver Disease (MELD) score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR). It was originally developed to predict survival following transjugular intrahepatic portosystemic shunt placement, but it has also been used to predict survival among patients with acute liver failure (13). The MELD score accurately predicts short-term mortality in patients with end-stage liver disease (ESLD) who are awaiting liver transplantation. The higher the MELD score, the greater the risk of short-term mortality. The score is based solely upon liver transplant candidate characteristics and accurately estimates the risk of death without transplantation (14).

1.2.2 DRI

The donor risk index (DRI) by Feng et al. (15) describes specific donor characteristics and their risk on post-transplant graft failure. DRI can be useful in allocation of liver grafts. It can help
with the balanced choice (based on the quality of the donor liver graft) that transplant physicians have to make in an attempt to maximize acceptor benefit (14).

This index is based on age (<40, 40-49, 50-69 or >69 years); cause of death (trauma, anoxia, cerebrovascular accident (CVA) or other); race (African, American, White or other); donation after cardiac death; partial/split liver graft; height of donor; organ allocation (local, regional or national) and cold ischemia time in hours (14, 15).

Braat et al. (16) have recently described a European transplant donor risk index (ET-DRI) for an optimal allocation possibility for the Eurotransplant region. The factor race as used in the DRI is not registered in the Eurotransplant region and cannot be optimally used for allocation purposes (16).

1.2.3 Graft recipient weight ratio

In the allocation process of a liver graft it is important that the correct graft size is allocated to the acceptor. In partial graft liver recipients with graft recipient weight ratio (GRWR) smaller than 0.8% a higher incidence of post-operative complications were possibly found. This includes small-for-size syndrome (SFSS). Worse graft survival has been described but Hill et al. (17) showed that this is not the only factor of expected graft survival. The degree of portal hypertension, MELD score, and splenic size are factors involved as well (18).

1.3 Anaesthetics

In this study the effects of propofol and sevoflurane anaesthesia on liver function are compared.

1.3.1 Propofol

Propofol is an intravenous anaesthetic that is commonly used for sedation of patients. It is rapidly metabolised by the liver in minimally active metabolites which are renally excreted. Propofol is an agonist of the gamma-aminobutyric acid A (GABA-A) receptor (19). GABA is the chief inhibitory neurotransmitter of the central nervous system. Propofol is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which reduces release of glutamate
(20). Less is known about propofol’s duration of effect following long-term administration. The elimination of propofol is not impaired by hepatic or renal dysfunction. In liver transplantation propofol is often used when the patient suffers from encephalopathy, often a sign of decompensated liver disease (18).

1.3.2 Sevoflurane

Sevoflurane is the most frequently used inhaled agent for induction of anaesthesia because it is the least pungent and irritating to the airways and it has a rapid onset of action (21). Also it has a low blood-gas solubility which makes it suitable to use for maintenance of anaesthesia. It undergoes less hepatic metabolism than other volatile anaesthetics (e.g. isoflurane) (22). Sevoflurane acts primarily as a positive modulator of the GABA-A receptor. However, it also acts as a NMDA receptor antagonist, potentiates glycine receptors and inhibits acetylcholine and 5-HT3 receptors.

1.4 Ischemia and reperfusion injury

Solid organ transplantation can result in prolonged deprivation of tissue oxygen and activation of the anaerobic pathway. The restoration of oxygen delivery during reperfusion leads to organ injury. This phenomenon is known as ischemia and reperfusion (I/Rp) injury. The injury is inherent to organ transplantation and can result in primary non-function or delayed function of grafts, which is associated with a significant morbidity and mortality after transplantation (1).

Ischemia and reperfusion injury produces molecular and cellular changes. It results in local injury to the liver and systemic organ injury as a result of free radical production, nitric oxide (NO) depletion and release of cytokines and chemokines (23). That ultimately leads to deterioration of cell function and cell death which severity is related to the intensity of the injury (1).

Strategies to attenuate I/Rp injury are important in transplantation and surgery. In this way the donor pool also might be extended. Despite the development of multiple protective strategies against I/Rp injury in experimental models, only few have demonstrated efficacy in human studies and made the transition to the clinical practice. Preconditioning by either ischemic
preconditioning or pharmacologic pre-, post-, and continuous conditioning (before, during or after inflow occlusion) are among the protective strategies currently used in human transplantation (1).

