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Establishing a HOPE Program in a Real-life Setting: A Brazilian Case Series

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Background. Although hypothermic oxygenated perfusion (HOPE) improves posttransplant outcomes, setting up machine perfusion programs may be subjected to specific obstacles under different conditions. This study aims to describe the establishment of HOPE in a real-life setting in Brazil. **Methods.** Extended criteria donors in donation after brain death organs preserved by HOPE were accepted for higher-risk candidates needing expedited transplantation, perceived as those who would benefit most from the technique because of its limited availability. Extended criteria donors was defined by the Eurotransplant criteria. High-risk transplant candidates were characterized by suboptimal surgical conditions related to the recipient or the procedure. **Results.** Six HOPE-preserved grafts were transplanted from February 2022 to August 2022. The mean donor risk index was 1.7 (SD 0.5). One organ was severely steatotic, and 3 had an anticipated cold ischemia time above 12 h. Recipients' mean model for end-stage liver disease was 28.67 (SD 6.79), with 1 case of retransplant, 1 of refractory ascites, and 1 of acute-on-chronic liver failure. The mean cold ischemia time was 5 h 42 min (SD 82 min), HOPE 6 h 3 min (SD 150 min), and total preservation time 11 h 46 min (SD 184 min). No case had early allograft dysfunction. The mean length of hospital stay was 10 d with 100% graft and patient survival and no ischemic cholangiopathies at a median follow-up of 15 mo (min 12, max 18). Costs and country-specific legal regulations for device utilization were the major hurdles to implementing the program. **Conclusion.** We presented a pathway to introduce and rationalize the use of HOPE in a scenario of challenging donor-recipient matching with good results. These findings may aid in implementing machine perfusion programs, especially in settings with limited resources or complex transplant logistics.

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The hypothermic oxygenated perfusion (HOPE) technique has shown its benefits in donation after circulatory death[1,2] and extended criteria donors (ECD) in donation after brain death (DBD) liver transplantation.[3] Mechanistically, HOPE improves cellular liver bioenergetics.[4,5] Clinically, HOPE-treated ECD DBD organs presented with reduced early allograft dysfunction (EAD) rates, lower incidence of liver-related serious complications, and improved graft and patient survival.[3,6-9] Additionally, measuring the mitochondrial complex I injury marker flavin mononucleotide (FMN) during HOPE was predictive of liver graft function and loss.[10]

Despite the proven advantages, the clinical application of HOPE may encounter scenarios not anticipated in controlled studies. This aspect is even more relevant when considering the development of machine perfusion (MP) programs in developing countries, which frequently face challenges such as difficult access to the healthcare system with high-risk liver transplant candidates, long waiting lists, difficulties with organ procurement, poor organ donor care, and a disproportionally high rate of ECD DBD organs[11] and are not necessarily portrayed by the donor risk index (DRI).[12] Thus, an important challenge that transplant centers worldwide may face concerning MP is finding a pathway to introduce and rationalize the use of the technique while coping with all the specific difficulties and constraints that characterize different settings.

The pivotal European multicenter randomized controlled trials predominantly studied standard to low-risk recipients to avoid confounding factors and were performed in optimal

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management conditions and ideal settings.[3,7] Although this approach is required to guarantee internal validity, it compromises generalizability. Therefore, this study aims to describe the introduction and use of HOPE in a usual care setting of ECD DBD organs in Brazil, with limited equipment availability and suboptimal real-life conditions related to the recipient or the procedure or both, together with their difficulties and solutions.

MATERIALS AND METHODS

Study Population and Design

Adult (≥18 y old) patients assisted at the Transplant Program of the Hospital Israelita Albert Einstein, São Paulo, Brazil, and on the waiting list for liver transplantation from February 2022 to August 2022 were included in the study. The local Research Ethics Committee approved the study protocol (opinion 4.740.772, CAAE 45630421.0.0000.0071), and all participants confirmed their acceptance to take part and agreed to the possibility of receiving a graft treated with MP by signing an informed consent.

Baseline donor and recipient clinical features, transplant operation details, preservation times, radiological investigations, laboratory tests, management of drugs administered and immunosuppression, and patient and graft outcomes were prospectively extracted from electronic medical records and prospectively analyzed. All laboratory tests and imaging investigations were done as part of standard care. Only DBD donor organs were included in this study because there was no legal regulation and authorization for DCD organ transplantation in Brazil.

The study has not changed any retrieval or donor organ allocation practice, which followed all the specified national regulations for organ transplantation. Once a liver was clinically accepted for transplantation, HOPE could be performed after liver transport to the transplant center, hence in an end-ischemic approach, for consented patients. HOPE treatment was considered for donor's livers characterized as an ECD DBD organ, according to the Eurotransplant criteria,[13] allied to the perceived risk factors for a negative outcome in the recipient and/ or the surgical procedure, as described below. Finally, the limited availability of disposables for the perfusion device because of costs was also taken into consideration when deciding to perfuse a donor's liver.

