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Anaesthesiological strategies to improve outcome in liver transplantation recipients

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Abstract. – Graft and patients survival are the main goal of anesthesiological management in patients undergoing liver transplantation (LT). Even if anesthesiological practice sustained major developments over time, some evidence-based intraoperative strategies have not yet been widely applied. The aim of this review was to summarize intraoperative anesthesiological strategies which could have the potential to improve LT graft and/or recipient survival.

Monitoring must be as accurate as possible in order to manage intraoperative hemodynamic changes. The pulmonary artery catheter still represents the more reliable method to monitor cardiac output by using the intermittent bolus thermodilution technique. Minimally invasive hemodynamic monitoring devices may be considered only in stable cirrhotic patients. Goal-directed fluid-therapy has not yet defined for LT, but it could have a role in optimizing the long-term sequelae associated with volume depletion or overload. The use of vasopressor may affect LT recipient's outcome, by preventing prolonged hypotension, decreasing blood products transfusion and counteracting hepato-renal syndrome. The use of viscoelastic point of care is also warranted in order to reduce blood products requirements. Decreasing mechanical ventilation time, when it is feasible, may considerably improve survival. Finally, monitoring the depth of anesthesia when integrated into an early extubation protocol might have a positive effect on graft function.

Key Words:

Liver transplantation, Hemodynamic monitoring, Outcome, Blood products transfusion, Early extubation.

Introduction

Liver transplantation (LT) recipients suffer from relevant cardiovascular, respiratory, renal, neurological, and gastroenterological co-morbidity[1]. Moreover, LT is a major surgical procedure with the potential for significant hemodynamic instability, coagulopathy, and metabolic disturbance.

Even if anesthesiological practice sustained major developments over time, in line with surgical techniques progress, effective practices and evidence-based intraoperative management have not yet been applied in many institutional protocols[2]. Indeed, other than the use of a single device, drug or technique, the anesthesiologist's level of experience has a significant effect on LT recipients outcome. In a recent study[3], it has been found an increased mortality and graft failure during the first 5 cases.

The aim of this review was to summarize intraoperative anesthesiological strategies which could have the potential to improve LT graft and/or recipient survival, reporting the advantages of some aspects of cardiovascular monitoring, drugs use, fluid therapy, blood product transfusions and extubation time.

Cardiovascular Aspects

The intraoperative course of LT is often characterized by significant hemodynamic derangement, due to the severe recipients conditions and surgical maneuvers[2]. Since intraoperative hemodynamic instability is an independent predictor of graft failure and recipient mortality[4], it is mandatory to optimize hemodynamic parameters such as cardiac output (CO), arterial blood pressure (ABP), pulmonary arterial pressure (PAP).

Recent interest in hemodynamic monitoring has arisen as a consequence of the higher Model for End-Stage Liver Disease Score (MELD) scores, and growing incidence of coronary artery disease and dysmetabolic comorbidities of LT candidates related to their increasing age[5].

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Cardiac Output Monitoring

Hemodynamic measurements are still mainly performed by pulmonary artery catheter (PAC), even if transthoracic thermodilution method and transesophageal echocardiography (TEE) are also used in many institutions. Among PAC, the PAC-Continuous Cardiac Output (PAC-CCO) is, now, largely used to counteract hemodynamic derangement, even if it still suffers from well-known limitations mainly related to the delay in reading the actual CO[6]. However, intermittent bolus thermodilution by using PAC still represents the more reliable method to monitor CO in LT setting[7]. In addition, PAC provides the measure of the mixed venous oxygen saturation (SvO_2), central venous pressure (CVP) and notably pulmonary artery pressures (PAP)[7]. The potential complications due to vascular puncture during PAC positioning may be reduced by using the ultrasound (US) guide[8]. Nowadays, there is a growing interest in the helpfulness of TEE in LT setting, as it is recommended by both the American Society of Anesthesiologists (ASA) and Society of Cardiovascular Anesthesiologists (SCA)[9]. A recent study demonstrated a widespread use of TEE during LT in US centers with an overall utilization rate near 70%[9]. Although TEE has proven to be safe in LT, the concern for injury in patients with esophageal varices impairs its habitual use. It is well known that TEE does not allow direct pressure measurement; it allows estimation of the cardiac chambers size but it does not give numerical values, and its precision relies on good view acquisition (operator dependence). TEE has also been proposed for estimating PAP but, in the absence of tricuspid regurgitation, PAP is very difficult to assess. Therefore, in many centers, TEE monitoring is used in addition to PAC placement; this seems to be a rationale option particularly for the most serious cases.

