Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	**Normothermic machine perfusion of donor livers prior to transplantation.**
Topic exploration report number:	TER234

Introduction and aims

End-stage liver disease (ESLD) is associated with significant morbidity and mortality and may ultimately require donor liver transplantation. The gold standard for organ preservation is currently static cold storage (SCS). Once the donor organ is retrieved from a deceased donor it is flushed in situ with cold organ preservation solution and placed in sterile bags in an icebox. The preservation solution seeks to prevent cell swelling while the organ is deprived of oxygen and cooling reduces the metabolic demand of the organ. The liver is then transported to the selected transplant hospital and transplanted as soon as possible. Assessment of the suitability of the organ for transplantation is based on the characteristics of the donor before retrieval and the appearance of the liver - no functional assessment of the organ is possible after retrieval. SCS is therefore limited by: (1) the ability to assess the viability of the organ prior to transplant which may affect discard rates; and (2) storage times of around 12 hours due to anaerobic cellular activity which causes damage to the liver.

Portable devices which use normothermic machine perfusion (NMP) to preserve and maintain donor livers have the potential to reduce liver graft injury in patients undergoing liver transplantation and to reduce the rate of organ discard. This can have wider benefits by reducing waiting time lists and associated mortality. NMP can be used as a preservation method for livers already accepted for transplantation, or to undertake a functional assessment on livers which may be suitable for transplantation (potentially reducing discard rates). The devices are estimated to prolong storage times up to 24 hours between retrieval and transplantation, maintaining the liver in a functional state by creating a physiological environment and delivering oxygen and nutrients to the liver at normal body temperature (37°C). This also enables the function of the liver to be tested and supports decisions over the viability of the liver for transplantation. These devices are typically classed as CE mark III (or IVDD Annex II list A, or IVDR class D).

Health Technology Wales researchers searched for evidence of the clinical and cost effectiveness of NMP for donor livers prior to transplantation.

Summary of evidence

Overview

NICE guidance on ex-situ machine perfusion (normothermic or hypothermic) prior to liver transplantation was published in January 2019 (IPG636). This recommended that the procedure only be used with special arrangements for clinical governance, consent, audit or research. Prior to the NICE guidance being published, a systematic review by Jayant et al. (2018) compared NMP to SCS prior to liver transplantation. Most of the studies in this were included by NICE, with the exception of one observational study (Liu et al. 2017). Jayant et al. (2018) found no significant difference in graft survival at 30 days, 3 or 6 months; mortality; primary non-function; hospital stay length; or major complications. Findings were mixed for early graft dysfunction and length of ICU stay.

Another more recent review comparing machine perfusion to SCS prior to kidney or liver transplantation reported subgroup meta-analysis for NMP of liver grafts and was published in 2019 (Bellini et al. 2019). The authors report including a second RCT (Ghinolfi et al. 2019) in addition to the one included by NICE and Jayant et al. (2018) (Nasralla et al. 2018), which would have been published after these reviews were conducted, and an additional observational study (Jassam et al. 2018). Other systematic reviews were identified but these tended to combine NMP and HMP with subgroup analysis less well reported. Bellini et al. (2019) also found no difference between NMP and SCS for primary non-function, or for peak serum AST or bilirubin, but did find that early allograft dysfunction was significantly lower for NMP. One ongoing systematic review is looking at the usefulness of viability assessment parameters collected by NMP in determining the suitability and safety of livers for transplantation. The anticipated completion date of this review is May 2021.

The primary evidence base was not searched given the amount of secondary evidence identified. However, a number of recent case series and observational studies were identified. Some of these compared SCS with NMP initiated upon arrival at the recipient centre with immediate initiation of NMP after retrieval (Bral et al. 2019). Others looked at the usefulness of NMP in identifying otherwise discarded livers suitable for transplant (Mergental et al. 2020; Reiling et al. 2020).

A de novo decision analytic cost-effectiveness model was recently published (after the NICE 2019 guidance) comparing NMP to SCS. This used clinical effectiveness estimates from the RCT by Nasralla et al. (2018). It found NMP to be both more effective and more costly with an estimated ICER of £7,876 per QALY gained. Probabilistic sensitivity analysis found NMP to have a 99% probability of being cost-effective at a £20,000 willingness-to-pay threshold. An estimated 54 additional livers were utilised using NMP.

