EDITORIAL OPEN ACCESS

Anaesthetic management of organ transplant patients

Zoka Milan, Miriam Cortes-Cerisuelo

INTRODUCTION

Organ transplantation is a medical field that has undergone marked improvements over the last half a century. The first kidney transplant was performed in 1954, followed by liver, pancreas, lung, intestine and heart transplants in the 1960s [1]. The most marked improvements have been achieved in the areas of immunosuppressive therapy, surgical techniques, peri-operative treatment and data analysis [2].

Reconstructive transplantation (RT) or composite tissue allograft (CTA) transplantation, an emerging multi-disciplinary speciality that integrates the principles of plastic surgery and transplantation surgery, and which was introduced several decades after the above developments, has now made transplantation of an upper extremity, craniofacial tissue, vascularized joints, abdominal wall, larynx and trachea a clinical reality [3].

Anaesthetic management of solid organ transplant and RT patients involves similar underlying principles, which we will discuss in this paper. In addition, peri-operative care for solid organ transplant patients has certain characteristics that differ according to the type of organ requiring replacement.

Pre-assessment

Anaesthetic pre-assessment forms part of a multidisciplinary approach to the transplantation of any organ. All transplant patients should have their medical history recorded and undergo an appropriate physical examination; 12-lead and resting-state echocardiograms should also be obtained, in addition to laboratory tests and organ-specific investigations. The major risk factors for peri-operative cardiovascular complications are as follows: history of ischaemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency and cerebrovascular disease [4]. The step-wise approach to cardiac evaluation of surgical patients of the American College of Cardiology/American Heart Association (ACC/AHA) provides useful guidance for further testing, with consideration of the particular organ being transplanted [5]. Recently, cardiopulmonary exercise testing (CPET) has been used as an indicator of cardiorespiratory reserve when under stress [6]. In the peri-operative period, and particularly during reperfusion, demands are placed on organ systems due to the increase in metabolic rate. CPET can also be used for risk stratification, and even to obtain rough estimates of the length of hospital stay (LOS) and outcome [7]. In recent years, attention has been focused on the pre-operative increase in functional reserve that can be achieved through exercise, appropriate nutrition, and psychological preparation [6].

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Intraoperative management

The main difference between transplantation and other surgeries is the presence of a donor organ and post-reperfusion syndrome (PRS). Post-reperfusion syndrome is defined as a decrease in mean arterial pressure of more than 30% from the baseline value, and for more than one minute during the first five minutes after graft reperfusion [8]. The incidence of RPS varies among the different types of organ transplantation [9].

The main goal during organ transplantation is to maintain the recipient in a normothermic, euvolemic state, and to avoid anaemia, correct any electrolyte imbalances and ensure organ perfusion.

Ischaemia-reperfusion injury

Ischaemia-reperfusion injury (IRI) is a phenomenon commonly encountered in transplant surgery and has been defined as cellular damage to the graft following reperfusion of previously viable tissues [10]. IRI results from temporary oxygen deprivation and hypothermia, followed by reoxygenation and rewarming [11].

Ischaemia-reperfusion injury is associated with a high rate of morbidity and is a significant contributor to primary graft dysfunction [12]. There are numerous clinical manifestations of IRI, which vary markedly by

organ; for example, IRI of the lung may result in mild hypoxia, or a condition as severe as acute respiratory distress syndrome [13]. The occurrence of IRI poses a significant challenge to transplant surgeons and anaesthesiologists, and has thus been the target of extensive study. Here, we briefly discuss some of the key pathophysiological mechanisms underlying IRI and explore some of the preventative strategies against IRI recently described in the literature.

Pathophysiological mechanisms underlying ischaemia-reperfusion injury

In IRI, the microcirculation is affected, which can lead to the attraction, activation, adhesion and migration of polymorphonuclear neutrophils (PMNs), Kupffer cells, endothelial cells (ECs) and complement, which in turn causes local tissue destruction via the release of proteases and oxygen-free radicals (OFRs), and with the maximum effects seen 48 hours after reperfusion [14].

