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Impact of machine perfusion of the liver on post-transplant biliary complications: A systematic review

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Abstract

AIM

To review the clinical impact of machine perfusion (MP) of the liver on biliary complications post-transplantation, particularly ischaemic-type biliary lesions (ITBL).

METHODS

This systematic review was performed in accordance with the Preferred Reporting Systematic Reviews and Meta-Analysis (PRISMA) protocol. The following databases were searched: PubMed, MEDLINE and Scopus. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". Clinical studies reporting results of transplantation of donor human livers following *ex situ* or *in situ* MP were analysed. Details relating to donor characteristics, recipients, technique of MP performed and post-operative biliary complications (ITBL, bile leak and anastomotic strictures) were critically analysed.

RESULTS

Fifteen articles were considered to fit the criteria for this review. *Ex situ* normothermic MP was used in 6

studies, *ex situ* hypothermic MP in 5 studies and the other 4 studies investigated *in situ* normothermic regional perfusion (NRP) and controlled oxygenated rewarming. MP techniques which have *per se* the potential to alleviate ischaemia-reperfusion injury: Such as hypothermic MP and NRP, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques. There is currently less clinical evidence available to support normothermic MP as a mitigator of biliary complications following liver transplantation. On the other hand, restoration of organ to full metabolism during normothermic MP allows assessment of hepatobiliary function before transplantation, although universally accepted criteria have yet to be validated.

CONCLUSION

MP of the liver has the potential to have a positive impact on post-transplant biliary complications, specifically ITBL, and expand extended criteria donor livers utilisation.

Key words: Liver transplantation; *Ex situ* machine perfusion of the liver; Donation after circulatory death; Non-anastomotic intra-hepatic stricture; Ischemic-type biliary lesions; Extended criteria donors

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Core tip: Post-transplant biliary complications are one of the main culprits responsible for the high patient morbidity following extended criteria donor liver transplantation. In its most severe form, ischaemic-type biliary lesions, can lead to graft failure and re-transplantation. Machine perfusion (MP) of the liver is a promising approach in reconditioning high-risk organs. Clinical studies have, so far, focussed on the impact of MP on hepatocellular function recovery and assessment. In this review we present the clinical evidence of the effect of MP on post-transplant biliary complications and discuss how, in the future, this approach can reduce these complications further.

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INTRODUCTION

Post-transplant biliary complications: The current scenario

Post-transplant biliary complications often require laborious and costly interventions, placing a heavy burden on health resources and adversely affecting patient outcomes^[1,2]. The incidence of these complications is increasing as a

result of the growing utilisation of extended criteria donor (ECD) organs, mainly from donation after circulatory death (DCD). Biliary complications such as biliary leak and anastomotic strictures are primarily related to surgical technicalities and are usually successfully managed with endoscopic procedures^[3]. The most severe form of post-transplant biliary complication is non-anastomotic intrahepatic strictures (NAS). NAS is characterised by the occurrence of diffuse intra-hepatic strictures in the biliary tree and it was initially associated with hepatic artery thrombosis^[4]. The ischaemic donor biliary tree was found to develop necrosis with fibrotic strictures, dilatations and potentially biliary casts^[4]. Thereafter it was demonstrated that similar lesions occurred in the presence of a patent hepatic artery without evidence of recurrence of biliary disease. This entity was subsequently classified as ischaemic-type biliary lesion (ITBL)^[5].

The reported incidence of ITBL is approximately 10%-30% for controlled DCD and 1%-3% for donation after brain death (DBD) organs^[6-10]. Patients generally present with elevated liver function tests suggesting cholestasis (bilirubin, alkaline phosphatase and gamma-glutamyltransferase) within a few months of transplantation and may be asymptomatic initially. Initial work-up includes exclusion of hepatic artery thrombosis and anastomotic biliary strictures. Imaging investigations consist of non-invasive magnetic resonance cholangiopancreatography (MRCP) and computed tomographic cholangiography, or direct cholangiographic methods, such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography. Due to the high reliability of current non-invasive imaging techniques in diagnosing biliary strictures, invasive procedures are currently reserved for scenarios where an intervention is planned, such as stricture dilatation, stenting or stone extraction^[11,12]. With ITBL, imaging confirms the presence of fibrotic strictures, in most cases located around the bifurcation of the common bile duct leading to dilatation of the intra-hepatic biliary system^[1,8]. Figure 1 illustrates these typical imaging features of ITBL following liver transplantation. The obstructive strictures cause cholestasis with formation of sludge and casts that predispose to cholangitis, frequently requiring surgical or endoscopic intervention. Despite these measures, approximately 50% of patients with ITBL require re-transplantation or die^[13].