The phenomenon of an exposure to a brief period of ischemia or mild oxidative stress before a severe ischemic insult is called preconditioning (24). This would help the organ to minimize the sequels of ischemia. The concept of pharmacologic preconditioning is based on mimicking the protective mechanisms and biologic effects induced by ischemic preconditioning (IP). Recent laboratory and clinical studies demonstrated a promising role for volatile preconditioning (25). The study of Beck-Schimmer (25) et al. demonstrates that application of sevoflurane 30 minutes before the inflow, hepatic occlusion would reduce perioperative injury to hepatocytes in patients undergoing liver resection with inflow occlusion (24-27).

Volatile conditioning has been studied in the cardiovascular system. Volatile anaesthetic agents protect from ischemic myocardial damage. Desflurane and sevoflurane reduce postoperative mortality and the incidence of myocardial infarction following cardiac surgery. The myocardium has an endogenous adaptive response to ischemic insults by preconditioning with patients undergoing CABG. The key roles are ATP-dependent potassium channels in mitochondrial membranes, reactive oxygen species, the apoptotic cascade, nitric oxide, and intracellular overload of calcium have potentially a role in preconditioning (19-20).

One of the major limitations of IP is related to the timing of the procedure as it has to be instituted before the initiation of ischemic injury. In clinical practice or emergency situations, is not always possible. Attempts to overcome this limitation have prompted the development of a new concept called “ischemic postconditioning” which is performed at the onset of reperfusion. Postconditioning is the most appealing strategy because the onset of reperfusion is easy to define and can be applied selectively to patients who had a need for prolonged periods of inflow occlusion (28). Several extracellular factors produced endogenously are known to play an essential role in ischemic postconditioning (adenosine, bradykinin, opioid peptides, and reactive oxygen species) (1).

A RCT shows evidence that pharmacological postconditioning with a volatile anaesthetic agents gives a high degree of protection in patients undergoing liver resection under inflow occlusion. The postoperative liver injury and mortality, evaluated by complications after surgery, was decreased after resection. The clinical outcome was also improved (21).

Some studies suggest that propofol also offers some protection against hypoxia/reoxygenation
damage in several tissues (brain, heart, liver) by inhibition of lipid peroxidation, enhancement of the cellular antioxidant defence system by modulating the ceramide pathway, and activation of the MEK-ERK pathway (29).

1.5 Research goal and hypotheses

The goal of this study was to explore the effect of the administered anaesthetic on the biochemical markers of liver function. We used the study of Song et al. as a guide for the development of this research. In many studies there has been a comparison between propofol (intravenous) and sevoflurane (volatile) anaesthetic agents in liver function after liver surgery. Liver function was evaluated by the transaminase levels (30) and clinical outcome or complications (25, 28). Secondly postoperative biochemical markers (WBC, PT, fibrinogen, glycaemia, bilirubin, albumin, plasma lactate, urea, creatinin, YGT and ALP) were evaluated and compared between both groups. In our study these biochemical markers after liver transplantation were evaluated to see if sevoflurane offers a protective role in outcome after the transplantation.

Also factors as urgency of transplant, split transplantation, hemodynamic stability during surgery, DRI and GRWR were compared.

We hypothesised that continuous pharmacological conditioning can also provide protection against ischemia and reperfusion injury as seen in pharmacological pre- and postconditioning.
2. Methods

2.1 Study design and population

The study was designed as an observational retrospective study of patients undergoing orthotopic liver transplantation during the period of 1 January 2010 until 31 September 2013. Permission was given by the Ethics Committee of Ghent University Hospital.

In this period, 186 patients were included. There were 20 missing anaesthesia records, which brings the total to 166 patients. Exclusion criteria was re-transplantation in the observational period (1 January 2010- 31 September 2013). In total there were 23 re-transplantations (6 were also missing anaesthesia records). Of these remaining 143 patients data were collected. Propofol was given to 30 patients and sevoflurane to 113 patients. Figure 1 shows the flow of participants through the study.

*Figure 1 Process of data collection*
The anaesthetic which had been used during the procedure was found in the anaesthesia records of the scanned documents or archives. In the EPD (electronic patient record) biochemical parameters were collected from blood sample results or arterial blood gas analysis pre- and postoperatively. All other data were collected from the transplantation list, anaesthesia sheet, surgical timing, pre-operative liver transplant sheet and donor data. When not found in anaesthesia sheet or record, the timing of reperfusion was calculated as mean of the time of the surgical procedure.

Anaesthesia was performed intravenously with propofol (target controlled infusion) or inhaled anaesthesia with sevoflurane. Choice of anaesthetic was up to the anaesthesiologist.

BIS monitoring (an EEG derived depth of anaesthesia monitor) was used in all patients with a target range of 40-60).