The standard institutional immunosuppressive therapy and the preferential surgical technique are presented in the **Supplemental Material** (**SDC**, http://links.lww.com/TXD/A588).

Liver Inclusion Criteria

A donor organ was considered for HOPE if it was classified as an ECD DBD according to the Eurotransplant criteria[13]; therefore, if it meets at least 1 of the following criteria: age >65 y old, intensive care unit (ICU) stay >7 d, body mass index >30 kg/m^2, liver steatosis >40%, serum sodium >165 mmol/L, alanine aminotransferase (ALT) >105 U/L, aspartate aminotransferase (AST) >90 U/L, and total serum bilirubin >3 mg/dL.

Whenever the retrieval surgeon reported worrisome graft steatosis or macroscopic appearance, pretransplant graft histologic assessment was organized by liver biopsy and frozen section examination.

Recipient Inclusion

To provide insights into the real-life effectiveness of HOPE, apart from the age, there are no other fixed recipient inclusion criteria. Real-life recipient or surgical-related conditions perceived as risk factors for unfavorable outcomes in the setting of ECD DBD transplantation were considered when deciding upfront on HOPE deployment. These variables include (1) anticipated cold ischemia time (CIT) over 12 h by logistical issues related to donor organ transport or surgical technicalities of the case and (2) recipient conditions requiring timely acceptance of a donor organ for transplantation, for example; (a) high Model for End-Stage Liver Disease (MELD) scores, representing the severity of the end-stage liver disease (ESLD); (b) occurrence of acute-on-chronic liver failure (ACLF) (according to the Chronic Liver Failure-consortium organ failures score)[14]; and (c) situations with high mortality risk not portrayed by the MELD score, such as retransplant cases and specific debilitating complications of the ESLD, for example, refractory ascites and hepatorenal syndrome.

Examined Outcomes

The following clinical endpoints were described: occurrence of acute kidney injury (AKI) requiring renal replacement therapy, rate of postreperfusion syndrome (PRS), rate of EAD (as defined by Olthoff et al[15]), peak levels of AST and ALT within the first 7 postoperative d, peak lactate level in the recipient at the transplant operation, grade ≥3 complications rate according to Dindo et al,[16] length of hospital and ICU stay, the Comprehensive Complication Index[17] at the discharge from the index admission, acute rejection rate, biliary complication rate, and patient and graft survival.

AKI was defined and graded according to the 2012 Kidney Disease Improving Global Outcomes guidelines.[18] PRS was characterized by a 30% drop in mean arterial pressure within 5 min lasting for 1 min, according to Aggarwal et al.[19] Posttransplant biliary complications, vascular complications, and acute rejection were investigated with standard practice radiological image tests and liver biopsy, when appropriate, only if there was clinical suspicious by patient examination or alteration in liver enzymes, as everyday clinical practice.

Prognostics Scores

Prognostic scores were calculated for all cases to characterize and estimate the donor and the matched donor-recipient risk. The following scores were examined: the DRI by Feng et al[12]; donor age and MELD (D-MELD)[20]; balance of risk (BAR)[21]; and the early allograft failure simplified estimation (EASE score).[22] The EASE score was developed by Avolio et al to assess graft failure (retransplant or death) within 90 d after transplant in a more comprehensive model.[22]

MP Technique

End-ischemic HOPE was performed using a pressure, and flow-controlled MP device (VitaSmart; Bridge to Life Ltd.) with 1–3 mm Hg portal vein pressure at 8–12 °C and recirculating oxygenated perfusate (3 L of Belzer UW-MPS; Bridge to Life Ltd.). The portal vein flow was stable at 250 mL/min (limited by the device setting) throughout perfusion without any episode of increased hepatic resistance (constantly lower than 0.02 mm Hg/mL/min). The aimed partial pressure of oxygen in the perfusion solution was greater than 60 kPa. HOPE was started after the back table preparation was finished and

stopped at the end of the recipient hepatectomy when the graft was disconnected from the device and transferred to the recipient's table for implantation. Perfusate temperature was constantly monitored by the device's wireless thermometer. Sterile ice (from frozen bags of sterile saline) was replaced in the bowl (outside the cap containing the donor organ and perfusion solution) every time the temperature reached 8 °C, which occurred approximately every 2 h. No predetermined minimum perfusion time was set, and the perfusion duration lasted until the recipient hepatectomy was finished.