Although the pathogenesis of ITBL is still not fully understood a growing body of evidence suggest that it is partially associated with ischaemia-reperfusion injury (IRI)^[14,15]. Noack *et al*^[16] in a well-designed *in-vitro* study using rat-derived bile duct cells showed that they were more resistant to anoxia than hepatocytes, however during reoxygenation they produced higher amounts of reactive oxygen species (ROS). This was associated with increased rates of bile duct cell death when compared to hepatocytes^[16]. It has been shown that mitochondrial ischaemic induced injury leads to ROS production during reperfusion which in turn causes

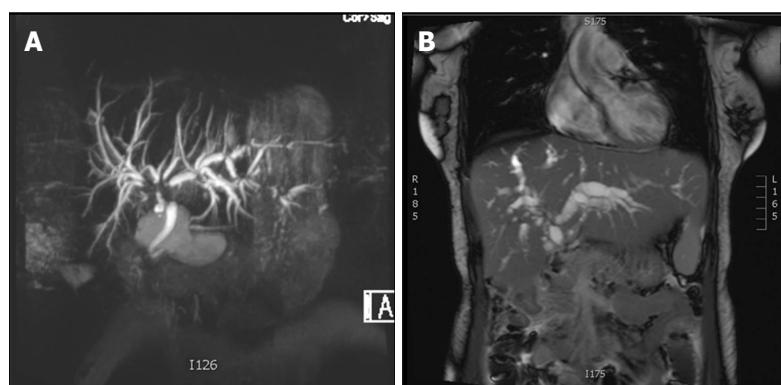


Figure 1 Magnetic resonance cholangiopancreatography images of ischemic-type biliary lesions following liver transplantation. The images show two recipients of livers from donation after circulatory death donors that developed ischemic-type biliary lesions within 60 d following transplantation. Hepatic artery thrombosis and anastomotic biliary strictures were ruled out. A: A typical lesion is seen affecting the bifurcation of the common hepatic bile duct with moderate dilatation of the intrahepatic biliary tree; B: The image shows strictures at the bifurcation of the common hepatic bile duct, diffuse intra-hepatic strictures and a severe dilatation of the intrahepatic biliary tree.

oxidative injury and activation of the inflammatory cascade^[17,18]. Conversely, clinical series have reported severe injury to the biliary epithelium just after cold static storage^[19,20]. Garcia-Valdecasas *et al.*^[15] using a porcine transplantation model suggested a direct relationship between prolonged ischaemic times and cell injury. Indeed, other clinical series have confirmed the association of longer cold ischaemic time (CIT) and higher rates of ITBL^[21-24]. A similar relationship has been observed with warm ischemic time in DCD liver transplantation^[15,25]. A large clinical series of donor bile duct biopsies before liver transplantation showed similar injury to the biliary epithelium after static cold storage (SCS), and that it was exacerbated after reperfusion; however, this did not correlate with the development of ITBL^[26]. Nevertheless, the authors reported a strong association between ITBL and damage to the peribiliary vascular plexus and peribiliary glands. As progenitor biliary cells are known to reside in the peribiliary glands, the former finding suggests an association between ITBL and an attenuated regenerative capacity of the biliary epithelium^[26,27]. Ischaemic injury is likely to play a major role in ITBL pathogenesis, although other factors have also been shown to be implicated. Immunological mediated injury to the biliary epithelium has been associated with ITBL^[28]. It may be the result of direct immunological damage to the biliary epithelium *via* a rejection reaction^[29]; or, indirect, secondary to the development of arteriopathy^[29,30]. This cross reactivity is described in scenarios of cytomegalovirus infection^[30], ABO incompatibility^[31] and transplantation for primary sclerosing cholangitis^[1]. Bile salt toxicity has also been investigated as a potential cause for ITBL by having a direct detergent effect on phospholipid cellular membranes of the biliary epithelium^[28]. Flushing of the biliary tree during organ procurement is necessary in order to remove all bile salts that could damage cholangiocytes^[5,28]. Furthermore, an imbalance in the post-transplant bile composition, with a higher bile salt/phospholipid ratio, due to inefficient ATP-dependent

biliary transporters has been suggested as a predictive factor for ITBL^[32]. While detail of the pathogenesis of ITBL is beyond the scope of this review, information on the implicated mechanisms can be found in a number of published reviews^[9,28].

Machine perfusion of donor livers

The utilisation of DCD livers is increasing. In 2017, in the United Kingdom, they constituted 28% of the livers transplanted^[33]. Furthermore, the rising prevalence of donor obesity (body mass index greater than 30 kg/m²) and an ageing population continue to compound the risks to those livers^[33]. These high-risk ECD organs are associated not only with a higher risk of graft dysfunction post-transplantation but also increased rates of ITBL^[34]. Despite these disadvantages, their utilisation is required to tackle the ever-growing discrepancy between organ donor supply and demand. Machine perfusion (MP) of the liver is being developed as a means of assessment and reconditioning of ECD donors, potentially allowing for safer transplantation of these high-risk livers^[34,35]. Different techniques of MP have been developed; it can be performed *in situ* during organ procurement or *ex situ* after the procedure. With regards to livers, the only technique of *in situ* MP described so far is normothermic regional perfusion (NRP)^[8]. *Ex situ* MP protocols vary in terms of oxygenation (active or pre-charged oxygenation), perfusate temperature (hypothermic, subnormothermic, gradual rewarming and normothermic), timing of perfusion (preservation or end-ischemic) and *via* of organ perfusion (portal vein alone or dual portal vein and hepatic artery perfusion)^[34,36].

Hypothermic machine perfusion (HMP) has been performed around 10 °C in most studies^[37,38]. At this temperature liver metabolism is reduced; and, passive oxygen delivery by diffusion in an oxygen carrier-free perfusate is enough to support the organ^[39]. The first published clinical series employed pre-charged oxygen delivery to the organs^[37], technique that was later followed by active oxygenation of the perfusate^[40].