2.2 Study outcome

The primary endpoint was postoperative liver function defined by peak alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels over 3 postoperative days as used in previous trials (25, 28, 30). Additional endpoints were peak values of white blood cells, prothrombin time, fibrinogen, bilirubin, urea levels, creatinine levels, albumin levels, lactate, gamma-glutamyl transferase (γGT) and alkaline phosphatase. All outcomes were measured before and 1, 2 and 3 days after reperfusion. In figure 2 the course of transplant is shown.

The Donor Risk Index (DRI) described by Feng et al. (14) was calculated for each patient in our data set. For living related (split) transplants no DRI score was calculated because donor was not deceased. Because the factor race is not registered all patients were classified as white for the term race. For the term organ location following criteria have been used: local (transplant centre is in the procurement area), regional (transplantation and procurement are within the same country) and extra regional (anywhere in Eurotransplant region, but outside the region) (15).

GRWR was calculated as described in Hill et al. (17) and used as a graft weight/recipient weight ratio (GW/RW).
Patients’ hemodynamic stability was categorised instable when hyper dynamic profile or hypotension or large need of supportive medication (Levophed > 100 ng/kg/min, dopamine, vasopressin, diuretics …).

Figure 2 Course of transplantation

2.3 Statistical Analysis

For the statistical analysis SPSS 22 (Statistical Package for the Social Sciences, IBM company, USA) was used.

For each variable normality (Kolmogorov-Smirnov and Shapiro Wilk test in combination with Q-Q plots) was checked. If the population was normally distributed, a parametric test was used. If the population was not normally distributed a non-parametric test was used (Mann Whitney U test and Chi Square test).

Peak transaminases (primary outcome) were compared between the sevoflurane and the propofol group. We expressed differences between groups for continuous variables as median differences with interquartile range (25 to 75 percentile). Categorical variables were expressed as percentages. For determining significance the P-value was used. Significance level was set at P < 0.05.
3. Results

3.1 Patient Characteristics

One hundred forty-three patients underwent liver transplantation in the Ghent University Hospital. Thirty patients (21%) have been given propofol anaesthesia and 113 patients (79%) have been given sevoflurane anaesthesia.

In the propofol group of 30 patients 20 were men (67%) and 10 were women (33%). In the sevoflurane group 113 patients 64 were men (57%) and 49 were women (43%).

*Figure 3 Anaesthetic given to the patients (%)*
Median age in the propofol group was 47.5 years in propofol group and 56 years in the sevoflurane group. In total there were 11 children (0-19 years) in this population, 1 in the propofol group (3%) and 10 in the sevoflurane group (9%).

Median length was 172 cm in propofol group and 169 cm in sevoflurane, median weight was 72.5 kg in propofol group and 74 kg in sevoflurane group. Respectively median BMI was 24.8 kg/m² and 25 kg/m².

Median MELD score was 32 in the propofol group and 19 in the sevoflurane group.

The median time of cold ischaemia was 7 hours and 27 minutes (IQR 23 minutes) for the propofol group. The median time of warm ischaemia time for the propofol group was 41 minutes (IQR 2 minutes). The median time of cold ischaemia was 7 hours and 27 minutes (IQR 23 minutes) for the sevoflurane group. The median time of warm ischaemia time for the sevoflurane group was 41 minutes (IQR 2 minutes).

A summary of the baseline patient characteristics for the 2 groups is shown in Table 2.

### Table 2 Patient characteristics, summary

<table>
<thead>
<tr>
<th></th>
<th>PROPOFOL</th>
<th>SEVOFLURANE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>113</td>
</tr>
<tr>
<td>AGE (YEARS), MEDIAN (IQR)</td>
<td>47.5 (20)</td>
<td>56 (18)</td>
</tr>
<tr>
<td>SEX, MEN-WOMEN, %</td>
<td>67-33</td>
<td>57-43</td>
</tr>
<tr>
<td>LENGTH, CM (IQR)</td>
<td>172 (14)</td>
<td>169 (13)</td>
</tr>
<tr>
<td>WEIGHT, KG (IQR)</td>
<td>72.5 (21)</td>
<td>74 (20)</td>
</tr>
<tr>
<td>BMI, KG/M² (IQR)</td>
<td>24.8 (3.5)</td>
<td>25.0 (5.6)</td>
</tr>
<tr>
<td>MELD (IQR)</td>
<td>32 (20)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>COLD ISCHAEMIA TIME (IQR)</td>
<td>7h17m (19m)</td>
<td>7h27m (23m)</td>
</tr>
<tr>
<td>WARM ISCHAEMIA TIME (IQR)</td>
<td>37m (2m)</td>
<td>41m (2m)</td>
</tr>
</tbody>
</table>