Histopathological changes in the liver can include cell swelling and vacuolization, EC disruption, and PMN infiltration with apoptosis of the EC and coagulative necrosis [15]. Reperfusion disrupts the intracellular energy metabolism and enzyme function, resulting in the depletion of adenosine triphosphate, accumulation of intracellular sodium and cellular oedema [16]. The energy state of the cell at reperfusion is important to determine the extent of cell recovery or injury. After reperfusion, the cell can be rescued, but further damage may also be induced at the microcirculatory level by flow disturbances, which affect red blood cells (RBCs) and PMNs, and by platelet adhesion to ECs and sinusoidal congestion [17].

In a clinical setting, extended criteria donors (ECDs; e.g., elderly donors and donors after cardiac death [DCDs]) are becoming an increasingly common source of organs; however, such organs are more susceptible to ischemic insult. The occurrence of IRI affects subsequent organ function and contributes to the shortage of organs available for transplantation. Indeed, IRI plays a central role in post-transplant complications, including primary non-function, graft dysfunction, kidney injury and rejection. For example, liver grafts from ECDs are at higher risk of graft failure, in part due to the higher incidence of IRI. Therefore, the expansion of donor criteria necessitates new approaches to avoid further organ damage during preservation and reperfusion, and thus ensure acceptable outcomes in transplantation surgery [18].

Many different strategies for reducing the effects of IRI have been proposed in the literature. Here, we briefly discuss ischaemic preconditioning (IP), use of volatile anaesthetic agents and ex vivo perfusion.

Ischaemic preconditioning

The technique of IP essentially involves exposing tissues to brief periods of ischaemia to protect them from the harmful effects of subsequent prolonged ischaemia. In the literature, two types of IP are described: acute preconditioning, wherein the interval between the initial brief IP and later prolonged insult is less than two hours; and delayed preconditioning, in which tissues exposed to initial insult are subjected to prolonged ischaemia after 24 hours [19]. Numerous experimental studies [20–24] have demonstrated that IP could in theory protect against IRI; for example, Pasupathy et al. used animal models of various different organs (e.g., liver, lung, kidney, intestine, skeletal muscle and brain) to demonstrate that tissues subjected to IP develop ischaemic tolerance (manifested in reduced energy requirements, altered energy metabolism, improved electrolyte homeostasis and genetic reorganisation) and reperfusion tolerance (lower levels of reactive oxygen species and activated neutrophils, reduced apoptosis and improved microcirculatory perfusion) [25]. Translation of these theoretical benefits to the clinical arena, however, has proven far from straightforward. The findings of recent studies have hinted at the possibility that IP may help improve clinical outcomes [26, 27], but other recent trials performed in a surgical setting suggest that IP does not positively influence clinical outcomes [28–30]. Hence, although IP shows much promise, it is evident that its clinical application requires significant further study before it can be recommended in routine practice.

Volatile anaesthetic agents

The use of volatile anaesthetic agents has long been discussed as a possible preventative strategy against IRI [31]. Typically, volatile anaesthetics have been found to be protective against IRI. However, similar to IP, the benefits associated with the use of anaesthetic agents have been largely experimental and many of them have been reported only in animal models [32–35]. For example, Liu et al. evaluated the effects of isoflurane and sevoflurane on IRI in isolated rat lungs and found that both agents significantly reduced the overall impact of IRI (as indexed by the coefficient of filtration, lactate dehydrogenase [LDH] and tumour necrosis factor-alpha [TNF-α] levels, the wet/dry lung weight ratio and levels of nitric oxide metabolites) [36]. However, these findings contrast with those of Nielsen et al., who reported two studies in which volatile anaesthetics exacerbated IRI [37, 38]. Although there are many differences in study design between the work of Nielsen et al. and that of Liu et al., which the latter authors acknowledge [36, 37], volatile anaesthetics for the prevention of IRI cannot yet be considered for routine use, similar to IP. Further studies, particularly in a clinical setting, would be beneficial to resolve this issue.