Hypothermic oxygenated MP can be performed *via* portal vein alone (HOPE) or *via* portal vein and hepatic artery (dual hypothermic oxygenated perfusion - D-HOPE)^[41-43]. Both techniques have shown the capacity of improve mitochondrial oxidative function prior to rewarming, resulting in increased adenosine triphosphate (ATP) synthesis and a reduction in ROS production, oxidative tissue injury and activation of the inflammatory cascade^[42,43].

Normothermic machine perfusion (NMP) maintains the organ at physiological temperatures (37 °C) and therefore restores full metabolic activity. This enables the possibility of functional or viability assessment prior to transplantation, a major advantage of NMP when compared to other perfusion techniques^[44,45]. It also opens up a window of opportunity for *ex situ* therapeutic interventions^[34]. Furthermore, previous studies have reported on the safety of extended normothermic perfusion of organs, which may facilitate transportation and logistical management of busy transplant units^[46]. However, potential drawbacks of NMP are that it requires obligatorily the inclusion of an oxygen carrier in the perfusate, and NMP inevitably induces reperfusion injury to some extent.

Subnormothermic machine perfusion (SMP) has been performed at around 20 °C in most studies. It encompasses purely SMP and the controlled oxygenated rewarming (COR) from 10 °C to 20 °C^[47,48]. The increase in temperature from HMP to SMP is suggested to be enough to increase liver metabolism to an extent that it would allow assessment of organ function without inducing the detrimental changes associated with organ reperfusion at normothermic temperatures^[48]. Evidence for the clinical benefits is available for COR perfusions, it was associated with lower markers of hepatocellular injury after transplantation and enhanced graft function through the avoidance of subtle changes in organ temperature^[47].

For DCD livers, there are encouraging reports of *in situ* oxygenated NRP. It has been successfully applied to controlled DCD donors (withdrawal of life support in patients with irreversible clinical conditions) and uncontrolled DCD (witnessed cardiac arrest without response to resuscitative measures)^[8,49,50]. NRP limits ischaemia and prevents depletion of energy stores prior to SCS and this is suggested to be essential for uncontrolled DCD donors and beneficial for controlled DCD^[8].

More recently, combinations of MP techniques have been shown to merge the advantages of individual protocols, enhancing the rescue of liver function what may potentially improve graft function after transplantation^[51,52]. Despite differences between techniques, MP has the potential to limit ischaemic injury to the organ, thus offering a safer preservation environment and an opportunity for organ reconditioning which could mitigate IRI.

As discussed herein, the current evidence shows that cholangiocytes are more vulnerable to IRI than

hepatocytes and that the pathogenesis for biliary injury goes beyond IRI. Therefore, investigation of the impact of MP on biliary function specifically, and not only on hepatocellular function, is fundamental. The aim of this review was to investigate the current clinical evidence available regarding the effect of MP on post-transplant biliary complications, focusing on ITBL.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Systematic Reviews and Meta-Analysis (PRISMA) protocol^[53].

The following databases were searched for the development of this review: PubMed, MEDLINE and Scopus. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". The literature review was performed until June 20, 2018 and there were no limits on the date for inclusion of publications. The literature search strategy used for one database is presented in the Supplementary Table S1.

The screening and selection of articles were independently performed by two authors (Yuri L Boteon and Amanda PCS Boteon). There was no disagreement in study selection between authors. Manuscript titles that were not related to the main scope of the review were excluded. Full abstracts were then read and excluded if found not to be relevant to the review. Finally, full papers were assessed for eligibility and included in this review. The flow diagram for the literature selection process is shown in Figure 2.

Inclusion criteria were: (1) clinical studies reporting results of transplantation of donor human livers following *ex situ* or *in situ* MP; and (2) articles written in English and published. Exclusion criteria were: (1) absence of transplantation following MP; (2) exclusively animal models; (3) single case report; (4) review articles; and (5) articles not written in English.

Details relating to donor characteristics [type, age, donor risk index (DRI), warm ischaemic time (WIT), CIT], recipients [age, model for end-stage liver disease (MELD)], perfusion (type of perfusion, oxygenation, timings) and post-operative biliary complications (ITBL, leak and anastomotic strictures) were retrieved from each manuscript and critically analysed. Studies were assessed in terms of study design, methods and outcomes. No review protocol was registered before this review was started. No simplifications or assumptions were made, and any identified risk of bias is discussed throughout the review.

RESULTS

Fifteen articles were considered to fit the criteria for this review. A diagrammatic summary of the screening process is provided in Figure 2.