### 3.2 Indication of transplant

In the propofol group 3 of 30 patients (10%) were operated for malignancy (HCC). Non-malignant indications were trauma in 1 patient (3.3%), ethylic cirrhosis in 10 patients (33.3%),
non-alcoholic steatohepatitis (NASH) in 1 patient (3.3%) and other indications in 15 patients (50%). Other diseases included fulminant hepatitis (e causa ignota); toxic induced autoimmunity, primary non function or biliary complications after earlier transplantation, hepatitis B (HBV) or hepatitis C (HCV), non-A or non-B hepatitis, acute liver failure (HSV, HBV, medication) and HELPP syndrome. Also combinations of HCC with hepatitis B, C or ethylic cirrhosis was seen as indication of transplantation need.

In the sevoflurane group 33 patients were operated for malignancy, 32 patients had HCC (28.3%) and 1 patient had epitheloid hemangio-endothelioma (eHAE) (0.9%). Other nonmalignant indications were trauma in 1 patient (0.9%), ethylic cirrhosis in 20 patients (17.7%), primary sclerosing cholangitis (PSC) in 10 patients (8.8%), NASH or alcoholic steatohepatitis (ASH) in 5 patients (4.4%) and other indications in 45 patients (40%). Other diseases included: mucoviscidosis and liver failure, biliary atresia, polycystosis, Arteria Hepatica thrombosis, primary hyperoxalosis, fulminant hepatic toxic failure, hepatitis C, hepatic pulmonary syndrome/NASH, cryptogen hepatitis, auto-immune hepatitis, biliary complications, primary biliary cirrhosis (PBC), primary non function or biliary complications after earlier transplantation, Budd Chiari syndrome, adenomatosis, protein C deficiency, fulminant toxic liver and hepatitis B. Also combinations of HCC with hep C, alfa-1- deficiency, ethylic cirrhosis, PBC, hepatitis B, NASH was seen as indication of transplantation need. These were classified as malignancy (HCC). Indications of transplant is summarised in table 3.

Table 3 Indication of transplant, summary

<table>
<thead>
<tr>
<th></th>
<th>PROPOFOL (N)</th>
<th>SEVOFLURANE (N)</th>
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<td></td>
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<tr>
<td>HCC</td>
<td>3</td>
<td>32</td>
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<td>eHAE</td>
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<td>1</td>
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<tr>
<td><strong>NON-MALIGNANCY</strong></td>
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<td>ETHYLCIRRHOSIS</td>
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<td>PSC</td>
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<td>TRAUMA</td>
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</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>15</td>
<td>45</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma – eHAE: epitheloid hemangio-endothelioma – PSC: primary sclerosing cholangitis – PBC: primary biliary cirrhosis – NASH/ASH: (non-)alcoholic steatohepatitis
3.3 Risk factors

3.3.1 High Urgency

In the propofol group 29 patients (1 missing data file) were analysed. There were 18 non urgent patients (62%) and 11 high urgent patients (38%). In the sevoflurane group 108 patients were analysed (5 missing data files): 99 non urgent (92%) and 9 high urgent (8%). The distribution in both groups is shown in figure 4.

![Urgency of transplant in propofol group and sevoflurane group](image)

*Figure 4 Urgency of transplant in propofol group and sevoflurane group*

3.3.2 Hemodynamic stability during transplant

In the propofol group there were 19 stable patients (63 %) and 11 instable patients (37 %). In the sevoflurane group 102 were analysed (11 missing data files): 76 stable patients (75%) in comparison with 26 instable patients (25%).

The distribution of hemodynamic stability in both groups is shown in figure 5.
3.3.3 Split transplantation

In the propofol group there were 29 non split transplantations (96.7%) and 1 split transplantation (3.3%) which was an extended right lobe donation (non-related). In the sevoflurane group 108 patients were analysed (5 missing data files). There were 102 non split and 12 split (11.1%) liver grafts. The split consisted of 6 living related transplant (right lobe) and 6 non-living related transplant (3 extended right lobe and 3 left lateral segment).

The number of patients in both groups is shown in figure 6.

Figure 5 Stability during operation for propofol group and sevoflurane group.
3.3.4 Donor risk index

For the propofol group all 30 patients were analysed. The median DRI in the propofol group was 1.79 (with IQR 0.72). For the sevoflurane group 107 patients were analysed (6 missing data files). The median DRI was 1.67 (with IQR 0.66).