FMN Measurement

To evaluate the HOPE's potential to assess graft quality or viability, the FMN was measured in the perfusate by fluorescence intensity in a conventional plate reader (Varioskan LUX multimode microplate reader; Thermo Fisher, MA; 485-nm excitation and 528-nm emission). Because of understaffing, surgical team members collected perfusate samples and analyzed them in the laboratory. Consequently, although samples for some cases could be freshly collected and analyzed during HOPE, others needed to be freshly frozen in liquid nitrogen and analyzed posteriorly. To judge the quality of the organ, the suggested thresholds in the literature are <5000 absorbance units, accepted the organ for any recipient; ≥5000–absorbance units, only accept for recipients with limited risk; and ≥8800 absorbance units, declined liver for transplantation.[23]

Statistical Analysis

Quantitative data are shown as the mean ± SD or the median with interquartile range. Qualitative variables were expressed as absolute and relative frequencies or presented in the form of reports. Statistical analysis was performed with SPSS version 22.0 (IBM Corp, Armonk, NY).

RESULTS

Study Population

Forty-eight deceased donor liver transplants were performed at the center during the study period. From those, 6 HOPE perfusions were completed (12.5%), and all grafts were transplanted. The recipients' mean MELD was 28.67 (SD 6.79), with 1 retransplant and 3 ACLF cases. All the ACLF cases were inpatients at the time of transplantation. Two cases (cases 3 and 6) had already recovered from the condition at the time of transplantation, and case 1 was transplanted in ACLF 2 (liver and coagulation failure).

Contrary to the poor clinical condition, case 5 presented with the lowest MELD value in the series, 20 at the time of transplantation. The patient was frail with impaired quality of life secondary to the ESLD, refractory ascites, hepatorenal syndrome, and recurrent hepatic encephalopathy. Table 1 details the demographical and clinical data of the cases and summarizes the recipient, or surgical-related condition indicating the HOPE use.

Two of 6 donor organs were deemed to have moderate steatosis and 1 severe steatosis on retrieval surgeon macroscopic evaluation. After arriving at the transplant center, the transplant surgeon considered 1 liver to have no steatosis (case 2), and the other organ (case 3) was biopsied because of the suspicion of moderate steatosis. Nevertheless, it did not preclude the start of HOPE perfusion. The liver biopsy later revealed 15% macrovesicular steatosis in frozen and paraffin examinations. The suspicion of severe steatosis was confirmed for case 5 by histological examination, with 60% macrovesicular steatosis and 10% microvesicular steatosis. In addition, 3 donor organs (cases 1, 5, and 6) had an anticipated CIT >12 h because of national/regional organ location. Table 1 also portrays the donor data.

Donor Recipient Matching, HOPE Procedure, and Operation Details

The sole donor risk can be estimated by the mean DRI of 1.7 (SD 0.5). The mean CIT was 5 h 42 min (SD 82 min), and the BAR score was 11 (SD 3.3) when considering the donor-recipient features. However, reflecting the donor recipient matching risk, the mean D-MELD was 1489 (SD 708). The HOPE treatment duration was 6 h 3 min (SD 150 min). This includes case 6, with the most prolonged HOPE duration of 11 h 20 min, and case 5, with the shortest period of 3 h 30 min. Case 6 was a retransplant case for chronic graft failure, primary transplant 16 y before, with portal vein thrombosis requiring an interposition portal vein graft, an aortohepatic infrarenal conduit for graft revascularization, and a Roux-en-Y hepaticojejunostomy for biliary reconstruction. Finally, the mean total preservation time was 11 h 46 min (SD 184 min). The median Comprehensive Complication Index at discharge from the index admission was 26.63 (SD 11.83), and grade ≥3 Clavien-Dindo complications were 16.67%. This corresponds to case 1, who developed AKI Kidney Disease Improving Global Outcomes 3 requiring temporary renal replacement therapy and completely recovered renal function after 5 d. There was no case of EAD according to the Olthoff criteria, and the mean EASE score was −3.57 (SD 1.22), classifying all recipients at a low to very low risk for early allograft failure at d 90. Two patients (cases 5 and 6) presented PRS without major implications. Table 2 describes the detailed prognostic scores for all cases and operative features.

Liver Transplant Outcomes

For 4 cases (cases 1, 3, 5, and 6), the perfusate could be freshly collected and analyzed during HOPE, being used as a decisional element. For 3 cases (cases 3, 5, and 6), the FMN measurements were above the minimum safety threshold of 5000 A.U. at 30 min of perfusion (for any recipient), although with a trend of slow increase up to 60 min. The mean ALT peak was 364 U/L (SD 232), and AST was 564 U/L (SD 348). The mean length of hospital stay was 10 d (SD 2), and ICU stay was 2 d (SD 1). The 1-y patient and graft survival was 100%, and there were no vascular complications up to this time after the transplants. Case 1 developed an anastomotic biliary stricture 11 mo after the transplant identified by deranged liver enzymes and ultrasonography, requiring endoscopic retrograde cholangiopancreatography for diagnostic confirmation and treatment with the placement of a single fully covered self-expandable metal stent across the anastomosis. There was no other biliary complication. Additionally, no case presented with acute cellular rejection despite increased recipient risk with 1 case of autoimmune hepatitis, 1 of primary sclerosing cholangitis, and a retransplant. Table 3 shows all the transplant outcomes investigated for the HOPE case series.