Pulse Contour Continuous Cardiac Output (PiCCO) system, that allows the computation of stroke volume from an arterial pressure waveform (usually femoral artery), has been introduced with the aim to simplify the interpretation of cardiovascular performance. However, it has been hypothesized that the arterial pressure waveform can be altered as a consequence of significant changes in vascular tone[7]. PiCCO and other minimally invasive hemodynamic monitoring devices, such as LiDCO (lithium dilution cardiac output monitoring), Flotrac and esophageal Doppler monitor should be considered only in stable cirrhotic patients, despite its proved efficacy and safety[10,11].

Arterial Blood Pressure

It is necessary to precisely evaluate APB in each LT phase as its derangements are independently associated with adverse outcome[12,13]. Arnal et al[13] measured a gradient between systolic femoral artery blood pressure (FABP) and systolic radial artery blood pressure (RABP) during LT. Accordingly to this gradient, the rates of post-reperfusion syndrome (PRS) based on FABP, RABP, and non-invasive blood pressure (NIBP) measurements were found to be significantly different: 50.0%, 80.6%, and 50.0%, respectively[12]. Therefore, FABP reflects central arterial blood pressure more accurately and should be preferred to RABP[12]. If FABP monitoring cannot be achieved, NIBP measurement in combination with RABP may be a reliable alternative for evaluation of hemodynamic instability, particularly during the post-anhepatic phase and may prevent deleterious over-treatment[12,13].

Preload Indexes

Accurate assessment of the preload status and an optimal intraoperative fluid management are two major concerns in LT recipients[14]. Although traditional static preload indexes, including central venous pressure (CVP) and pulmonary artery occluding pressure (PAOP), have been commonly used to guide volume management, these pressure-based measurements represent only an indirect estimate of preload, and thus may not appropriately reflect changes in cardiac preload[7]. A reduced need for blood products has been associated with a low CVP during anhepatic and reperfusion phases[15]. On the other hand, both CVP and PCWP have demonstrated little positive predictive value in guiding hemodynamic management[15]. Volumetric approaches, such as determination of the right ventricular end-diastolic volume index (RVEDVI), obtained from PAC, has been demonstrated to better reflect preload than other static indexes[16]. In fact, during LT, heart compliance may significantly vary as a result of changes in intrathoracic pressure, chest volume, surgical retraction and variable pressure on the diaphragm, and this may modify clinical significance of filling pressures[7].

Non-invasive hemodynamic monitoring systems have allowed the introduction into clinical practice of the so-called dynamic indexes of fluid responsiveness, such as stroke volume variation

(SVV), pulse pressure variation (PPV) and systolic pressure variation (SPV), which have been regarded as good indicators of response to fluid-therapy[7].