Figure 7 shows a box and whiskers plot with the comparison of the DRI between the propofol group and the sevoflurane group.
3.3.5 Graft recipient weight ratio

In the propofol group 26 patients were analysed (4 missing data files). Median GRWR is 1.95 with IQR 0.9. In the sevoflurane group 77 patients were analysed (36 missing data files). Median GRWR is 2.00 with IQR 0.8. Figure 8 shows a box and whiskers plot of both anaesthesia groups.

No ratio under 0.8% was found in the propofol group. In the sevoflurane group 7 patients with GRWR <0.8% were found. Table 4 shows characteristics of those patients.
### Table 4 Characteristics of patients with GRWR < 0.8%

<table>
<thead>
<tr>
<th></th>
<th>GRWR</th>
<th>SPLIT</th>
<th>AGE (YEARS)</th>
<th>MELD SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>Split LRT LL</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>Split LRT RL</td>
<td>65</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>0.58</td>
<td>Split LRT</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>0.67</td>
<td>Split LRT</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>Split LRT RL</td>
<td>51</td>
<td>missing</td>
</tr>
<tr>
<td>6</td>
<td>0.54</td>
<td>Split, unknown</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>0.33</td>
<td>Split, unknown</td>
<td>43</td>
<td>7</td>
</tr>
</tbody>
</table>

**Figure 8** Comparison of GRWR between propofol group and sevoflurane group.
3.4 Baseline biochemical markers

Table 5 shows a summary of the baseline biochemical markers of the liver function. Box and whiskers plot of the statistically significant (described in section 3.7) markers are shown.

**Table 5 Baseline biochemical markers, summary**

<table>
<thead>
<tr>
<th>BIOCHEMICAL MARKER</th>
<th>PROPOFOL BASELINE</th>
<th>SEVOFLURANE BASELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>WBC (<em>10³/µL)</em></em></td>
<td>Median (IQR) 5.96 (8.62)</td>
<td>Median (IQR) 5.75 (3.21)</td>
</tr>
<tr>
<td><strong>PT (%)</strong></td>
<td>30 (21)</td>
<td>68 (34.5)</td>
</tr>
<tr>
<td><strong>FIBRINOGEN (mg/dL)</strong></td>
<td>121 (91)</td>
<td>280 (222)</td>
</tr>
<tr>
<td><strong>GLYCAEMIA (g/dL)</strong></td>
<td>1.15 (0.30)</td>
<td>1.03 (0.33)</td>
</tr>
<tr>
<td><strong>BILIRUBIN (mg/dL)</strong></td>
<td>9.6 (22.6)</td>
<td>1.3 (3.75)</td>
</tr>
<tr>
<td><strong>UREA (g/dL)</strong></td>
<td>0.42 (1.24)</td>
<td>0.34 (0.27)</td>
</tr>
<tr>
<td><strong>CREATININ (mg/dL)</strong></td>
<td>1.09 (0.9)</td>
<td>0.91 (0.5)</td>
</tr>
<tr>
<td><strong>ALBUMIN (g/dL)</strong></td>
<td>2.6 (0.9)</td>
<td>3.5 (1.25)</td>
</tr>
<tr>
<td><strong>LACTATE (mg/dL)</strong></td>
<td>13.7 (19.9)</td>
<td>16 (12.95)</td>
</tr>
<tr>
<td><strong>AST (U/L)</strong></td>
<td>282 (809)</td>
<td>54 (52)</td>
</tr>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td>168 (1126)</td>
<td>35 (46)</td>
</tr>
<tr>
<td><strong>ƔGT (U/L)</strong></td>
<td>47 (120)</td>
<td>70 (91)</td>
</tr>
<tr>
<td><strong>ALP (U/L)</strong></td>
<td>133 (95)</td>
<td>133 (91)</td>
</tr>
</tbody>
</table>
3.4.1 Bilirubin

Figure 9 Baseline bilirubin: comparison between propofol group and sevoflurane group
3.4.2 Urea

![Box plot comparing Urea baseline between propofol and sevoflurane groups](image)

*Figure 10 Urea baseline: comparison between propofol group and sevoflurane group*
3.4.3 Creatinin

![Creatinin baseline comparison between sevoflurane and propofol group.](image)

*Figure 11 Creatinin baseline: comparison between sevoflurane and propofol group.*
3.4.4 Albumin

Figure 12 Albumin baseline: comparison between propofol group and sevoflurane group.
3.5 Peak biochemical markers

Table 6 shows a summary of the peak biochemical markers of the liver function. Box and whiskers plot of the statistically significant (described in section 3.7) markers are shown.