MP and ischemic type biliary lesions (ITBL)

Eight out of fifteen clinical studies utilised an end-

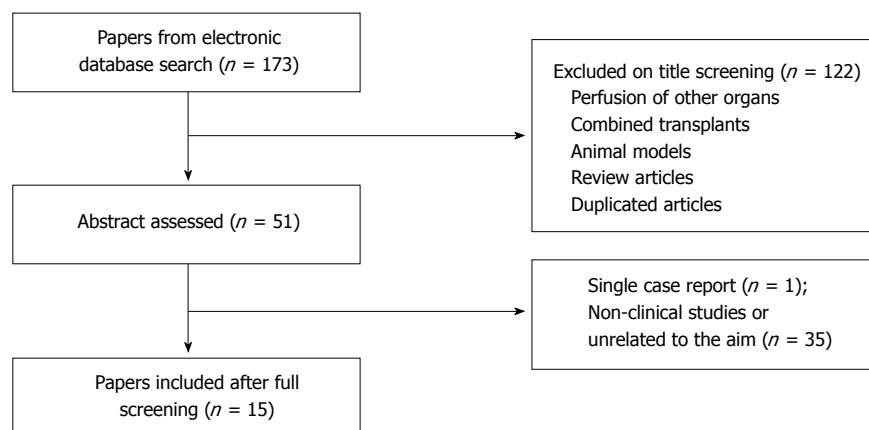


Figure 2 Study flow diagram for systematic review of the literature on the impact of machine perfusion of the liver and post-transplant biliary complications. Following literature search duplicate articles were excluded and the titles screened. The selected abstracts were then read and non-clinical studies or reports unrelated to the aim of the review were excluded.

ischemic model of MP (MP commenced after a variable period of SCS), 4 studies utilised preservation MP (MP from organ procurement up to transplantation) and 3 employed NRP. NMP was used in 6 studies, HMP in 5 studies and the other 4 studies investigated NRP and COR. HMP with active perfusate oxygenation (HOPE and D-HOPE) studies were seen to be currently focused on DCD organs and HMP with pre-charged oxygenation on DBD organs. NMP studies used both donor types, however preservation studies explored a higher proportion of DBD compared to DCD organs. The contrary was seen for end-ischemic NMP.

Donor and recipients characteristics, of the cases included in individual studies, are presented in Table 1. It also reports the rates of ITBL. Table 2 describes the incidence of bile leak and anastomotic biliary stricture within the different studies. Studies characteristics were described therein, as it was their design.

NMP and post-transplant biliary complications

The largest clinical trial involving NMP as a preservation strategy was recently published by Nasralla *et al.*^[46]. Following procurement, transplantable livers were randomised and allocated to the intervention group that had NMP up to the point of transplantation or a control group that had conventional SCS. From the 121 livers perfused, 87 were from DBD donors and 34 from DCD donors. Results did not show differences in bile duct complications between groups, with one patient in each arm developing ITBL within the first year, both requiring re-transplantation. On MRCP, the rates of NAS were similar between groups for DBD (NMP 7.4% vs SCS 5.4%; $P = 0.678$) and DCD (NMP 11.1% vs SCS 26.3%; $P = 0.180$). The incidence of anastomotic strictures was also similar for DBD or DCD organs (NMP 40.7% vs SCS 41.8%; $P = 0.909$; and, NMP 48.1% vs SCS 57.9%; $P = 0.515$, respectively)^[46].

Other clinical studies investigating NMP using a preservation approach^[54-56] involved smaller patient numbers, the majority of which were from DBD donors,

and did not specifically report the incidence of ITBL (Table 1). Ravikumar *et al.*^[55] published the first phase 1 clinical trial demonstrating the safety and feasibility of NMP in a preservation approach, as an alternative to SCS. In all, 20 donor livers (16 DBD and 4 DCD) were transplanted following NMP. The 30-day graft survival was similar to static cold stored livers and the median peak aspartate aminotransferase within the first 7 post-operative days was lower. In terms of biliary complications, the authors reported the occurrence of 4 cases of anastomotic biliary strictures in the NMP group^[55].

The two studies of NMP after a period of SCS (end-ischaemic model) involved organs that were deemed too high risk for transplantation^[57,58]. These studies predominantly used DCD livers and applied predefined viability criteria prior to transplantation. Mergental *et al.*^[57] did not observe any biliary complications at 7 mo of follow up post-transplantation. Watson *et al.*^[58] reported the occurrence of 4 cases of ITBL in 16 DCD liver transplants, of which 3 needed re-transplantation. The authors of the latter study concluded that that NMP per se does not prevent ITBL but may provide biomarkers to identify livers that are high risk, such as maximum bile pH > 7.5 and bile glucose ≤ 3 mmol/L or ≥ 10 mmol less than perfusate glucose^[58].

HMP and post-transplant biliary complications

The first clinical study using HMP prior to transplantation was performed by Guarrera *et al.*^[37] Twenty DBD livers were perfused after a period of SCS in a non-actively oxygenated model of HMP. ITBL rate was reported as 5%, half of the incidence of the control matched cohort that was subjected to SCS. Additionally, there was one case of bile leak and 1 report of anastomotic biliary stricture^[37]. The same approach was repeated later in a study of DBD livers declined by the United Network for Organ Sharing region for transplantation^[59]. The authors found a significant decrease in the rate of biliary stricture in comparison with SCS (10% vs 33%, $P = 0.031$). One report of bile leak was noted in the HMP group and 3 in

Table 1 Comparison between donor, recipient, perfusion characteristics and the reported rates of ischemic-type biliary lesions