Difficulties and Solutions Setting an MP Program

During the establishment of the MP program, several challenges were faced. Although the solutions to overcome each

TABLE 1.

Demographic and clinical characteristics of the 6 liver transplant recipients and organ donors

Recipient data						
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Age (y)	22	49	53	23	47	34
Gender	Male	Male	Male	Female	Male	Male
Etiology of ESLD	AIH	ALD	ALD	PSC	ALD	Re-LT
Complications of ESLD	Ascites, SBP	Ascites, SBP, VB	Ascites, HCC	Ascites, VB	RA, VB, HRS, HE	Ascites, VB
ACLF before LT	Yes	No	Yes	No	No	Yes
Comorbidities	Asthma	AH	Depression			T2DM
BMI (kg/m^2)	25	35	27	21	24	22
MELD-Na	42	25	31	27	20	27
Recipient/surgical HOPE requirement	ACLF 2, high MELD, anticipate CIT ≥ 12 h	High MELD, surgical technicality (obesity)	ACLF recovered, high MELD	High MELD, septic shock for cholangitis	RA, frailty, anticipate CIT ≥ 12 h	Re-LT, PVT, high MELD, anticipate CIT ≥ 12 h
Donor data						
Age (y)	61	31	61	66	22	55
BMI (kg/m^2)	31	31	27	27	31	28
Height (cm)	170	175	162	160	181	164
Race	African American	African American	Other	White	White	White
Cause of death	Other	CVA	CVA	Trauma	Trauma	Anoxia
Organ location[a]	National	Local	Local	Local	National	Regional
Cardiac arrest, time	No	No	No	No	No	Yes, 45 min
Alcohol or drug abuse	Yes	No	No	Yes	Yes	No
ICU stay (d)	6	4	8	3	3	8
High inotropes[b]	Yes	No	Yes	No	Yes	No
Last sodium (mmol/L)	147	136	141	136	178	172
Last ALT (IU/L)	86	23	17	13	39	292
Last AST (IU/L)	127	94	37	35	35	104
Last TB (mg/dL)	0.88	0.80	1.07	0.32	0.97	0.40
Last GGT (IU/L)	38	116	286	15	29	81
Steatosis (surgeon)	Mild	Moderate[c]	Moderate	Mild	Severe	Mild
Liver weight (g)	1700	1950	1490	1200	1600	1130
Liver biopsy	Yes	No	Yes	No	Yes	Yes
Microsteatosis (%)	0	NA	10	NA	10	30
Macrosteatosis (%)	10	NA	15	NA	60	0
Other findings	GI liver fibrosis		GI liver fibrosis		GI liver fibrosis	

[a]Local, greater São Paulo area; Regional, State of São Paulo; National, outside the state of São Paulo.
[b]Defined as >0.5 μg/kg/min of norepinephrine or need for rescue therapy with vasopressin.
[c]After arriving at the transplant center, the transplant surgeon considered the liver to have no steatosis.
ACLF, acute-on-chronic liver failure; AH, arterial hypertension; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; CIT, cold ischemia time; CVA, cerebrovascular accident; ESLD, end-stage liver disease; GGT, gamma-glutamyl transferase; GI, grade I; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; ICU, intensive care unit; MELD, model for end-stage liver disease; NA, not available; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; RA, refractory ascites; Re-LT, retransplantation of the liver; SBP, spontaneous bacterial peritonitis; T2DM, type 2 diabetes; TB, total bilirubin; VB, variceal bleeding.

obstacle can vary depending on the characteristics of different settings, we provided a comprehensive list based on our initial experience in Brazil in Table 4.

DISCUSSION

This case series describes the initial successful implementation of HOPE in a real-world scenario of routine clinical practice with limited equipment availability and suboptimal conditions. Without selective inclusion criteria, the HOPE indication was based on the concept of donor organ match. The HOPE-treated ECD DBD organs were transplanted into patients with a perceived higher risk of death, considering the sum of unfavorable conditions related either to the recipient, the procedure, or both, as illustrated in Figure 1. Using this approach, we propose a rationale for implementing and using the technique in these challenging contexts and report optimal patient and graft survival rates with a low frequency of postoperative complications.

MP is expected to increase the pool of transplantable organs.[4,24] Nevertheless, implementing this technology outside the controlled environment of RCT. is full of challenges imposed by clinical practice. Firstly, the setting of a perfusion program leads transplant teams to difficult decisions that start with which MP technique to choose, especially in contexts of limited availability of the technology and the high prevalence of ECD organs. The reported cases herein were the institution's first liver MP cases. The choice for HOPE, rather than normothermic MP or variations, was based on its high practicability, which facilitates the implementation of an MP program. The back-to-base procedure permits the easier setting of the machine and does not compromise the donor hospital or the retrieval and transplant teams' logistics. HOPE does not lead to the risk of organ

TABLE 2.