Table 6 Peak biochemical markers, summary

<table>
<thead>
<tr>
<th>BIOCHEMICAL MARKER</th>
<th>PROPOFOL PEAK</th>
<th>SEVOFLURANE PEAK</th>
<th>P-VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (*10⁹/µL)</td>
<td>9.29 (1.78)</td>
<td>9.46 (9.71)</td>
<td>0.708</td>
</tr>
<tr>
<td>PT (%)</td>
<td>74 (23)</td>
<td>75 (24.50)</td>
<td>0.237</td>
</tr>
<tr>
<td>FIBRINOGEN (mg/dL)</td>
<td>252 (139)</td>
<td>288 (147.5)</td>
<td>0.375</td>
</tr>
<tr>
<td>GLYCAEMIA (g/dL)</td>
<td>1.75 (0.61)</td>
<td>1.61 (0.57)</td>
<td>0.413</td>
</tr>
<tr>
<td>BILIRUBIN (mg/dL)</td>
<td>4.1 (6.30)</td>
<td>2.4 (2.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>UREA (g/L)</td>
<td>1.14 (0.81)</td>
<td>0.66 (0.59)</td>
<td>0.007</td>
</tr>
<tr>
<td>CREATININ (mg/dL)</td>
<td>1.68 (0.88)</td>
<td>1.08 (1.47)</td>
<td>0.006</td>
</tr>
<tr>
<td>ALBUMIN (g/dL)</td>
<td>2.5 (0.4)</td>
<td>2.8 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LACTATE (mg/dL)</td>
<td>9.7 (13.5)</td>
<td>9.8 (9.9)</td>
<td>0.714</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>543 (717)</td>
<td>467 (580)</td>
<td>0.957</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>560 (666)</td>
<td>551 (461)</td>
<td>0.833</td>
</tr>
<tr>
<td>ЬГТ (U/L)</td>
<td>90 (97)</td>
<td>81 (74)</td>
<td>0.254</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>86 (28)</td>
<td>89 (101)</td>
<td>0.254</td>
</tr>
</tbody>
</table>

*as described in section 3.7
Figure 13 Bilirubin peak: comparison between propofol group and sevoflurane group.
3.5.2 Urea

Figure 14 Urea peak: comparison between propofol group and sevoflurane group.
3.5.3 Creatinin

Figure 15 Creatinin peak: comparison between propofol group and sevoflurane group.
3.5.4 Albumin

![Box plot of Albumin peak comparison between propofol group and sevoflurane group.]

*Figure 16 Albumin peak: comparison between propofol group and sevoflurane group.*

3.6 Normality test

In the propofol group PT peak (P=0.667) and creatinin peak (P=0.115) the Shapiro Wilk was not significant, which means they are normally distributed. Other baseline biochemical markers were not normally distributed. In the sevoflurane group the fibrinogen peak (P=0.365) and albumin peak (P=0.085) were normally distributed. Other peak biochemical markers were not normally distributed. Because of differences between both groups we chose the Mann Whitney U test, a non-parametric test for unpaired groups for the continuous variables and Chi Square test for categorical variable “stability” during operation.
3.7 SPSS results

3.7.1 Mann Whitney U test

No significance between both groups was found for transaminases (primary outcome AST and ALT). P-value was respectively 0.957 and 0.833.

No significant difference was found for white blood cells (P= 0.708), prothrombin time (P= 0.237), fibrinogen (P=0.375), glycaemia (P= 0.413), lactate (P=0.714), gamma-glutamyl transferase (P=0.254) and alkalic phosphatase (P=0.254).

Also for the DRI no significant difference between both groups was found (P=0.165)

A significant difference was shown between groups for peak bilirubin (P=0.006), peak urea (P=0.007), peak creatinin (P=0.006) and peak albumin (P< 0.001).

3.7.2 Chi Square test

There was no significant difference between the propofol group and sevoflurane group (P=0.231) for instability during the operation as seen in table 7.

Table 7 Crosstable instability and anaesthetic (propofol and sevoflurane)

<table>
<thead>
<tr>
<th>Instability * Anaesthetic Crosstabulation</th>
<th>Anaesthetic</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>prop</td>
<td>sevo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instability Stable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>19</td>
<td>76</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Expected Count</td>
<td>21.6</td>
<td>73.4</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>% within Anaesthetic</td>
<td>63.3%</td>
<td>74.5%</td>
<td>72.0%</td>
<td></td>
</tr>
<tr>
<td>Instable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>11</td>
<td>26</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Expected Count</td>
<td>8.4</td>
<td>28.6</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>% within Anaesthetic</td>
<td>36.7%</td>
<td>25.5%</td>
<td>28.0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>30</td>
<td>102</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Expected Count</td>
<td>30.0</td>
<td>102.0</td>
<td>132.0</td>
<td></td>
</tr>
<tr>
<td>% within Anaesthetic</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>
4. Discussion

4.1 General

Pharmacological preconditioning with anaesthetics seems suitable for transplantation settings since cold/warm ischemia and reperfusion are factors that can easily be controlled (31).