Ref.	Yr	Perfusion type	Timing MP	n	Donor age	Donor risk index	Recipient age	Recipient MELD	DBD (n)	DCD (n)	DBD ITBL (%)	DCD ITBL (%)	CIT (min)	Func. WIT (min)	Re-Tx (n)
<i>Ex situ</i> normothermic machine perfusion															
Nasralla <i>et al.</i> ^[46]	2018	NMP	Preserv	121	56 (16-84)	1.7 ¹	55	13 (6-35)	87	34	7.4	11.1	126	21	3
Selznert <i>et al.</i> ^[54]	2016	NMP	Preserv	10	48 (17-75)	1.9	57	21 (8-40)	8	2	0	0	103	NA	0
Bral <i>et al.</i> ^[55]	2017	NMP	Preserv	9	56 (14-71)	1.6 (0.9-2.7)	53 (28-67)	13 (9-32)	6	3	0	0	167 (95-293)	22	0
Ravikumar <i>et al.</i> ^[55]	2016	NMP	Preserv	20	58 (21-85)	NA	NA	12 (7-27)	16	4	0	0	NA	21	0
Watson <i>et al.</i> ^[58]	2018	NMP	End-Isch	22	57	2.3	NA	NA	6	16	0	25	386	12	3
Mergental <i>et al.</i> ^[57]	2016	NMP	End-Isch	5	49 (29-54)	2.3	56 (47-66)	8 (8-13)	1	4	0	0	422	28	0
<i>Ex situ</i> hypothermic non-oxygenated machine perfusion															
Guarnera <i>et al.</i> ^[59]	2015	HMP	End-Isch	31	57 (± 18) ¹	1.9 (± 0.5) ¹	57 (± 8.0) ¹	19 (± 5.9) ¹	31	0	9.7	NA	558	NA	0
Guarnera <i>et al.</i> ^[57]	2010	HMP	End-Isch	20	39 (± 2.5) ¹	NA	55 (± 6.2) ¹	17 (± 7.4) ¹	20	0	5	NA	306	26	0
<i>Ex situ</i> hypothermic oxygenated machine perfusion															
van Rijn <i>et al.</i> ^[45]	2017	DHOPE	End-Isch	10	53 (47-57)	1.9 (1.5-2.2)	57 (54-62)	16 (15-22)	0	10	NA	10	331	15	0
Dutkowski <i>et al.</i> ^[38]	2015	HOPE	End-Isch	25	54 (36-63)	NA	60 (57-64)	13 (9-15)	0	25	NA	0	188 (141-264)	31 (26-36)	0
Dutkowski <i>et al.</i> ^[40]	2014	HOPE	End-Isch	8	54 (NA)	2.2 (NA)	60 (NA)	12 (NA)	0	8	NA	0	141 (NA)	31 (22-41)	0
<i>In situ</i> normothermic regional perfusion															
De Carlis <i>et al.</i> ^[60]	2017	NRP	NRP	7	48 ¹	NA	54 ¹	10.6 ¹	0	7	NA	0	414 ¹	33	0
Oniscu <i>et al.</i> ^[49]	2014	NRP	NRP	11	46 (16-74)	NA	68 (43-74)	NA	0	11	NA	0	389 (169-450)	26 (13-48)	0
Minambres <i>et al.</i> ^[50]	2017	NRP	NRP	11	58 (50-67)	NA	55 (± 13) ¹	NA	0	11	NA	0	266 (± 82.7) ¹	12 (11-16)	0
Controlled oxygenated rewarming															
Hoyer <i>et al.</i> ^[47]	2016	COR	End-Isch	6	58 (51-71)	1.9 (1.5-2.5)	52 (43-65)	18 (11-23)	6	0	0	NA	508 (369-870)	NA	0

¹Data presented as median or median (± SD), if available. Otherwise, all data presented as median (Interquartile range); ²Combined hypothermic oxygenated machine perfusion after normothermic regional perfusion. Six uncontrolled DCD were included in this study; ³Eurotransplant DRI. MP: Machine perfusion; MELD: Model for end stage liver disease; DBD: Donation after brain death; DCD: Donation after circulatory death; ITBL: Ischemic-type biliary lesions; CIT: Cold ischemic time; Func: Functional warm ischemic time; Re-Tx: Re-transplantation; NA: Not applicable or not available; Preserv: Preservation; End-Isch: End ischemic; NMP: Normothermic machine perfusion; HMP: Hypothermic machine perfusion; DHOPE: Dual vessel hypothermic oxygenated machine perfusion; HOPE: Hypothermic oxygenated machine perfusion; NRP: Normothermic regional perfusion; COR: Controlled oxygenated rewarming.

SCS respectively (Table 2).

Following these initial studies, the Zurich group developed the concept of HOPE, with active oxygenation of the perfusate, and applied this MP strategy to DCD donors^[38,40]. Their first clinical trial was published in 2015, reporting the results of transplantation of 25 DCD livers^[38]. The authors reported no cases of ITBL at one year follow-up of patients who received perfused DCD livers, whereas control livers subjected to SCS developed a significantly higher rate of ITBL (0/25 vs 11/50, $P = 0.013$). The same benefit of HOPE was not seen for extra-hepatic biliary complications, as the reported rates of leaks and anastomotic strictures were similar (HOPE 5/25 vs Control 12/50)^[38].