Donor recipient prognostic scores, donor organ preservation, and operative characteristics of the study

Donor recipient matching and prognostic scores	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
DRI (points)	2.79	1.34	2.00	1.53	1.19	1.58
D-MELD (points)	2562	775	1891	1782	440	1485
BAR score (points)	15	7	12	11	7	15
EASE score	–2.1	–3.6	–4.1	–2.6	–5.9	–3.1
EASE class	Low risk	Extremely low risk	Extremely low risk	Low risk	Extremely low risk	Low risk
EASE risk of failure (%)	10.6	2.8	1.6	6.7	0.3	4.2
Preservation and operation details						
CIT	6 h 19 min	7 h 07 min	3 h 50 min	3 h 48 min	7 h 00 min	6 h 03 min
HOPE duration	5 h 19 min	6 h 23 min	4 h 50 min	5 h 00 min	3 h 30 min	11 h 20min
Total preservation time (min)	11 h 38 min	13 h 30 min	8 h 40 min	8 h 48 min	10 h 30 min	17 h 23 min
Recipient WIT (min)	28	29	38	27	30	29
PRBC units	3	0	2	2	2	8

BAR, balance of risk score; CIT, cold ischemia time; D-MELD, donor model for end-stage liver disease; DRI, donor risk index; EASE, early allograft failure simplified estimation score; HOPE, hypothermic oxygenated perfusion; PRBC, packed red blood cells; WIT, warm ischemia time.

TABLE 3.

Transplant outcomes of HOPE-treated livers in a real-life scenario of the suboptimal recipient and surgical conditions

Perfusion data	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
FMN—30 min	3097	3555	7105	3375	5119	6805
FMN—60 min	3201	3789	8172	4223	7548	7832
Transplant outcomes						
Stage 2-3 AKI	Yes	Yes	Yes	No	Yes	Yes
Dialysis post-LT	Yes, 5 d	No	No	No	No	No
PRS	No	No	No	No	Yes	Yes
EAD	No	No	No	No	No	No
ALT peak (U/L)	750	280	117	176	608	256
AST peak (U/L)	1211	560	410	182	773	250
Peak lactate at LT	3.6	2.5	2.0	2.3	2.2	1.2
Grade ≥3 CD complications	Yes	No	No	No	No	No
Hospital stay (d)	13	10	10	12	7	10
ICU stay (d)	5	1	2	2	1	2
CCI discharge	48.1	24.2	32	24.2	8.7	22.6
Biliary complication	Yes, AS	No	No	No	No	No

AKI, acute kidney injury; ALT, alanine aminotransferase; AS, anastomotic biliary stricture; AST, aspartate aminotransferase; CCI, Comprehensive Complication Index; CD, Clavien-Dindo classification; EAD, early allograft dysfunction; FMN, flavin mononucleotide; ICU, intensive care unit; LT, liver transplant; PRS, postreperfusion syndrome.

injury in the case of machine failure and does not demand any oxygen carrier or complex supplements. Additionally, because HOPE may be performed even for short periods of 1–2 h[1,2] during recipient hepatectomy, it does not require additional periods in the operation room or a dedicated perfusion room because anesthesiology, machine preparation, and back table of the donor organ can be done at the same time. Nevertheless, if needed, prolonged HOPE preservations are proven safe.[25]

However, there are still several hurdles in setting up an MP program, which one needs to cope with pretending to develop this initiative, even if a highly practical method such as HOPE is chosen. Firstly, obtaining funding for implementing this new technology is challenging. This is because although evidence suggests the economic benefit of the technique, more conclusive cost-effectiveness data to assure hospital managers is awaited.[26,27] Herein, funding schemes ranging from local or national commissioning to hospital or patient funding, charity, and grant support may be explored.[27] Secondly, hurdles regarding regulations and registration of perfusion devices for clinical use are ongoing worldwide.[28] Therefore, thus far, to cope with these difficulties, MP programs frequently start with the research pathway. This path may provide a funding opportunity and facilitate the introduction of the technology in the country before the time-consuming final regulatory body authorization for clinical use and avoid the enormous tax rates for device internalization.

On the other hand, this path demands knowledge of clinical research and institutional support to deal with the perfusion device's importation and regulatory clearing process. Furthermore, as research projects, MP studies are expensive compared with other research areas, making them less competitive and highly selective for major grants. Not less

TABLE 4.