Cardiovascular Drugs

Cardiovascular drugs are often used to counterbalance hemodynamic instability during LT. The use of vasopressor may affect LT recipient's outcome, by preventing prolonged hypotension and optimizing fluid replacement and blood products transfusion. Moreover, a lower prevalence of postoperative tracheal reintubation has been observed in LT patients who received an adjuvant vasopressor together with controlled fluid-therapy compared to fluids administration alone[17]. Pre-treatment with epinephrine and phenylephrine has proved to be useful to counteract the post-reperfusion syndrome (PRS), even if no influence on the overall in-hospital mortality rate and on the lengths of the hospital and ICU stays has been noted[18]. On the other hand, other authors have suggested that the occurrence of PRS may affect recipients' outcome, and suggest to prevent PRS by methylene blue, Nacetylcysteine and pentoxifylline[19]. Koelzow at al[20] demonstrated that methylene blue attenuated the hypotension during the PRS in LT recipients with reduced need of vasopressor but without impact on hospitalization time. The use of dobutamine is indicated in the presence of myocardial depression[19].

Finally, Fayed at al[21] reported the positive effect of terlipressin infusion during living donor LT on postoperative renal function. In this study terlipressin, reduced the use of vasoactive agents for PRS. Terlipressin also reduces the risk of bleeding by decreasing the portal pressure[21]. When portopulmonary hypertension is diagnosed, NO may be useful, as well as milrinone, when right heart failure occurs[19].

Fluid-Therapy and Transfusions

There is still an ongoing debate about the correct amount and type of fluids that should be administered during LT. Complications associated with poorly managed perioperative fluid-therapy are well known: decreased circulating volume results in hypoperfusion of end-organs as well as excessive fluid loads cause peripheral and pulmonary edema[22].

Goal Directed Fluid Therapy (GDFT) is a spectrum of fluid and/or pharmacological strategies with patient-specific end points; its aim is to optimize the long term-sequelae associated with volume depletion or overload. Nevertheless, the best perioperative GDFT has not yet defined for major surgery including LT[23]. However, it should be taken into consideration that qualitative toxicity exists for iatrogenic acute kidney injury and metabolic acidosis, due to the use of synthetic colloids and isotonic saline[23].

As regards allogeneic blood products, it has been stated that their use during liver transplantation may increase morbidity and mortality[24]. In the study of Rana et al[25], an intraoperative blood transfusion volume ≥ 28 units was found to be a significant risk factor for mortality in 233 consecutive LT recipients. Risk factors for intraoperative blood requirement were warm ischemia time, bilirubin levels, previous surgery and hepatectomy duration[25]. Steib et al[26] were unable to identify risk factors for bleeding during LT, even if an association was found with severe liver disease, previous abdominal surgery, use of a veno-ovenous bypass and poor team surgical experience[27]. Lower platelet count and higher MELD were identified as possible predictor factors without being significant in the regression models in a retrospective analysis. Therefore, blood loss remains difficult to predict before LT.

The generic risks related to blood transfusion include immunomodulatory effects and long-term autoimmune disorders[28]. Red blood cells (RBCs) transfusions in LT recipients increase rates of infection (7% for each unit of RBCs transfused) and has been associated with hepatic artery thrombosis. Cacciarelli et al[28] showed a significant improvement in patients and graft survival when less than 5U of RBCs were intraoperatively transfused in 225 LT recipients. Ramos et al[29] showed that more than 6U of RBCs was associated with a longer hospital stay and reduced survival. The results of these studies suggest that blood loss should be kept to a minimum during LT. Some scholars recommended to keep the hematocrit between 30 and 35%; others consider acceptable to maintain it between 26 and 28%. Guidelines for optimal use of packed RBCs have not been developed; however, considerable progress has been made on properly balancing intraoperative fluid, on preventing and treating clotting abnormalities as well as on "individualizing" transfusion triggers. Blood salvaging techniques are controversial during LT as they reduce allogeneic RBCs requirements but increase fibrinolysis due to the release of fibrinolytic compounds from collected blood cells[30].

The use of fresh frozen plasma and platelets is associated with higher levels of transfusion-related acute lung injury if compared with RBCs. Platelets contain many cytokines and vasoactive and inflammatory mediators, which are released on activation by various stimuli after reperfusion[30].