The Groningen group published the first clinical series using D-HOPE in 2017^[43]. Ten DCD livers were transplanted following two hours of D-HOPE, one patient in the perfusion group developed ITBL compared to 7 out of 20 in the control group. The case in the D-HOPE group was described as NAS in segments II and III of the liver and was managed with endoscopic stenting. Three control livers which developed ITBL required re-transplantation. The rate of anastomotic biliary strictures was comparable between groups (D-HOPE 2 vs Control 3, $P = 1.000$) as was the reported rate of biliary cast formation (D-HOPE 3 vs Control 3, $P = 0.372$)^[43].

Normothermic regional perfusion and post-transplant biliary complications

The first series reporting the results for transplantation of livers following NRP was published in 2014 by Oniscu *et al.*^[49]. The authors reported the results of transplantation of

Table 2 Prevalence of bile leak and anastomotic biliary strictures between clinical studies using different techniques of machine perfusion of donor livers

Ref.	Yr	Study design	Perfusion type	Timing machine perfusion	n	DBD (n)	DCD (n)	Bile leak (n)	Anastomotic stricture (n)
<i>Ex situ</i> normothermic machine perfusion									
Nasralla <i>et al</i> ^[46]	2018	RCT	NMP	Preservation	121	87	34	0	0
Selznert <i>et al</i> ^[54]	2016	PS	NMP	Preservation	10	8	2	0	0
Bral <i>et al</i> ^[56]	2017	PS	NMP	Preservation	9	6	3	0	0
Ravikumar <i>et al</i> ^[55]	2016	PS	NMP	Preservation	20	16	4	0	4 (DBD)
Watson <i>et al</i> ^[58]	2018	DS	NMP	End-Ischaemic	22	6	16	0	0
Mergental <i>et al</i> ^[57]	2016	DS	NMP	End-Ischaemic	5	1	4	0	0
<i>Ex situ</i> hypothermic non-oxygenated machine perfusion									
Guarrera <i>et al</i> ^[59]	2015	PS	HMP	End-Ischaemic	31	31	0	1	0
Guarrera <i>et al</i> ^[37]	2010	NCS	HMP	End-Ischaemic	20	20	0	1	1
<i>Ex situ</i> hypothermic oxygenated machine perfusion									
van Rijn <i>et al</i> ^[43]	2017	PS	DHOPE	End-Ischaemic	10	0	10	0	2
Dutkowski <i>et al</i> ^[38]	2015	PS	HOPE	End-Ischaemic	25	0	25	5 (in total)	
Dutkowski <i>et al</i> ^[40]	2014	PS	HOPE	End-Ischaemic	8	0	8	1	1
<i>In situ</i> normothermic regional perfusion									
De Carlis <i>et al</i> ^[60]	2017	DS	NRP	NRP	7	0	7*	0	1
Oniscu <i>et al</i> ^[49]	2014	DS	NRP	NRP	11	0	11	1	1
Minambres <i>et al</i> ^[50]	2017	DS	NRP	NRP	11	0	11	NA	NA
Controlled Oxygenated Rewarming									
Hoyer <i>et al</i> ^[47]	2016	PS	COR	End-Ischaemic	6	6	0	NA	NA

*Combined hypothermic oxygenated machine perfusion after normothermic regional perfusion. Six uncontrolled DCD were included in this study. RCT: Randomised controlled trial; PS: Single-arm non-randomised pilot study; DS: Descriptive study; NCS: Non-randomised cohort studies; DBD: Donation after brain death; DCD: Donation after circulatory death; NA: Not applicable or not available; NMP: Normothermic machine perfusion; HMP: Hypothermic machine perfusion; DHOPE: Dual vessel hypothermic oxygenated machine perfusion; HOPE: Hypothermic oxygenated machine perfusion; NRP: Normothermic regional perfusion; COR: Controlled oxygenated rewarming.

11 controlled DCD livers, with a minimum follow-up of 3 mo, with no clinical or radiological evidence of ITBL. One patient developed an anastomotic stricture, treated endoscopically by cholangio-pancreatography (exact intervention performed is not described), and one patient had a bile leak^[49]. Minambres *et al*^[50] 2017, studying controlled DCD transplantation after NRP, reported no cases of ITBL after 1-year follow-up. De Carlis *et al*^[60] 2017 performed NRP on 1 controlled DCD liver and 6 uncontrolled DCD. On arrival at the transplant centre, the livers were subjected to D-HOPE until transplantation. No cases of ITBL were observed and one patient had an anastomotic biliary stricture 45 d after transplantation, which was successfully treated with endoscopic stenting^[60]. In terms of SMP, Hoyer *et al*^[47] reported transplantation of 6 DBD livers following COR perfusion. No biliary complications were reported within a follow-up period of six months.

DISCUSSION

Post-transplant biliary complications are associated with high rates of morbidity and re-transplantation and are a major obstacle to the wider clinical utilisation of ECD livers. There is a growing body of evidence suggesting that MP can offer safer organ preservation when compared to SCS, and also offer an opportunity for organ assessment and/or reconditioning prior to transplantation^[38,43,46,49,58]. In this review we have assessed the available literature investigating the impact

of MP on post-transplant biliary complications, with special reference to ITBL. MP techniques which have per se the potential to alleviate IRI, such as HMP and NRP, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques.