Technology assessments

NICE produced guidance on ex-situ machine perfusion (normothermic or hypothermic) for extracorporeal preservation of livers for transplantation in January 2019 (IPG636). They found that the evidence available raised no major safety concerns but was limited in quantity on efficacy. They recommended that the procedure only be used with special arrangements for clinical governance, consent, audit or research. The rapid review conducted at the time identified and included one RCT (Nasralla et al. 2018), three case-control studies (Ravikumar et al. 2016; Bral et al. 2017; Selzner et al. 2016), two non-randomised controlled studies (Hoyer et al. 2016; Watson et al. 2017), and one case series (Mergental et al. 2016) which used NMP (and four case control studies which used hypothermic MP). The Committee noted

that the evidence on machine perfusion methods varied by temperature used (hypo- or normothermic); the point at which machine perfusion was started; and the duration. However, it was also that it may allow for better assessment of marginal livers and increase the number available for transplantation. A research recommendation was issued that further research on ex-situ machine perfusion for extracorporeal preservation of livers for transplantation should report the exact method of perfusion used (hypo- or normothermic), graft survival, and use of marginal grafts.

Systematic reviews

Jayant et al. (2018) undertook a review of prospective trials comparing NMP to SCS prior to liver transplantation and identified five trials (Nasralla et al. 2018; Liu et al. 2017; Bral et al. 2017; Selzner et al. 2016; Ravikumar et al. 2016). Where reported, no studies found a significant difference in graft survival at 30 days, 3 months or 6 months; mortality; primary non-function, hospital stay days, or major complications between groups (three, two, three, two, three, four and two studies reported this respectively). One study found a significant difference in early graft dysfunction compared to three which did not (though this was the only RCT included). One study found a significant difference in ICU stay days compared to three which did not. The authors concluded that NMP may extend the safe utilisation of more marginal spectrum liver donor grafts but that this remains to be proven in practice. However, safety and efficacy has been demonstrated.

Bellini et al. (2019) undertook a systematic review and meta-analysis looking at organ viability and risk of reperfusion injury in machine perfusion compared to SCS for kidney and liver grafts. Of the included articles, four compared NMP to SCS for liver grafts – two of which were RCTs (Ghinolfi et al. 2019; Nasralla et al. 2018) and two of which were observational in nature (Jassem et al. 2018; Ravikumar et al. 2016). Meta-analysis found no difference between NMP and SCS for liver grafts for primary non-function (though an odds ratio was only estimable for one study – Nasralla et al. 2018), peak serum AST (four studies) and peak serum bilirubin (four studies). Meta-analysis did find early allograft dysfunction rates were significantly lower for NMP than for SCS (3 studies).

Other systematic reviews of machine perfusion prior to liver transplantation were identified but subgroup analysis for NMP was less well reported. For example, Lai et al. (2018) undertook a systematic review of machine perfusion prior to liver transplantation. They included 27 articles on 173 cases, of which 65 cases were of NMP. Overall, post-transplantation outcomes were reported to be excellent. Jia et al. (2020) compared machine perfusion and SCS of liver allografts. NMP was not found to significantly protect grafts from total biliary complications and ischaemic cholangiopathy (unlike hypothermic). There were also no significant differences in primary non-function, hepatic artery thrombosis, postreperfusion syndrome, 1-year patient survival, or 1-year graft survival. Lai et al. (2020) undertook a review of machine perfusion to evaluate liver grafts with macrovesicular steatosis. Of the 54 cases identified (in 16 included articles), NMP was performed in 32 (59%). Overall, no differences were found in terms of post-transplant death or severe complications. Boteon et al. (2018) looked at the impact of machine perfusion of the liver on post-transplantation biliary complications. Of the 15 articles included, six were of NMP. Some biliary complications, such as biliary leak and anastomotic biliary strictures, were reported with similar incidences with all machine perfusion techniques. The authors found overall there was less clinical evidence available to support NMP.

In addition, there was a horizon scanning report on the use of OrganOx metra for liver preservation during transplantation produced by NIHR in 2013.(2) One ongoing study was identified which completed in 2013 (ISRCTN14355416).

Ongoing systematic reviews

One ongoing systematic review was identified which is looking at the usefulness of viability assessment parameters collected by NMP in determining the suitability and safety of livers for transplantation. The anticipated completion date is May 2021. There is also an ongoing systematic review of NMP and HMP compared to SCS for transplanted heart, lungs, liver and kidneys which will report subgroup analysis of the different organs. It is not clear if subgroup analysis will be reported for NMP and HMP separately. The anticipated completion date was September 2020.