Difficulties and possible solutions for setting an MP program

Difficulties	Solutions
Which MP technique to choose?	• Consider the clinical need of the specific center (DCD transplant program existence; rate of ECD DBD; usual recipient features; number of transplants performed at the center; typical cold ischemia times). • Consider the available resources (blood components, antibiotics, perfusate components). • Consider the equipment price and related costs (perfusion device, perfusate components, device transportation). • Consider the practicability (back-to-base approach; interference with retrieval teams' practice; vessels needing cannulation; bench preparation and arterial reconstructions; machine transport; complexity of perfusion technique). • Consider the typical logistics at the transplant center (usual donor organ distance; travel times).
Funding for the MP use	• Consider the current literature on MP cost-effectiveness to talk to hospital administrators (increased organ availability, improved patient care, decreased postoperative complication rates, shorter hospital stays, reduced readmission rates). • Consider the equipment price and the most suitable acquisition method (renting, purchasing, leasing, amongst others). • Consider lessening the fixed running cost (costs related to the perfusion device disposables, perfusate components, real-time analyses needed, maintenance of the perfusion device, and additional periods of operating room for preparing the MP). • Consider your needs and viable options before setting a contract with the vendor (minimal number of disposables; involve hospital stakeholders, device companies, and administrators). • Set your center's most feasible funding scheme (national or local commissioning, hospital or patient funding, medical insurance, charity, or grant support).
Path of an MP program implementation	• Research pathway (research funding, research regulations to use the equipment without final clinical regulatory approvals). • Consider the expertise needed to write the research project and grant proposal. • Clinical pathway (hospital administrator support needed; demonstrate the current evidence of the benefits of MP and the advantages for the center pioneering the absorption of new technologies).
Country-specific perfusion device registration and regulation	• Consider the usual costs and legal requirements from regulatory bodies in the specific country when new technologies are evaluated. These aspects may delay the beginning of perfusions. • Consider if clinical studies would facilitate the technology introduction when choosing the best path.
Hospital regulatory authorization	• Discuss the proposal with hospital administrators, including the advantages for patients and the hospital. • Understand which departments must be involved (pharmacy, surgical theater, and clinical engineering). • Minimizing the need for complex perfusate analyses must facilitate the introduction of the technique. • If the research pathway is chosen, consider involving other researchers at the center and plan to collect samples for future analyses.
Multidisciplinary and surgical team training	• Organize staff education and training sessions, including surgeons, anesthetists, and nurses. Hands-on sessions are fundamental. • Involve the blood bank team if you use packed red blood cells in the perfusate. • The training must be a continuum due to changes in procedures, staff, or technology updates. • Facilitate constant feedback to the device manufacturer company.
MP dedicated staff	• Organ perfusionists are desirable. • A research team for monitoring the health and safety of patients and collecting research samples and data is desirable if the research pathway is chosen. • Consider transplant surgeons, PhD candidates, research fellows or students to run the perfusions if dedicated organ perfusionists are unavailable. Nevertheless, they must have the surgical expertise necessary for perfusion and monitoring. • Anticipate potential problems according to the MP technique (system failure and vessel kinking).
Perfusion environment	• Consider the need for a dedicated perfusion room or if the machine setup could be done in the surgical theater concomitantly to the beginning of anesthesia and donor organ preparation. • If all can be done together at the surgical theater, consider that perfusionists, anesthesiologists, surgeons, and nurses could observe the perfusion. • In the case of a separate perfusion room, consider the staff required to oversee the perfusion.
When to deploy MP technology?	• Consider your local clinical needs to address the most limiting factor to increase the number of transplants/ benefit most patients. • Consider the difficulties and constraints characteristics of your specific setting when planning the perfusion program. • Consider the usual donor and recipient characteristics of that specific transplant center. Adopting a donor-recipient matching approach may guarantee a successful indicator of when to deploy the technology;

CD, donation after circulatory death; DBD, donation after brain death; ECD, extended criteria donor; MP, machine perfusion.

importantly, countries' importation tax rates, margins of distributors, and registration costs add an extra layer of complexity and cost to the process. For example, in Brazil, the tax rates for biomedical devices increase their prices 2–3 times compared with other countries.[28]

Additionally, setting the program demands multidisciplinary team training and hospital administrative authorizations. For example, clinical engineering must revise and approve the equipment before clinical use, even in a research project. Nurses working in hospital operating theaters must be presented with the equipment and informed on its purposes, and team needs during the perfusions. Finally, understaffing at the beginning of a perfusion program is frequent. Ideally, a perfusionist to run the perfusion while the surgical team is operating is desirable, together with a dedicated research staff capable of monitoring the health and safety of patients and collecting research samples and data.