Organ preservation strategies

Currently, organ preservation strategies are based on static hypothermia, namely, static cold storage (SCS), but they remain insufficient for decreasing IRI,

especially in the context of ECDs. Recently, there has been a resurgence of interest in machine perfusion as a means of increasing the donor pool by optimizing organ preservation, as well as in the possibility of conducting quality assessments during ex vivo perfusion. End-ischaemic hypothermic oxygenated perfusion (HOPE) of the liver is an emerging organ preservation technique designed to reverse metabolic depletion of the donor liver at low temperatures by oxygenating the organ, resulting in reduced oxidative stress and cell death and increased levels of adenosine triphosphate (ATP) in the liver tissue after reperfusion [39].

Early results suggest that HOPE may improve early allograft function and reduce the rate of post-liver transplantation biliary complications, and the length of hospital stay, in comparison to that of patients receiving a liver preserved by SCS alone [40–42].

Another emerging organ preservation modality is normothermic machine perfusion (NMP), which was designed to keep the organ metabolically active during storage to prevent the injury associated with low temperature and promote the physiological organ repair that naturally follows ischemic cell damage. Several animal studies have demonstrated the feasibility and superiority of normothermic liver perfusion over SCS, as shown by a reduced inflammatory response after reperfusion and longer survival time [43–44].

Blood loss and blood replacement

The amount of blood loss during transplantation can vary between none and hundreds of units of RBCs [45-46]. Anaesthesiologists require specialised knowledge of blood products and blood replacement. In addition to clinical observation and standard blood clotting results, point-of-care management has significantly reduced perioperative blood loss [47]. Anti-fibrinolytic agents applied for prevention rather than as a treatment, and used for a maximum of 2 hours post-fibrinolysis, can also significantly reduce peri-operative bleeding [48]. Use of a cell-saver system is also important in all types of transplant surgery, particularly when blood loss exceeding four units is expected or at least deemed a possibility [49].

In recent years, hypercoagulability has emerged as a significant concern during organ transplantation. The balance between hypocoagulability and hypercoagulability, occlusion of the blood supply to the transplanted organ and postoperative thrombo-embolic events are attracting the attention of many specialists involved in organ transplantation [50] .

Major blood loss during solid organ transplantation can occur during the dissection phase and tends to worsen as transplantation progresses. Such blood loss should also be expected during the release of microvascular clamps, that is, when the maximum allowable ischaemic time has been reached.

The Pittsburgh Upper Extremity Transplant Anesthesiology Protocol (PUETAP) includes a trauma resuscitation protocol based on providing one unit each of RBCs and fresh frozen plasma (FFP) plus 250 ml of normal saline. Use of this protocol can achieve anhaematocrit (Ht) of 26%–28% within the Rapid Infusion System (RIS; Haemonetics, Inc., Braintree, MA, USA). In this context, the blood bank must ensure the availability of ten units each of RBCs and FFP [51]. Blood and fluid warming systems constitute an essential component of the equipment for transplantation.

Extended anaesthesia time

Long surgical times and the requirement to work outside of normal hours deter many anaesthesiologists from becoming, or staying, involved in transplantation programmes. At present, this problem tends to be addressed by enrolling more anaesthesiologists into the programmes, to reduce the number of calls per individual and allow long surgeries (6–10 hours) to be attended by multiple anaesthesiologists. Nevertheless, anaesthesiologists must seek to improve their own mental and physical ability to cope with long and antisocial hours [52] .

Invasive haemodynamic monitoring

Almost all transplant recipients should be subjected to invasive blood pressure management and central venous pressure (CVP) measurement via central venous catheters (CVCs). Invasive blood pressure measurements should be tailored according to the type of organ transplantation. For example, during bilateral upper limb transplantation, an arterial catheter must be placed in the lower limb, with some treatment centres targeting the radial and femoral arteries for invasive pressure monitoring during liver transplantation [53, 54]. Direct pressure measurement and vascular access in small children can be challenging. In patients with redo transplants, vascular access for rapid fluid replacement, bypass or CVP measurement can be almost impossible [55] .

