A Scandinavian multicentre study of machine perfusion technology to mitigate the impact of out of hours liver transplantation on patient outcomes, staff well being and service delivery

Summary

Out-of-hours surgery is associated with increased morbidity and mortality due to higher incidence of intraoperative events and anaesthetic complications. Night time activity poses a risk to employee's health and safety, with increased levels of fatigue, a decrease capacity for undertaking mental or physical tasks and sick leave, all of which may lead to increased healthcare costs.

Liver transplantations (LT) are often performed at night due to complex logistics and to minimise the cold ischemic time to maintain good outcomes. LT are highly complex procedures that are consultant-led and require large multi-disciplinary teams on-call overnight. Novel liver perfusion technologies have demonstrated a clinical benefit and allow prolonged preservation of livers that may enable shifting LT activity to daytime. However the implications for service delivery, outcomes and impact on the wider operating planning are unknown.

This study aims to first determine the impact of night-time transplantation on patient outcomes, team well-being and the associated health economics costs. Secondly it aims to evaluate if machine perfusion technology enables daytime LT and analyse the outcomes and the health economic impact of this approach. This is a Scandinavian multicentre study involving all adult LT between 2019-2023 (2000 patients) in the Nordic liver transplant centres. We will compare the Comprehensive Complication index (CCI®) at 90 days postoperatively and compare costs between daytime and night-time surgery.

We will also undertake a prospective comparison of how timing of surgery affects healthcare workers by undertaking a fatigue assessment, psychomotor vigilance tests and a continuous real time evaluation of 13 vital signs using a wearable device (BioBeat®) during surgery.

We will then undertake a prospective study to evaluate the role of machine perfusion in transforming LT into a daytime activity. We will compare normothermic with hypothermic machine perfusion and evaluate which is better in enabling daytime transplantation. We will evaluate liver function on machine, compare the CCI® between these transplants and a matched cohort from WP1 and determine the health economics of this shift.

Background

Out-of-hours surgery has been shown to lead to increased morbidity and mortality due to intraoperative events and anaesthetic complications. In Scandinavia, as in most parts of the world, most surgical procedures are planned as daytime elective surgery if not considered emergent and requiring to be performed out-of-hours. Such an approach is difficult to apply to liver transplantation (LT) due to challenges with logistics, the complex interplay with donor organ recovery operation and the need to keep ischemia times as short as possible to achieve a successful outcome. The organ retrieval is frequently undertaken at other hospitals than the transplanting centre and is often scheduled out-of-hours to minimise the disruption of the local elective surgical programs. In Scandinavia the transplant centres can rarely demand at what time of the day the donor surgery is performed because of downstream implications for ICU beds and end of life care pathways and therefore transplant practice must be flexible.

Furthermore, in the setting of LT there is no option to delay transplantation to an elective daytime procedure as longer cold ischemic times (CIT) has been heavily linked with higher rates of primary non-function (PNF) and increased graft loss. Due to these reasons practice in LT in Scandinavia has shifted to a large numbers of LTs undertaken out-of-hours to keep CIT within a window that allows for successful outcome.

LT are highly complex procedures and as such are consultant-led and require large specialised multi-disciplinary teams. This translates into a significant amount of personnel being on-call in the event of a transplant. Current literature showed on-call and nighttime activity poses a risk to employee's health with increased levels of fatigue and sick leave. There is also a lack of studies on the health economic impact of a primarily out of hours activity with increased economical compensation and compensatory rest for staff, which might impact the delivery of daytime activity or the costs of the health care delivery in the hospital. Data from other surgical specialties suggests that in-house out of hours senior activity is not cost effective compared to daytime activity. Studies have also shown that approximately 2/3 of the cost of running an operating room (OR) is due to the cost of staffing and as these are much higher for out of hours activity, the cost of overnight OR activity increase significantly. Some studies have demonstrated increased costs for out-of-hours practice with elective procedures starting after 3pm compared to before 3pm.
Novel liver perfusion and preservation technologies have improved the utilisation of organs for transplantation and provide better clinical outcomes. A recent study demonstrated the safety of this approach for hypothermic machine perfusion, where livers were preserved for 14.5 hours on the machine before being transplanted during daytime. No serious adverse effects were reported with this approach, but no health economic calculation was undertaken. A second report from the US demonstrated that the use of normothermic machine perfusion allows for an increased utilization of marginal livers with excellent results whilst allowing a shift to day time transplantation.
Currently, there is conflicting evidence on whether a heavy out-of-hours activity component impacts on patient and graft survival. Earlier studies suggested no differences in outcomes (perhaps influenced by the low proportion of overnight transplant activity), whilst more recent ones demonstrate significant differences comparing night-time with daytime activity. Furthermore, data on the incidence and cost of managing complications as well as a health economic analysis are lacking.