Without a dedicated research team in our program, these aforementioned demands were entirely up to the transplant team responsible for the study. The back table was done, and the liver perfusions were set while the patient was anesthetized. After the beginning of the surgery, during perfusions, 1 surgeon

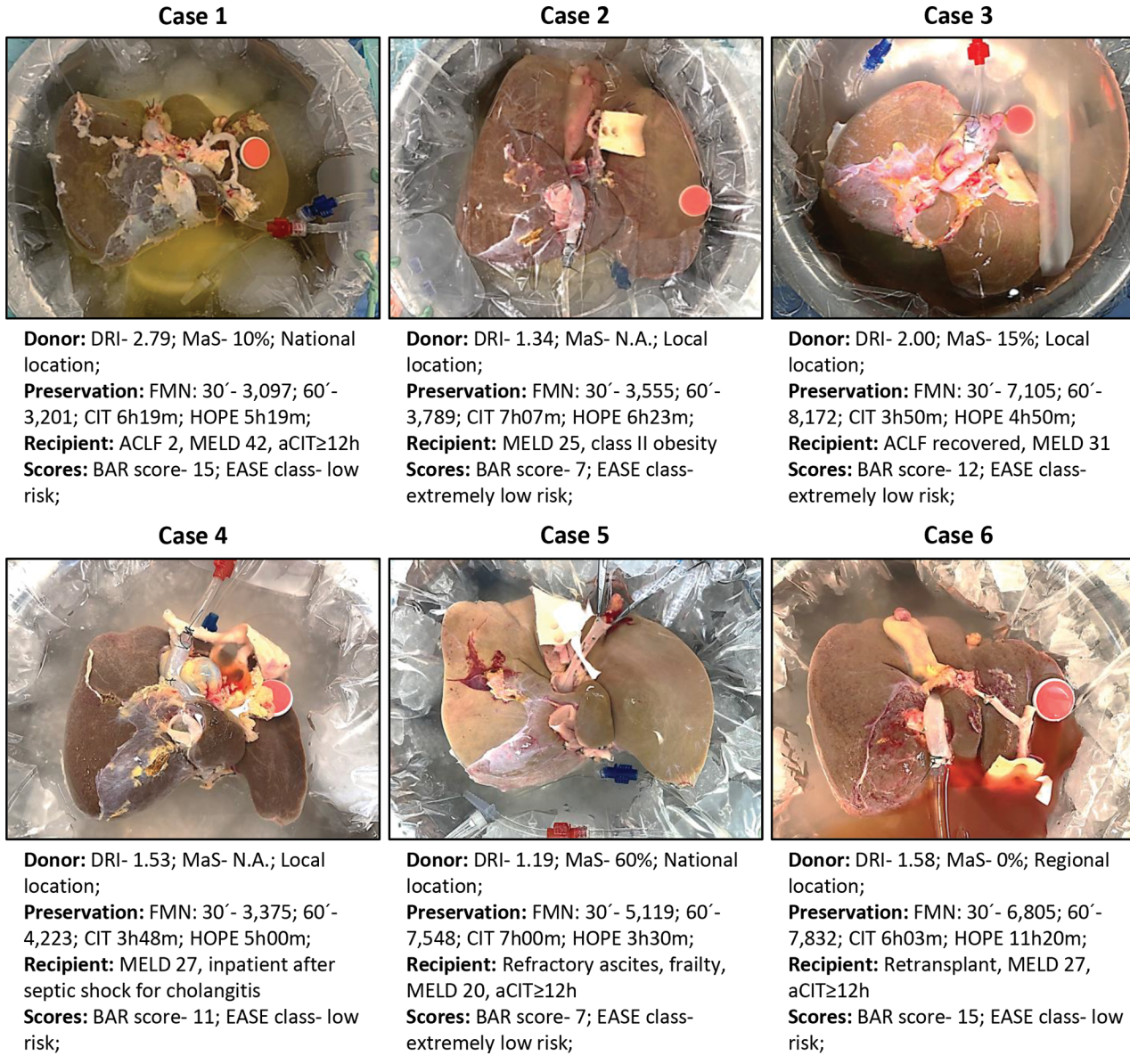

FIGURE 1. Illustrative summary of key donor, preservation, recipient details, and prognostic donor recipient matching scores. aCIT, anticipated cold ischemia time; ACLF, acute-on-chronic liver failure; BAR, balance of risk; CIT, cold ischemia time; DRI, donor risk index; EASE, early allograft failure simplified estimation score; FMN, flavin mononucleotide; HOPE, hypothermic oxygenated perfusion; MaS, macrovesicular steatosis; MELD, model for end-stage liver disease.

involved in the study and trained to run the device needed to periodically leave the procedure to oversight the perfusion for a few minutes, which, although assumedly not ideal, did not cause any delay or complication to the operations because we could count on fellows and younger surgeons. For long-lasting perfusions, one of the surgeons involved in the study was there for the entire perfusion, even if the surgery was not effectively ongoing.