Liver IRI is thought to be a major driver of biliary injury and, therefore, it is associated with complications following transplantation. More specifically, during ischemia, without oxygen as a terminal acceptor of electrons in the electron transport chain, succinate accumulates and acts as a store for electrons. Succinate oxidation during the early stage of reperfusion, blocks mitochondrial complex II of the electron transport chain resulting in a reverse flow of electrons towards mitochondrial complex I leading to accentuated leakage of electrons, and generation of ROS^[61]. Various experimental findings using the HOPE technique have shown that oxygen at hypothermic temperatures is able to promote mitochondrial metabolism of succinate prior to reperfusion^[36,42,62]. By re-establishing adequate mitochondrial oxidative function, HOPE is able to recover ATP stores, since during hypothermia mitochondria have lower energy requirements due to a minimum activation of the organ metabolism. Therefore, mechanistically, HOPE can in theory prevent the reverse flow of electrons during reperfusion, ROS generation and activation of the inflammatory cascade^[36]. These factors may mitigate IRI, which would be beneficial not only

for hepatocellular function but also for the prevention of further biliary injury.

Extensive research focussing on the effect of oxygenated HMP on post-transplant biliary complications has been performed by the Groningen group. In a recent publication exploring the effects of D-HOPE on bile duct biopsies from a previous published series of cases, they showed less injury to deep and periluminal peribiliary glands after reperfusion during transplantation in the perfused group in comparison with SCS control livers^[43,63]. Peribiliary glands have been described as stores for biliary progenitor cells, therefore injury to them would potentially decrease the regenerative capacity of the biliary system^[64,65]. The authors acknowledge that definitive evidence to support this would require a clinical randomized trial that has since been initiated at their centre^[63].

There is currently less clinical evidence available to support NMP as a mitigator of biliary complications following liver transplantation^[58]. Preservation NMP shortens the ischaemic injury and offers a more physiological environment for the organ before transplantation. Nevertheless, as previously discussed, the injury to biliary cells would not be restricted to an ischaemic mechanism but may also be worsened during reperfusion. This observation could imply that NMP is of limited benefit in terms of biliary complications, since biliary injury may worsen during organ reperfusion on the machine and is not prevented or mitigated beforehand. NMP restores the full metabolism of the organ, resulting inevitably in the production and circulation of ROS and potential activation of the inflammatory response leading to tissue injury^[66]. On the other hand, restoration of organ to full metabolism allows assessment of hepatobiliary function before transplantation, although universally accepted criteria have yet to be validated^[35]. Watson *et al.*^[58] suggested bile pH and glucose content as markers of bile duct injury and associated those with the development of ITBL, however the authors recognise that NMP was not able to prevent biliary damage.

Promisingly, *in situ* NRP has shown excellent biliary outcomes after transplantation of DCD livers^[49,50,60]. NRP may potentially prevent ischaemic injury and deterioration of ATP stores during organ procurement. Additionally, NRP allows assessment of the liver metabolism even before SCS^[8]. Despite these points, there is no mechanistic evidence available to demonstrate any alleviation in IRI after reperfusion. It is also difficult to rule out the possibility that this beneficial effect was as a result of a potential selection bias when recruiting organs for transplantation during the procedure.

The present body of work has several limitations. First and foremost, donor livers and recipient characteristics as well as MP technique protocols exhibit a high degree of variability between studies. So far, there has been no standardisation in terms of methodology and reporting of results. Furthermore, some studies neglect to report

important data variables, such as DRI, recipient age, recipient MELD and CIT. All these features are presented in Table 1 to allow an unbiased assessment of the retrieved information by the readers. Additionally, few clinical studies from each MP technique are available and most of them are originated from small pilot studies, which limit definitive interpretation of the data. MRCP was performed in some of the studies at different post-operative periods, but the significance of findings without clinical correlation is not clear. In addition, they have focussed mainly on evaluation of hepatocellular function rather than biliary function and injury. Despite the subject of this review being a relevant topic with important clinical implications, the direct effects of MP on biliary tree integrity are still relatively under-researched. More clinical randomized trials will be reported in the field in the next few years.

Higher rates of ITBL following transplantation of ECD livers, mainly DCD, place a major restraint on the wider use of these marginal livers. Each technique of MP offers different advantages and they all have the potential to tackle this problem. A feasibility study has shown that a combination of HOPE and NMP increased the rescue of metabolic parameters of high-risk ECD organs^[52]. This approach may derive benefits from the individual methods, thus optimising gains also in terms of biliary function. Pharmacological interventions during NMP may potentially alleviate IRI, positively affecting biliary cells^[67], and may have a direct effect on post-transplant biliary complications. Supplementation of the perfusate with substances that may induce proliferation and maturation of progenitor cells from peribiliary glands may be a feasible option to be considered^[9]. We hypothesize that therapies promoting increase in secretion of phospholipids and cholesterol in the bile would equilibrate the phospholipids/bile salts balance mitigating further injury to the biliary tree. Although promising, these are options that still need to be explored in future studies. A diagrammatic summary of the current and future impact of MP on ITBL is presented in Figure 3.