Liver enzymes are indicative of ischemia of the hepatocytes and are elevated after vascular occlusion/reperfusion. We can say that these enzymes and other liver markers are an indication for the ischaemia-reperfusion injury of the liver.

The effect of sevoflurane on the hepatic function has been examined in several studies in pre- and postconditioning and very recently during continuous pharmacological conditioning. Because of conflicting results this practice has not yet found its way to the clinical use.

4.2 Preconditioning

Preconditioning, the administration of sevoflurane during a short period (30 minutes) before reperfusion, has been studied by Beck-Schimmer et al (25). The process of preconditioning is illustrated in figure 17.

![Figure 17: preconditioning with sevoflurane ischemia](image-url)
Nitric oxide (NO) might be the mediator of the beneficial effects seen in ischemic preconditioning with sevoflurane in the liver (18). Possibly this phenomena is based on the release of inflammatory mediators upon hepatic ischemia-reperfusion, which could also trigger a pro-inflammatory cascade in organs other than the liver.

Also the importance of TLR4 is proven in the pathophysiology of ischemia-reperfusion in the heart, kidney and liver. Beck-Schimmer et al. (18) have proposed the hypothesis that the systemic administration of volatile agents might interfere by decreasing TLR4 expression or by blocking these receptors. This study suggests that sevoflurane preconditioning was protective against ischemia/reperfusion injury during liver resection. The volatile anaesthetic showed prevention of hepatic injury, defined by decreased transaminase levels and improved clinical outcome (25, 30). AST was chosen as primary outcome because it is a direct measure of organ damage, sensitive to changes over short periods of time and to treatment effects.

4.3 Pharmacological conditioning

Pharmacological conditioning of the liver consists of continuous administration of volatile anaesthetic agents during surgery, before and after reperfusion of the organ. Various studies failed to confirm the benefit of volatile anaesthetics over intravenous anaesthetics during liver resection with inflow occlusion in terms of peak levels of transaminases and morbidity and mortality (30). A very recent RCT of Beck-Schimmer et al. (32) shows no better effect of sevoflurane anaesthesia in comparison with propofol anaesthesia in liver transplantation.

In our study pharmacological conditioning before, during and after ischemia was performed. Our hypotheses is based on diminished increase of liver transaminases as primary outcome (enzyme markers of liver function). As secondary outcome biochemical markers of liver function were evaluated.

In our study no statistic significant difference between volatile anaesthesia with sevoflurane and intravenous anaesthesia with propofol could be shown during liver transplantation on postoperative transaminase levels. The peak after transplantation was lower for sevoflurane anaesthesia (for AST 543U/L with propofol anaesthesia and 467 U/L with sevoflurane anaesthesia and for ALT 560 U/L with propofol anaesthesia and 551 U/L with sevoflurane anaesthesia) but no significant difference could be shown (for AST and ALT P > 0.05). A decrease was also observed for glycaemia (1.61 g/L with propofol anaesthesia and 1.75 g/L
with sevoflurane anaesthesia) and YGT (81 U/L with propofol anaesthesia and 90 U/L with sevoflurane anaesthesia).

Albumin showed, in contrast, a significant higher peak in the propofol group (2.8 g/dL with sevoflurane anaesthesia and 2.5 g/dL with propofol anaesthesia. However for bilirubin sevoflurane anaesthesia showed a significant difference. Also for urea and creatinine (P < 0.05), peak values were lower in the sevoflurane group as described in table 8.

*Table 8 Significant different biochemical markers*

<table>
<thead>
<tr>
<th>Biochemical marker</th>
<th>Peak propofol</th>
<th>Peak sevoflurane</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>2.5</td>
<td>2.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>4.1</td>
<td>2.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Urea (g/L)</td>
<td>1.14</td>
<td>0.66</td>
<td>0.007</td>
</tr>
<tr>
<td>Creatinin (mg/dL)</td>
<td>1.68</td>
<td>1.08</td>
<td>0.006</td>
</tr>
</tbody>
</table>

The baseline values for bilirubin are in the propofol group 9.6 mg/dl and 1.3 in the sevoflurane group. For urea 0.42 g/L in the propofol group and 0.34 g/L in the sevoflurane group. Creatinin levels in the propofol group were 1.09 mg/dL and 0.91 mg/dL. There is a difference (and especially for bilirubin) already in baseline values between both groups. The significant decrease of peak levels of bilirubin after transplantation might be due to the baseline difference.