There is one systematic review ongoing looking at normothermic perfusion of the kidney prior to transplantation which is due to complete in June 2021.

Primary studies

Clinical effectiveness

NMP versus SCS

One RCT was identified by a number of sources and appears to be a key determining factor in the evidence base for NMP prior to liver transplantation. Nasralla et al. (2018) found significant reductions in peak serum aspartate transaminase (AST) and early allograft dysfunction (EAD) rates using NMP compared to SCS. Rates of organ utilisation and liver preservation times were also increased. The incidence of adverse events was lower for NMP compared to SCS. Incidence was 11.7% versus 18.3% for patients with Clavien-Dindo grade I adverse events respectively. Incidence was 3.9% versus 9.2% for grade IVa, 2.3% versus 5.5% for grade IVb, and 3.9% versus 1.8% for grade V respectively.

The review by Bellini et al. (2019) identified an additional RCT (Ghinolfi et al. 2019) which would have been published after the reviews by NICE (2019) and Jayant et al. (2018) were conducted.(20) This compared NMP following SCS to SCS in recipients of older liver grafts (≥70 years) (N=20). There was no significant difference between groups in mortality; primary non-function; graft loss; peak AST; peak ALT; peak bilirubin; vascular complications; biliary complications; early allograft dysfunction; post-reperfusion syndrome; and hospital stay. However, the study may not have been powered to detect these outcomes. There was no significant difference in peak aspartate aminotransferase between groups but there was histological evidence of significantly more reduction in ischemia/reperfusion injury (IRI) with NMP. The authors concluded that use of NMP with older liver grafts is associated with histological evidence of reduced IRI but that the clinical benefit remains to be demonstrated.

The Topic Proposer also submitted a case series (N=34) not yet published. Cardini et al. (2020) reported the findings of a single-site experience using NMP and found 25 (74%) livers were successfully transplanted after preservation of up to 38 hours. Graft and patient survival was 88% at 20 months. A single case report by Manzia et al. (2019) described a nonagenarian liver successfully transplanted after NMP.(29)

NMP versus SCS followed by NMP

Bral et al. (2019) was a non-randomised study (N = 46) comparing delayed NMP (transported with SCS and NMP initiated upon arrival at the recipient centre) with immediate initiation of NMP after retrieval (median hours of NMP were 7.8 and 10.3 respectively, while median total preservation time was 14.3 and 13.3 hours respectively). End perfusion lactate and hepatic artery flow were significantly lower with immediate initiation of NMP than with SCS then NMP, and portal vein flow was significantly higher. There was no difference between groups in peak perfusion AST, ALT or lactate, or in bile production. In recipients, there was no difference in EAD incidence, biliary complications, artertial stenosis, or in 30-day, 3-month or 6-month survival rates. However, ICU stay and hospital stays were significantly shorter in the SCS followed by NMP group.

Ceresa et al. (2019) reported a case series of 30 donor livers which underwent SCS for 3-8 hours followed by NMP. The 30-day and 12-month graft survival was 94% and 84% respectively. Median inpatient stay was 13 days and overall patient survival at 12 months was 90%. Three (10%) livers were discarded following NMP. Seven (23%) patients developed Clavien-Dindo grade 3b complications and 11 (35%) developed minor complications.

Usefulness of NMP in identifying otherwise discarded livers suitable for transplant

Mergental et al. (2020) reported the findings of the VITTAL trial which was a prospective, non-randomised trial to evaluate the usefulness of NMP in assessing the viability of livers deemed unsuitable for transplantation, and to transplant those that met predetermined criteria. A total of 31 previously discarded livers (25% of those suitable for trial consideration) were included and underwent NMP. Of these, 22 (71%) livers were transplanted. At 90 days graft survival was 100%. At 12 months graft and patient survival was 86% and 100% respectively. Seven (32%) patients developed Clavien-Dindo grade ≥3 complications. Median ICU and hospital stays were 3.5 days and 10 days respectively.

Reiling et al. (2020) reported a case series of patients who received liver transplants where NMP following SCS was used to assess the livers which had previously declined for transplantation. Median hospital stay was 11.5 days and three patients experienced complications.