Study rationale and aim

Preliminary data from the Karolinska University Hospital reveals that in 2023, 60% of the liver transplants have an out of hours component (defined as 20.00-08.00). Furthermore, 20% of the transplants took place exclusively out of hours. These transplants took on average an hour longer than daytime transplants and required more blood products during surgery. These preliminary data support our investigation strategy. Therefore the specific aims of this study are to:

a. Determine if there is a difference in the Comprehensive Complication index (CCI®) at 90 days postoperatively comparing daytime to night-time surgery and estimate the health economic costs of current nighttime operating practice.

b. Evaluate the perception of healthcare workers and compare the objective physiological differences between night-time and daytime operating using a wearable monitoring device.
c. Evaluate if the use of machine perfusion enables daytime transplantation and compare which approach provides most benefits and lowest health economic costs for this change in practice.

Materials and methods

Workpackage 1 (WP1) is a multicentre, international, investigator initiated observational retrospective study involving nearly 2000 adult liver transplants performed in the Nordic countries between 2019-2023. Data on time of surgery, complications, biochemistry, intraoperative events, and health economic data will be collected from patient medical records or local registries. The primary endpoint (Comprehensive Complication index (CCI®) at 90 days postoperatively) will be analyzed with a linear regression (ANCOVA) model with the time of surgery (within or outwith hours) as the main effect, adjusted for the stratification variables (recipient and donor risk factors, and study centre). The main effect factor (time of surgery) will also be divided into brackets defined by the time of the day the surgery was performed and cumulative effects will also be examined.
Secondary endpoints will include 1-year patient survival, 1-year graft survival, length of hospital and ICU stay, incidence and management of complications, intraoperative events (according to ClassINTRA classification), duration of surgery and anaesthesia, blood loss volume and required transfusions (erythrocytes and fresh frozen plasma) and cost of transplant procedure (staffing, OR and management of complications) and health related costs in the first-year post transplant.

WP 2 will be a prospective study to evaluate the role of machine perfusion in transforming LT into a daytime activity. We will perfuse livers overnight and proceed with daytime transplantation. Perfusion will be undertaken normothermic machine perfusion in Stockholm and Oslo and hypothermic machine perfusion in Goteborg. We will evaluate liver function during machine perfusion, compare the CCI® between these transplants and a matched cohort from WP1 and determine the health economics of this shift. We will also evaluate which of these technologies provides the highest benefit at the lowest cost.

We will also undertake a multicentre prospective comparison of how timing of surgery affects healthcare workers (surgeons, anesthetists and theatre staff) by undertaking a fatigue assessment, coupled with objective approaches (psychomotor vigilance test) and physiological parameters measurement in the form of 13 cardio-pulmonary vital signs collected in real time using a wearable device (BioBeat®) during surgery. BioBeat® is a CE marked device that allows continuous wireless monitoring of blood pressure, heart rate, pulse pressure, skin temperature, oxygen blood saturation, one lead ECG, stroke volume and cardiac index, systemic vascular resistance, mean arterial pressure and cardiac output. These will be then compared using the time of surgery as the key factor. We will include 20 staff per centre, divided into different categories of personnel.

Study duration

Additional ethical applications will be submitted locally according to the practice of each nation/ before participation/data collection. The study will be conducted in 5 liver transplant centres in Scandinavia. The study is planned to start 2025. Collection of data is estimated to take approximately 12 months for each centre for both the retrospective and prospective part. We estimate 3-6 months for data processing and statistical calculations and a written summary. Another 6 months are planned for any unforeseen delays and need of complimentary data collection and data quality checks.

Project collaborators

The study is designed as a Scandinavian multicentre study, is supported by the Nordic Liver Group and will include all active liver transplant centres in the Nordic countries (Stockholm, Gothenburg, Copenhagen, Helsinki, and Oslo). From each centre one junior and one senior surgeon will collaborate on the project, data analysis and manuscript authorship..
Senior collaborators:
Arno Nordin Helsinki
Markus Gäbel Gothenburg
Soren Pischke Oslo
Allan Rasmussen Copenhagen

Ethical application

DNR for ethical application for the study is 2024-08361-01.

Budget

Total study budget €487,900 of which € 59,900 are thought from Scandiatransplant research grant.

	Scandiatransplant	**Other**	**Total**
1. Salaries (calculated based on 15 days spent at each center x 4 external centres)	**23,300**	**8,000**	**31,300**
2. Laboratory expenses (costs of purchasing BioBeat® device, software, laboratory sample preparation for WP2)	**15,000**		**15,000**
3. Administrative costs	**8,000**		**8,000**
4. **Travel (**based on travel to 4 centres and 15 days spent in each centre collecting data**)**	**13,600**		**13,600**
5. Other (liver perfusion kits for WP2)		**420,000**	**420,000**

Plan of dissemination of study results

The study results will be presented at the Scandiatransplant meetings and all participating centres will be able to present data nationally and locally at meetings and conferences. Results will also be presented at international conferences such as ESOT, ILTS and ATC. Finally results will be published in peer-reviewed journals. Results may also be presented locally to hospital leadership to support wider machine perfusion implementation.