It has long been debated as to which haemodynamic monitoring method should be used during transplantation. Generally, haemodynamic monitoring is moving towards less invasive modalities, such as transoesophageal echo (TOE) and LiDCO (Cambridge, UK) systems. However, some centres still use the gold standard cardiac output monitoring method, namely, a Swan-Ganz catheter, or monitors that require a particular type of arterial catheter, such as PiCCO (Pulsion Medical Systems AG, Munich, Germany) [56–58]. Monitoring of the depth of anaesthesia is advised for long transplantation procedures, as this can help reduce the amount of anaesthetic used and facilitates fast-tracking to the surgical ward after transplantation of the organ [59]. Interestingly, a recent analysis of all monitoring equipment used in liver transplant operations worldwide showed that only certain instruments improved outcomes [60].

Antibiotic prophylaxis

Aggressive antibiotic prophylaxis is paramount given the immunosuppression that occurs post-transplantation. In cases with massive blood loss, repeated doses of antibiotics and escalation of treatment, including intraoperative anti-fungal agents, is advised [61].

Use of inotropes and vasoactive medications

There is a generally held belief that vasoconstrictors can jeopardise surgical outcomes, intensify PRS and reduce the blood supply to transplanted organs. Inotropes and vasoconstrictors are used when perfusion pressure is low despite fluid replacement. When inotropes are required for acidotic transplant patients, the dose of inotropes can be reduced with attenuation of acidosis. Inotropes are used in transplant surgery and no correlation between their administration and poor outcomes has been noted to date [62].

Regional anaesthesia

While regional anaesthesia is used only occasionally during solid organ transplantation [63] , its application is highly recommended for RT [64]. Ultrasound-guided preoperative brachial plexus block can be used during RT surgery, particularly upper extremity transplantation, with a single dose of local anaesthetic agent at the beginning of transplantation. Continuous infusion should be started as soon as transplantation has been completed; this approach avoids any potential contribution of upper extremity vasodilatation to brisk bleeding and hypotension on deflation of the surgical tourniquet [65].

There is no evidence that brachial plexus catheters contribute to a better surgical outcome. A retrospective study of 146 patients showed that continuous brachial plexus block (CBPB) had no effect on the survival of replanted digits at six months after hospital discharge [66].

It appears that solid organ transplantation has now progressed well beyond the original anaesthetic protocols. However, vascularized composite allograft (VCA) transplantation teams tend to be less experienced, such that the first guidelines published for anaesthetic management of patients undergoing upper-extremity transplantation, namely, PUETAP, are still extremely useful for the transplant community [66].

Fast tracking in transplantation surgery

Early extubation in transplant patients is practised by many transplant units. There are several scoring systems that can predict early extubation I liver and other organ transplantation. All scoring systems have several factors in common: short duration of surgery, minimal blood loss, low inotrope requirements at the end of surgery, lower ASA score before transplantation, hospitalisation on a day of transplantation etc. [67–69].

CONCLUSION

Anaesthesiologists involved in solid-organ or VCA transplantations generally require additional training, which may be provided via anaesthesia simulators as an adjunct to clinical placement. In addition to the realities of shift work, massive blood loss, blood product transfusion, fluid loss, rapid treatment of abnormal coagulation, invasive haemodynamic monitoring, and inotropic, antibiotic and immunosuppressive treatments, transplant anaesthesiologists should be cognizant of IRI and graft optimisation. Despite the complexity and long duration of transplant procedures, fast-tracking to the surgical ward after transplantation is becoming more popular and its benefits are well recognised.

Keywords: Anaesthesia, Fluid management, Ishaemic-reperfusion injury, Optimization, Transplantation, Vascular access

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Author Contributions

Zoka Milan – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Miriam Cortes-Cerisuelo – Acquisition of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.