Cost-effectiveness studies

A recent study by Javanbakht et al. (2020) reports on a de novo decision analytic model (decision tree and Markov model) comparing NMP (OrganOx metra) to SCS over a lifetime horizon. Clinical effectiveness estimates were based on the RCT by Nasralla et al. (2018). Incorporated costs included: the initial intervention (disposables, staff time, solutions, lease fee), use of an icebox, ICU stay, treatment of ESLD, additional days in hospital, transplantation, renal replacement therapy, medicines for the management of post reperfusion syndrome, and post-transplantation immunosuppressants. NMP was found to be more effective and more costly. The total costs per patient were estimated to be £46,711 and £37,370 for NMP and SCS respectively, while the effectiveness was estimated to be 10.27 and 9.09 QALYs respectively. The estimated ICER was £7,876 per QALY gained. Probabilistic sensitivity analysis found NMP to have a 99% probability of being cost-effective at a £20,000 willingness-to-pay threshold. An estimated 54 additional livers were utilised using NMP.

Areas of uncertainty

The evidence base continues to develop for both NMP compared to SCS for transport to recipient centres and for assessing donor livers that would otherwise have been discarded. The evidence for the former is relatively well developed with at least two RCTs and a cost effectiveness study. While the latter is still dependent on observational studies and case series. As noted by NICE (2019), studies prior to their review were often hampered by not separating out findings for NMP from HMP. This appears to have improved since the research recommendation was issued.

Conclusions

In summary, the evidence base has recently been assessed by NICE but is continuing to develop, with at least two new relevant studies published since. Initial findings suggest NMP does not improve most of the outcomes reported when compared to SCS for transport to the recipient centre. The exception to this is potentially graft dysfunction. There is also a developing evidence base around the use of NMP to assess otherwise discarded livers and improve donor availability, which could ultimately reducing waiting list times. A recent decision analytic cost-effectiveness model has been published which found NMP to be both more effective and more costly with an estimated ICER of £7,876 per QALY gained over a life-time time horizon. Probabilistic sensitivity analysis found NMP to have a 99% probability of being cost-effective at a £20,000 willingness-to-pay threshold. It is difficult to estimate whether inclusion of the recent clinical evidence generated would result in a different finding to the NICE guidance published in January 2019. However, recent cost-effectiveness evidence suggests that NMP may be a cost-effective intervention.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence/guidance/advice. Other organs: 1. Machine perfusion systems and cold static storage of kidneys from deceased donors. NICE (Multiple) Technology Appraisal Guideline 165. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/mta_resources/appraisal_165.aspx
Health Technology Assessment Group	We did not identify any relevant evidence/guidance/advice.
Health Information and Quality Authority	We did not identify any relevant evidence/guidance/advice.
EUnetHTA	We did not identify any relevant evidence/guidance/advice.
International HTA Database	2. OrganOx metraTM for liver preservation during transplantation. NIHR Horizon Scanning Centre (2013). https://database.inahta.org/article/13785 or http://www.io.nihr.ac.uk/wp-content/uploads/migrated/2500.0b3909be.FinalOrganOxMetraforliverpreservation.pdf Other organs: 3. Safety and effectiveness of perfusion machine in solid organ transplantation. Andalusian Health Technology Assessment Area (2016). https://database.inahta.org/article/18837 4. Portable normothermic cardiac perfusion system in donation after cardiocirculatory death: a health technology assessment. Ontario Health (2020). https://database.inahta.org/article/18798 5. An observational study of donor ex vivo lung perfusion in UK lung transplantation: DEVELOP-UK. NIHR Health Technology Assessment Programme (2016). https://database.inahta.org/article/12028 6. Machine perfusion in kidneys from deceased donors – a rapid assessment – synthesis. Belgian Health Care Knowledge Centr (2014). https://database.inahta.org/article/15200 7. The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic evaluation. NIHR Health Technology Assessment (2009). https://database.inahta.org/article/8471 8. LifePort kidney transporter: portable donor kidney transporter/perfuser. Adelaide Health Technology Assessment (2009). https://database.inahta.org/article/9321 9. Pulsatile machine perfusion compared to cold storage in kidney preservation. Technology Assessment Unit of the McGill University Health Centre (2007). https://database.inahta.org/article/6886 10. The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. NIHR Health Technology Assessment programme (2003). https://database.inahta.org/article/2911
UK guidelines and guidance	