The high incidence of post-transplant biliary complications, specifically ITBL, is a major constraint to wider utilisation of ECD livers. MP is currently considered a promising tool to increase ECD utilisation. However, the focus of most of the studies up to date has been the effect of MP on hepatocellular function. In this review we explored the clinical evidence currently available for the impact of MP on post-transplant biliary complications. From those studies that have looked at the effects of MP on biliary integrity, oxygenated HMP and NRP studies have been shown to exhibit better postoperative biliary outcomes in comparison with NMP and non-oxygenated HMP. However, larger clinical studies and randomised clinical trials powered for the occurrence of biliary complications as a primary endpoint are needed to confirm this data.

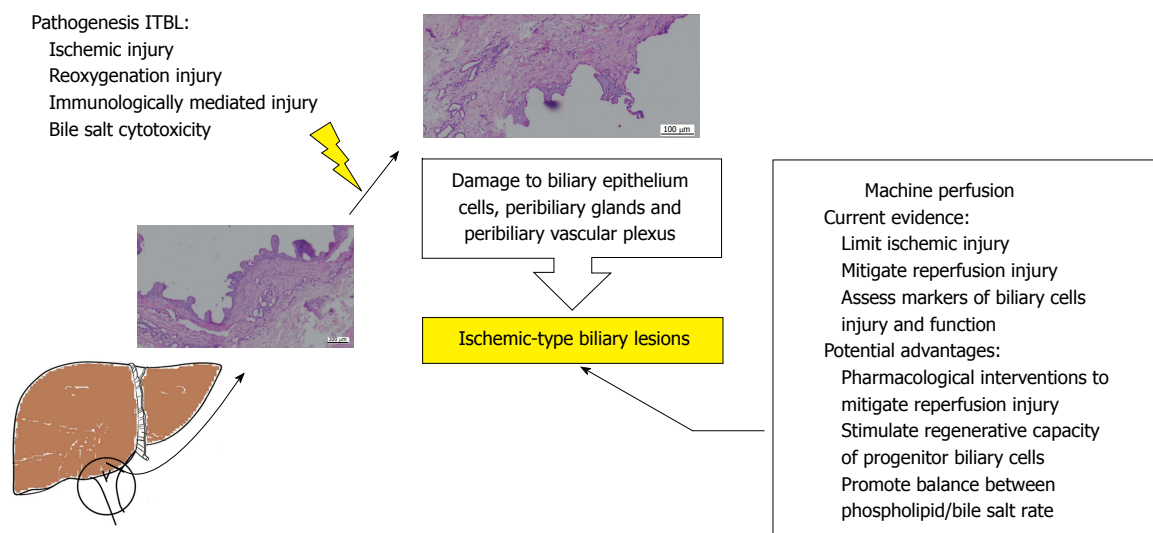


Figure 3 Diagrammatic summary of the current evidence for the impact of machine perfusion of the liver on post-transplant ischemic-type biliary lesions and future perspectives. The current evidence suggests that ischaemic-type biliary lesions (ITBL) have a multifactorial pathogenesis. These diverse factors lead to injury to the biliary epithelium, peribiliary glands and peribiliary vascular plexus. Currently, there is evidence for the potential benefits of machine perfusion on post-transplant ITBL. The figure summarises those and possible future interventions that could enhance increase these benefits further.

ARTICLE HIGHLIGHTS

Research background

The ever-growing discrepancy between donor organ availability and patients on the transplant waiting list has led to increased acceptance of extended criteria donors (ECD). However, ECD liver transplantation, mainly donation after circulatory death, is associated with poor patient and graft outcome. A major factor is the increased risk of biliary complications, in particular ischaemic type biliary lesions (ITBL). Machine perfusion (MP) of the liver is a promising tool to recondition ECD organs prior to transplantation. Therefore investigation of the impact of MP on post-transplant biliary complications is a highly relevant topic.

Research motivation

Understanding the current evidence available for the effect of MP on post-transplant biliary complications, in particular ITBL, may guide further studies in this field.

Research objectives

Revise the current clinical evidence available regarding the effect of MP on post-transplant biliary complications, focusing on ITBL.

Research methods

A systematic review was carried out with literature searches in PubMed, MEDLINE and Scopus databases. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". Only clinical studies reporting results of transplantation of donor human livers following *ex situ* or *in situ* MP were included.

Research results

MP techniques which have demonstrated the potential to mitigate ischaemia reperfusion injury, such as *ex situ* oxygenated hypothermic MP and *in situ* normothermic regional perfusion, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques. Clinical studies have focused on evaluation of hepatocellular function rather than biliary function and injury so far. The direct effects of MP on biliary tree integrity are still relatively under-researched and further studies are needed.

Research conclusions

Post-transplant biliary complications are a major obstacle to the wider utilisation

of ECD livers. MP has the potential to have a positive impact on this issue, specifically ITBL, and expand ECD livers utilisation. Mechanistically, mitigation of ischaemia-reperfusion injury appears to be the key mechanism involved.

Research perspectives

Supplementation of the perfusion fluid during *ex situ* MP with drugs can stimulate protective/regenerative mechanisms of the biliary tree. Pharmacological strategies may potentially modulate progenitor cells proliferation and equilibrate the phospholipid/bile salts balance in the bile.

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