Therefore, according to the literature evidence, goal-direct strategies are warranted to reduce blood products requirements; one of these strategies may be the use of viscoelastic point of care[31]. The use of coagulation point of care monitoring using blood viscoelastic testing, in LT setting, may reduce transfusion requirements and related costs[31].

Fast-track Approach and Anesthesia Depth Monitoring

A strong associations of prolonged mechanical ventilation with increased risks of death and graft failure has been found in LT recipients[32]. In the last years, early postoperative tracheal extubation following LT has been proposed as an indicator of the quality of care and as fast-track strategy with the aim of reducing ICU resource utilization and overall costs[33]. Decreasing duration of mechanical respiratory support might also have the potential to reduce postoperative respiratory complications in LT recipients[32,33]. Moreover, reduction in postoperative ventilation time in LT may result in intrapleural pressure decrease with improved venous return and hepatic blood flow and potentially better recovery of liver graft. Early extubation combined with restrictive fluid management may facilitate rapid recovery of hepatic function[32]. Taner et al[33] retrospectively noted a significantly shorter hospital stay and decreased mortality in 513 patients who underwent fast-track strategy with extubation immediately after surgery and direct transfer to the ward. However, patients were selected on the basis of health conditions and intraoperative course. Therefore, it is likely that early extubation may have advantages if it take place in selected cases, free from anticipated postoperative complications. On the contrary, lower survival rate in LT recipients requiring prolonged mechanical ventilation could be ascribed to factors that prevent early extubation, including hemodynamic instability, renal and/or cardiovascular failure, serious neurological impairment, pulmonary oedema, excessive blood loss indicated by administration 10 or more of packed red blood cells, an alveolar-arterial oxygen gradient < 200 mmHg, temperature dysregulation, severe coagulopathy, and planned take-back in the OR. Among 10,517 LT recipients, risk factors for prolonged mechanical ventilation included female gender, pre-transplant dialysis requirement and ascites, while hepatitis C was recognized as protective factors[34]. Encephalopathy and a BMI > 34 were predictors of immediate postoperative extubation failure[34]. Another hypnotized factor is the presence of pulmonary vascular abnormalities such as hepatopulmonary syndrome and portopulmonary hypertension frequently associated with liver failure which may contribute to hypoxia before and after transplantation[34]. However, the role of these factors has not well investigated.

Another hypnotized benefit of early extubation could be the reduction of postoperative cognitive dysfunction (POCD), that is an independent risk factor for increased mortality in the first year after major surgery[35]. Wang et al[36] demonstrated that hepatic function is determinant for inhalational anesthetic dose needed to reach the same depth of anesthesia measured by Bispectral Index (BIS) monitoring. As all modern anesthetics are associated with some degree of POCD[34], and optimization of anesthesia depth with BIS between 40 and 60 is associated with a reduction of POCD incidence after major surgery[35], the benefit of a strict BIS monitoring should be studied also during LT. Interestingly, Dahaba et al[37] demonstrated that a lower BIS gradient (cross-clamp nadir-reperfusion zenith) may discriminate patients with IPGF and PNF in both living-donor and cadaveric graft.

The utility of a strict BIS monitoring (maintaining a range value target of 40-60), when integrated into an early extubation protocol, on graft function and its role in cerebral protection remain to be determined.

Conclusions

Considerable efforts have been made to identify intraoperative factors associated with improved LT recipients outcome. Promising strategies are accurate hemodynamic monitoring, reduction of blood products requirements by optimizing fluid therapy and cardiovascular drug use. Fast-track approach including early extubation and cerebral monitoring are warranted in LT in order to minimize both pulmonary complications and neurological impairment. The strong association between blood products transfusion or me-

chanical ventilation time and postoperative mortality suggests that these could be a marker of greater disease severity. However, randomized trials are not always ethically feasible in this clinical setting making it difficult to draw firm conclusions on the best device, technique or drug for improving LT recipient outcome.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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