SIGN	We did not identify any relevant evidence/guidance/advice.
NICE	11. Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation (IPG636) (2019). https://www.nice.org.uk/guidance/ipg636 AND research recommendation (2019) https://www.nice.org.uk/researchrecommendation/further-research-on-ex-situ-machine-perfusion-for-extracorporeal-preservation-of-livers-for-transplantation-should-report-the-exact-method-of-perfusion-used-such-as-hypothermic-or-normothermic-graft-survival-and-the-use-of-marginal-grafts Other organs: 12. Normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death (IPG549) (2016). https://www.nice.org.uk/guidance/ipg549 13. Ex-situ perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplantation. In development (IPG10149). https://www.nice.org.uk/guidance/indevelopment/gid-ipg10149
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	14. Lai et al. (2018). Role of perfusion machines in the setting of clinical liver transplantation: a qualitative systematic review. https://www.epistemonikos.org/en/documents/4015c817fc2cbdbefed7931a8f3cc0fd15be2283 15. Jia et al. (2020). A systematic review and meta-analysis of machine perfusion vs static cold storage of liver allografts on liver transplantation outcomes: the future direction of graft preservation. https://www.epistemonikos.org/en/documents/fca25b74d93608786dc5cffe796e5cde6d9bceeb 16. Lai et al. (2020). Use of machine perfusion in livers showing steatosis prior to transplantation: a systematic review. https://www.epistemonikos.org/en/documents/10dec6f74fc204627824b9f753f1b355c42dd588 17. Boteon et al. (2018). Impact of machine perfusion of the liver on post-transplant biliary complications: a systematic review. https://www.epistemonikos.org/en/documents/a716b25ecaeb29a38fdd2510f0dc4d5f38360355 Other organs: 18. Prudhomme et al. (2020). Ex situ perfusion of pancreas for whole-organ transplantation: is it safe and feasible? A systematic review. https://www.epistemonikos.org/en/documents/15b4c5cb265d3fc8fac614260e805a14b63b4c09
https://www.tripdatabase.com/	19. Jayant et al. (2018). The role of normothermic perfusion in liver transplantation (TRaNsIT Study): a systematic review of preliminary studies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5985064/ 20. Bellini et al. (2019). Machine perfusion for abdominal organ preservation: a systematic review of kidney and liver human grafts. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723966/
Cochrane library	We did not identify any additional relevant evidence/guidance/advice.
Medline	We did not identify any additional relevant evidence/guidance/advice.
Primary studies	
https://www.epistemonikos.org/en/	Not searched – sufficient secondary evidence.
https://www.tripdatabase.com/	Not searched – sufficient secondary evidence.
Cochrane library	Not searched – sufficient secondary evidence.
Medline	Not searched – sufficient secondary evidence.
Ongoing primary or secondary research	
PROSPERO database	21. A meta-analysis on viability assessment criteria during normothermic machine perfusion of the liver. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=193764

	22. Normothermic and hypothermic machine perfusion versus static cold storage – evaluating graft and patient outcomes in the transplanted organs of the heart, lungs, liver, and kidneys as a systematic review. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=186389 23. The role of normothermic perfusion in liver transplant: a systematic review of preliminary studies. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=86034 Other organs: 24. Normothermic preservation of the kidney – a systematic review of perfusion solutions. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=192664
Clinicaltrials.gov	Not searched – sufficient secondary evidence.
Other	
	Evidence provided by the topic proposer – non-randomised comparative studies 25. Bral et al. (2019). A back-to-base experience of human normothermic ex situ liver perfusion: does the chill kill? Liver Transplantation 25: 848-858. Evidence provided by the topic proposer – cost-effectiveness studies 26. Javanbakht et al. (2020). Cost-utility analysis of normothermic liver perfusion with OrganOx compared to static cold storage in the United Kingdom. Journal of Medical Economics – ahead of print. Evidence provided by the topic proposer – case series 27. Cardini et al. (2020). Clinical implementation of prolonged liver preservation and monitoring through normothermic machine perfusion in liver transplantation. Transplantation – ahead of print. 28. Ceresa et al. (2019). Transient cold storage prior to normothermic liver perfusion may facilitate adoption of a novel technology. Liver Transplantation 25: 1503-1513. 29. Manzia et al. (2019). Liver transplantation with a normothermic machine preserved fatty nonagenarian liver: a case report. International Journal of Surgery Case Reports – ahead of print. 30. Mergental et al. (2020). Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nature Communications 11: 2939. 31. Reiling et al. (2020). Assessment and transplantation of orphan donor livers – a 'back-to-base' approach to normothermic machine perfusion. Ahead of print.

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Concepts used:	Normothermic machine perfusion; normothermic; perfusion; organox