Another difficult decision when starting an MP program is when to deploy the technology, especially in contexts of their limited availability. Although the use of MP of the liver was driven mainly by donor features thus far, conditions related to the recipient or the surgical procedure have started to gain interest amongst experts. Recipient conditions that demand accelerated liver transplantation may benefit from a perfused ECD organ if it appears timely. In this real-life study, HOPE was shown to be particularly beneficial for situations wherein the MELD score did not reflect the severity of the disease and expedited transplantation was required, for example, ACLF cases, refractory ascites with frailty, and retransplant; and also, for high MELD patients. MP may open up the possibility of using suboptimal grafts in these situations, wherein they were previously not considered because they were associated with poor outcomes after transplantation in the ACLF[29,30] and retransplant[31] settings.

Arguably, ACLF cases were not included in MP RCTs because their high morbidity and mortality may bias the results. Nevertheless, the high prevalence of the condition—estimated at 22.6%[14]—allied to the need to offer timely transplantation pressures the transplant teams in the clinical practice to take advantage of the availability of the perfusion equipment. We recently published the successful adoption of this approach.[32] The role MP may play in the ACLF setting is discussed in detail in a recent review article.[33]

Another exciting field for MP is liver retransplantation. Usually, only good-quality donor organs are acceptable for candidates needing a retransplant because the organ needs to tolerate longer CIT. Such recipients often cannot manage a turbulent PRS because the hepatectomy phase is already associated with more significant blood loss, prolonged operative time, and simultaneous previous organ dysfunction.[31] MP may mitigate these constraints in the operation by providing superior and prolonged organ preservation, alleviating the PRS; thus expanding the donor organ pool. These advantages were already suggested for NMP[31] and HOPE.[25]

Refractory ascites develop in approximately 10% of patients with ESLD and denote an advanced stage of cirrhosis with 1-y mortality rates of up to 52%.[34] This condition is frequently associated with renal dysfunction, regular paracentesis, frequent albumin infusions, sarcopenia, and frailty.[34-36] Despite the severity of the disease when there is a disproportionally high prevalence of complications from cirrhosis related to portal hypertension without liver dysfunction, the MELD and their priority for transplantation remains low.[37] The option for a perfused ECD DBD organ may be of interest. Herein, we transplanted a severe steatotic donor liver, confirmed by liver biopsy, treated by HOPE for 3 h 30 min after 7h 00 min of CIT. FMN was measured before the transplant surgery to ensure the surgical team was safe following the procedure. Previous studies have already proposed the safety of HOPE for steatotic donor livers and the possibility of this strategy expanding the donor organ pool.[38]

Regional discrepancies must also be taken into consideration when discussing MP preservation. Geographical barriers imposed by long territorial extensions sometimes imply prolonged organ preservation periods, lack of standardized organ donor care, and difficult access to healthcare specialists—which postpone patient evaluation and result in high-risk candidates for transplantation. Those problems are aggravated in developing countries. Consider Brazil as an example. On top of the aforementioned issues, poor donor care is often represented by hypernatremia, AKI, and high inotropes. Importantly, these donor risk factors are not well captured by common prediction models, including the DRI or BAR score. This is because CIT could not always be anticipated, and steatosis levels convey additional risk. A recent Brazilian retrospective study analyzing 1619 organ donors revealed the prevalence of ECD DBD at 78.31% when applying the Eurotransplant risk criteria.[11] This figure is well above the 50% reported in the Eurotransplant region[13] and for countries like Canada and the United States when other individual self-proposed criteria are applied[11] to DBD donors. To conclude, countries with long territorial extensions, sick recipients, long waitlists, and a high prevalence of ECD may need to adjust their donor organ preservation model; nevertheless, real-life studies demonstrating how the technology may attend to their daily practice issues are critical when considering their broad implementation.

The major strength of our study is the close association with routine clinical practice and the liberty to select recipients based on the perceived risk of the algorithm donor-recipient-operation, also considering everyday pressures and limitations to implementing an MP program based on an investigator-initiated research project. However, it does have several limitations. Most important is the small population studied because of the limited availability of the equipment because of financial constraints. Real-life studies have limitations, primarily from the lack of randomization and the need to apply the indications only within the local geographic context. Thus, the strategy for MP utilization proposed in this study is largely based on our experience and the only data of this kind currently available in the literature. This implies that the approach we describe regarding the use of HOPE on an everyday basis can only be indicative. However, they can guide transplant teams when dealing with similar situations.

CONCLUSION

In a setting of limited resources and complex transplant logistics, we describe the successful introduction of the HOPE procedure via the development of a research-based perfusion program. So far, costs and country-specific legal regulations for device utilization are the major hurdles to its more comprehensive implementation. The concept of donor recipient match may dictate the indication for MP and be a way to rationalize the use of the technique in these settings. Our initial experience performing HOPE in Brazil may help transplant teams implement perfusion programs worldwide, especially in developing countries or those with similar conditions.

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