Since albumin transfusion is very restricted, the observed difference in albumin levels is difficult to explain and might be due to other factors involved.

In general the overall population is very heterogeneous. The median age in the sevoflurane group is higher (56 years) in comparison with 47.5 years in the propofol group. More men than women are transplanted in both groups, but more women are transplanted with sevoflurane anaesthesia (43%) in comparison with propofol anaesthesia (33%). BMI score was slightly higher in the sevoflurane group (25 kg/m²) in comparison with the propofol group (24.8 kg/m²). The sevoflurane group has lower biochemical markers (WBC, glycaemia, AST and ALT) in comparison with the propofol group.

Also risk factors, such as high urgency transplantation, are higher in propofol group (38%) in comparison with only 8% in the sevoflurane group. Also the MELD scores were 19 in the
sevoflurane group in comparison with 32 in the propofol group. Before transplantation the patients in the propofol group are in a worse condition. DRI ratios were slightly higher in the propofol group (1.79) in comparison with the sevoflurane group (1.67). Both groups have a similar risk of failure as described by Feng et al (14).

The hemodynamic stability is lower in the propofol group (37%) in comparison with the sevoflurane group (25%) but no statistical significance was proven.

The fact that patients in the propofol group were in a worse medical condition compared to the sevoflurane group might have had an impact on our results.

4.4 Limitations

Patient related factors, as well as donor related and procedure related factors have an impact on outcome. In this heterogeneous population these factors aren’t matched for each group, we can say that the “conditioning” group was difficult to compare with the control group.

Propofol was mostly given to patients with encephalopathy or by choice of the anaesthesiologist. This might be a confounding factor.

Good patient selection is important. In our study patients with re-transplantation within the observed period were excluded. This is a confounding factor. Also no information was found weather extended donor criteria liver grafts were used. These are factors associated with lower graft survival.

This study looked to short term indicators, long term indicators were not the endpoint of this study due to complexity and shortage of time.

We did not look for complication ratio, length of stay (LOS), graft survival, liver enzymes after 1 month and 6 months follow up. There is a paucity of studies covering the long-term effects of preconditioning of the liver, and this might be a topic for future research.

We were only able to use rudimentary parameters such as liver enzymes to look for signs of organ protection. To investigate the complex signalling pathways involved in pharmacological preconditioning we would have needed more resources and expensive analysis.
4.5 Conclusion

Our aim to prove that sevoflurane anaesthesia is organ protective in liver transplantation and that it has an impact on clinical outcome couldn’t be proven. Further research might be advised because partially protective effects by sevoflurane anaesthesia (lower bilirubin levels after transplantation) can be shown after liver transplantation.
5. References


Attachments

1. Assignment Of Rights and confidentiality
CONFIDENTIALITY AND ASSIGNMENT OF RIGHTS
UNILATERAL DECLARATION

This declaration is addressed to:

**Ghent University**, public institution with legal personality, having its administrative offices in Belgium, B-9000 Gent, Sint-Pietersnieuwstraat 25, company registration number 0248.015.142 and duly represented by prof. dr. Anne De Paepe, Vice-Chancellor (hereinafter referred to as UGent)

by:

Nabila Belkaid

**student enrolled at UGent in the curriculum:** Master of Medicine in Medicine

**Project:** Dissertation presented in the 2nd Master year

In the course of my studies at UGent and more particularly in the performance of certain research activities in the context of the Project, I shall have access to certain information of a confidential nature belonging to or entrusted by third parties to Ghent University.

I accept this confidential information which shall be disclosed to me with the sole purpose of carrying out my tasks in the Project and shall, for a period of **ten years** counting from the effective date of this declaration, not use this information for any other purpose nor disclose it to any third party without UGent’s prior specific and written consent.

Additionally, I hereby transfer all rights, title and interest in any results of my research activities in the context of the Project to UGent.

This declaration, once signed, will replace all previous written or oral agreements between the parties relating to its subject matter, and contains the entire agreement between the parties.

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature</td>
<td>Preceded by a hand written notice “as agreed and approved”</td>
<td></td>
</tr>
</tbody>
</table>

Effective date: