Research Article

Liver Grafts Flush and its Relation to Hemodynamic Status in Recipients of Living Donor Liver Transplantation: An Egyptian Experience

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Abstract

Background: There have been limited data towards the hemodynamic (HD) changes in recipients of living donor liver transplantation (LDLT) especially during the reperfusion phase.

Purpose: Does surgical techniques affects the HD of the patients during reperfusion? We evaluated the differences between two surgical techniques done before the reperfusion phase of LDLT; one with liver graft flush and the other without flush.

Methods: A retrospective observational study conducted at Ain Shams University Hospitals, Center of organ transplantation. Analysis of 50 recipients HD data, usage of vassopressors, ICU stay and mortality during reperfusion phase and 20 min after it, thus comparing two different methods; one with liver flush through the portal vein (PV) of 100 ml-200 ml (1.5 ml/kg-2.5 ml/kg) of blood and venting it from hepatic vein (HV), other group without liver flush technique.

Results: Regarding the use of vassopressors; recipients underwent liver flush showed low initial and maintenance doses of nor-epinephrine compared to patients without flush (P ≤ 0.001), no differences detected regarding the HD state, intensive care unit (ICU) stay and blood products usage between the two techniques.

Conclusion: In patients candidates for LDLT there is an increased risk of a complex and not completely understood pathology of postreperfusion syndrome (PRS), antegrade Portal vein (PV) flushing with HV venting is a surgical technique with reduced doses of vassopressors with minimal PRS hemodynamic instability.

Keywords: Liver; Flush; Living; Donor; Transplantation

Introduction

The high prevalence of hepatitis C virus in Egypt led to an increased number of chronic liver disease due to virus inoculation, the experience of liver transplantation (LT) starting from the first case by Dr Starzl in 1967 at Pittsburgh [1] moving towards the development of immunosuppression in the early 1980 [2] had been transferred to our country, LT remains the gold standard procedure for patients with end stage liver disease [3]. In our country we still didn't implement a program for cadaveric LT although there is an established law for organ donation in 2010, therefore all of our cases at Ain Shams Center for organ Transplant are in the form of living donor LT; as we started our first case in 2003. Total numbers of LT till end of 2017 are 316 cases (108 Hepatocellular carcinoma (HCC), 170 HCV, 8 HBV, 24 others including autoimmune, metabolic disorder) and this number is expected to increase annually. For anesthesiologist; still hemodynamic disturbances remain the major serious issue especially during the reperfusion phase and possibility of postreperfusion syndrome (PRS). There is always limited data regarding the procedure of living donor LT (LDLT) due to the surgical differences and techniques compared to the cadaveric LT. Still the PRS events are the same in both types; which was first described by Aggarwal in 1987 [4] as a temporary, extreme cardiovascular collapse following grafted liver reperfusion. Several articles defined the event as profound bradycardia; hypotension and drop in the systemic vascular resistance (SVR) associated with pulmonary hypertension and elevated Central venous pressure (CVP) [4]. Before illustrating the unknown pathology of PRS; as an anesthesiologist we should be fully aware of the surgical techniques of LDLT after lobe hepatectomy from the donor's side, the grafted liver is perfused and prepared at the back-table through the portal vein using a cold preservation solution histidinetryptophan-ketoglutarate (HTK) solution [5]. Once the donor liver is placed in the recipient (after removing the diseased recipient liver), Three main vascular anastomosis are performed, in addition to the restoration of continuity of the bile duct. These are the portal venous, arterial (hepatic artery), and the Right hepatic Vein (in right hepatectomies) or Left hepatic Vein (in left hepatectomies) anastomosis which differs from the Caval anastomosis in beating heart cadaveric donors. After the technique is performed, before establishing full circulatory reperfusion of the graft through the vascular anastomosis, flushing out the preservation fluid from the donor liver should be carried out using the blood flow from the portal vein and drained through the Hepatic vein which is called the classic Orthotopic liver transplantation antegrade reperfusion or liver flush.

The reason for following this sequence is to ensure that the recipient liver receives blood in the quickest possible time as portal vein anastomosis is easier technically than hepatic artery anastomosis [6].

In addition, restoring the portal circulation first will allow quicker decompression of the venous drainage of the bowel since the venous return from the bowels are blocked when the diseased liver is removed. At this stage, in addition to flushing out the residual storage solution, or in place of that step, some circulatory blood can be let out or vented through the Hepatic vein with the aim of decreasing the potassium load and circulating factors released from the preserved liver so that they do not reach the heart, thereby decreasing the risk of severe hemodynamic changes associated with reperfusion [7].

Several theories for PRS have been explained, such as hyperkalemia, metabolic acidosis, air embolism, hypercalcemia and release of vasoactive substances at the time of reperfusion [8-10]. Trials of surgical interventions implemented to reduce the cardiovascular disturbances post reperfusion [11-12], after reviewing most of the studies; still most of the work on Cadaveric whole liver graft such as retrograde reperfusion through the IVC, sequential antegrade perfusion through the hepatic artery (initial arterial revascularization), and simultaneous antegrade perfusion (reperfusion starting simultaneously in the portal vein and hepatic artery), other technique done without venting of blood following reperfusion though the hepatic vein [13-15], Still limitations on LDLT besides currently no evidence to support or refute the use of any specific techniques of flushing or reperfusion during liver transplantation. Due to the paucity of data, absence of evidence should not be confused with evidence of absence of any differences [16].

The aim of this study is to review and analyze the intra and post-operative anesthetic and intensive care unit (ICU) records, blood transfusion, vassopressors support doses, and complications of the recipients of LDLT during the reperfusion phase, in order to report the various techniques of liver flush and its correlation with the hemodynamic stability of these patients. The created database will help in establishing conclusion and recommendations that will help to improve the anesthetic plan, intraoperative management, and increase the recipients' safety.

Materials and Methods

Successful anesthesia for Orthotopic Liver Transplantation depends on organized, scientific team-work, attention to details, availability of proper equipment and meticulous anesthetic care. A pre-emptive, anticipatory approach to the management of the complex problems involved is a common concept throughout the procedure. A thorough understanding of surgical technique, good communication and rapport with the surgeons, hepatologists, radiologist, intensivist and other members of the health care team are crucial.

The liver transplantation program at Ain Shams University Hospitals relies on related living donors. Extra care during anesthetic management of the donor is warranted because of clear ethical considerations.

After obtaining approval from the ethical committee of the Ain Shams University, the anesthetic records, blood transfusion, and complications perioperatively were retrospectively reviewed records of 50 recipients of LDLT in the period between 2012 and 2014.

Surgical technique: In the study group, LT was performed in piggy-back technique with antegrade reperfusion. Therefore, after completing the piggy-back anastomosis.

Liver flush technique: This is done by de-clamping the hepatic vein (right or left) and antegrade low pressure reperfusion of the graft with low oxygenated venous blood was established from the portal vein by partial de-clamping of the portal vein. Subsequently, portal anastomosis was performed using a running suture. Venous backflow *via* the hepatic vein was sucked into a separate suction device outside the patient in order to provide optimal antegrade liver perfusion by accurate calculation of the vented blood of 100 ml-200 ml. After completing portal anastomosis, the recipient portal vein was declamped immediately. During arterial anastomosis, the transplanted liver was antegradely perfused *via* the portal vein. After completing hepatic artery anastomosis, de-clamping of the hepatic artery was done and arterial perfusion started. Back-table flushing after donor's hepatectomy is done using the HTK solution. In the control group, LT was performed in standard technique without antegrade liver flush and venting of blood as described above.

The choice whether to flush or not is a pure surgical decision and is debatable by a Cochrane hepato-biliary group, in our study we only analyzed retrospectively the correlation between this technique and hemodynamic changes

Anesthetic techniques: Our main aim during preoperative preparation is to assess severity of liver disease (MELD score, Child-Pugh), detect co-morbidities, detect any contraindication to transplantation (e.g., severe ischemic heart disease, Cadriomyopathy, severe hepato-pulmonary syndrome, Portopulmonary hypertension .etc), detect correctable problems: Hepatorenal syndrome, Spontaneous bacterial peritonitis, encephalopathy. History of previous surgery, anesthetic history, Examination included airway, ascites, plan for vascular access, Body Weight, Height, preoperative Investigations: check complete blood picture, Albumin, coagulation, renal function, serum electrolytes, Lactate. etc. in relevance to intraoperative management, CRP (spontaneous peritonitis or active sepsis), cultures, Protein C, S (Hypercoagulability) and functional Cardiological and respiratory assessments including performance status and 6 min walk test.

General anesthesia was induced in the form of rapid sequence with Fentanyl 2 ug/kg-4 ug/kg, Propofol 2 mg/kg and Rocuronium 0.6 mg/kg dose. Two large-bore peripheral and a right internal jugular central venous catheter were placed. Anesthesia was maintained with a balanced anesthetic technique, consisting of a volatile agent (Sevoflurane 0.7-1 MAC) and a mixture of air and oxygen (FiO$_2$ 0.4). For intraoperative analgesia, fentanyl infusion 1 ug/kg/hr-2 ug/kg/hr were used Anesthetic management includes the use of two forced air warming blankets for upper and lower extremities and an infusion blood warmer.

Intraoperative monitoring included ECG, invasive arterial blood pressure (left radial artery), noninvasive blood pressure, continuous central venous pressure (CVP), body temperature, oxygen saturation (SaO$_2$), capnometry (EtCO$_2$) and urine output (mL).

During reperfusion phase intraoperative records of systolic and diastolic mean arterial blood pressure (MAP), Heart rate (HR), CVP, blood transfusion and administration of vassopressors support (Nor-epinephrine or Phenylephrine) were collected.

Types of outcome measures:

Primary outcomes:

- Hemodynamic measurements including Systolic and Diastolic MAP, HR, CVP (During reperfusion, and after 20 min).

- Blood products requirements.

- Use of vassopressors including Nor-epinephrine or phenylephrine.

Secondary outcomes:

- 28 days mortality.
- ICU stay.

Statistical analysis

Descriptive statistics was performed using means and standard deviations for quantitative variables, and frequencies and proportions for categorical variables. Differences of the hemodynamic parameters between the stage of reperfusion and after 20 min were performed by simple subtraction. Between-group comparisons were performed using t-test for two independent samples or, the equivalent non-parametric, Mann-Whitney U test. For all tests, the level of significance was set at p-value ≤ 0.05.

Results

This is a retrospective observational study performed at Ain Shams Center for Organ Transplantation between 2012 and 2014; we analyzed the data of 50 recipient's candidates for living donor liver transplantation (LDLT) (23 males and 27 females, 45 to 55 median age and IQR age), baseline characteristics and etiology of ESLD illustrated in Table 1, five patients with low MELD scores are transplanted due to the presence of hepato-cellular carcinoma (HCC), two mortalities reported due to post-operative sepsis (pulmonary) bacterial and fungal infection. Conventional standard anesthetic technique performed to all patients, 27 (55.5%) of patients underwent antegrade liver flush and venting during reperfusion phase. Regarding the hemodynamic (Systolic and Diastolic MAP, HR, and CVP) parameters showed no significant differences during reperfusion (P=0.144, 0.099, 0.218, 0.566) even 20 min after the reperfusion (P=0.697, 0.719, 0.164, 0.673).

Regarding the use of vassopressors; recipients underwent liver flush showed low initial and maintenance doses of nor-epinephrine compared to patients without flush (P ≤ 0.001), the decision to use vasopressors is based on the HD variables (MAP less than 50 mmHg) and it is not related to the pathological status of the patient, no differences detected regarding the intensive care unit (ICU) stay and blood products usage between the two techniques, Table 2.

Variables	n=50 (%)
MELD categories	
− ≤ 10	5 (1.03)
− 11-18	29 (58.6)
− 19-24	12 (24.1)
− ≥ 25	4 (6.9)
Underlying liver disease	
− HCV	39 (79.3)
− HCC	25 (51.7)
− HCV and HCC	22 (44.8)
− HBV	2 (3.4)
− Cryptogenic	5 (10.3)
− Autoimmune	2 (3.4)
Liver flush was performed	27 (55.5)
Mortality within 28 days	2 (3.4)

Table 1: Baseline characteristics of the study sample. MELD: Model for End-stage Liver Disease.

	Liver flush (n=27) mean ± SD	No flush (n=23) mean ± SD	P-value
Systolic MAP during reperfusion	89.58 ± 9.11	83.30 ± 13.29	0.144
Systolic MAP after 20 min	101.37 ± 7.90	102.8 ± 11.66	0.697
Diastolic MAP during reperfusion	54.05 ± 7.36	49.20 ± 7.12	0.099
Diastolic MAP after 20 min	60.16 ± 4.69	59.30 ± 8.07	0.719
Heart rate during reperfusion	101.42 ± 11.50	107.10 ± 11.58	0.218
Heart rate after 20 min	98.26 ± 9.66	103.60 ± 9.29	0.164
CVP during reperfusion	3.05 ± 1.39	3.40 ± 1.78	0.566
CVP after 20 min	5.37 ± 1.89	5.70 ± 2.16	0.673
Blood transfusion units	2.26 ± 1.41	2.5 ± 1.43	0.672
Initial dose of vasopressors (mic/kg/min)	8.74 ± 4.81	19.80 ± 7.73	<0.001
Maintenance dose of vasopressors (mic/kg/min)	4.37 ± 2.41	11.9 ± 3.11	<0.001
Days of ICU stay	7.42 ± 0.61	7.90 ± 0.88	0.095
Parameter differences between "during reperfusion and after 20 min"			

Systolic MAP[*]	-11.79 ± 11.70	-19.50 ± 14.26	0.126
Diastolic MAP[*]	-6.11 ± 8.64	-10.10 ± 11.66	0.286
Heart rate	3.16 ± 8.68	3.50 ± 9.77	0.839
CVP[*]	-2.32 ± 2.29	-2.30 ± 2.54	0.769

Table 2: Hemodynamic and clinical parameters of the group with liver flush versus the group without liver flush. MAP: Mean Arterial Blood Pressure; CVP: Central Venous Pressure; [*]negative sign indicates reduction.

Discussion

Risk factors associated with PRS should be understood especially in patients with high danger of aggressive hemodynamic collapse like LDLT, the occurrence of cardiovascular instability and PRS is usually unpredictable as mentioned in several studies [17-20]. Our main concerns as anesthesiologist is to predict the risk factors and prevent their occurrence such as electrolyte imbalance; hyperkalemia and hypothermia [20], increased cold ischemia time without portocaval shunting [17] as it is not applicable in LDLT, amount of blood products transfused [18] extensive liver and renal diseases [21], and left sided ventricular diastolic dysfunction [22].

Taking the decision to perform liver flush or not is a pure surgical decision, several debates had been discussed to compare the benefits of different methods of flushing and reperfusion following LT, a Cochrane hepato-biliary group concluded that there is no currently evidence to support or refute a specific technique of flushing during LT.

As working in a team, many surgical maneuvers have been discussed to reduce the PRS events, these interventions have been reported in several studies like Portal vein (PV) flushing and venting of the IVC [23, 24] but these reports were applicable on Cadaveric LT, in LDLT we usually use PV flushing and venting through the Hepatic Vein (HV) which correlates with our study regarding better hemodynamic stability and ICU stay and 28 days mortality. In our study; recipients without PV flushing nor venting (Group II) showed significant increase in the use of initial and loading doses of nor-epinephrine compared to patients with liver flush (Group I) (P ≤ 0.001) which reflects intraoperative degree of PRS manifested by hypotension and decreased SVR in Group II, but this hemodynamic instability is masked by the intra-operative use of nor-epinephrine in significant higher doses. It is essential to know that the surgical maneuvers and technique can affect the cardiovascular parameters although the LT, Hemodynamic status is like a roller coaster with marked variability. Liver flush is technically more feasible than any venovenous bypass [25] avoiding the hazards of venous cannulation and extracorporeal circulation which may increase the release of vasoactive, toxic markers. HV venting helps in the de-airing of the grafted liver, thus minimizing the air embolism which is one of the risk factors for PRS. One of the drawbacks of Liver flush is blood loss; as usually 1.5 ml/kg-2.5 ml/kg (100 ml-200 ml) of blood is flushed in a separate canister outside the body without using the cell salvage machine, but in our study there were no statistically differences between two groups regarding the amount of blood products administration, usually this amount of blood flushed is suitable for living donor grafts.

Studying the hazardous effects of vasopressors have been reported in several studies [26], continuous high infusion doses of nor-epinephrine may cause serious graft complications; like graft ischemia, renal impairment and death [26]. Therefore passing the reperfusion phase with minimal doses of vassopressors is of great benefit for the patient as observed in our study. The same study by Williams [26,27] reported that ischemic graft due to poor perfusion may lead to intractable PRS with a sequence of postoperative graft failure, renal failure and death; therefore we recognized the benefits of maintaining hemodynamics with minimal usage of high doses of vassopressors limiting their prolonged adverse effects.

Conclusion

In patients candidates for LDLT there is an increased risk of a complex and not completely understood pathology of PRS, antegrade PV flushing with HV venting is a surgical technique with reduced doses of vassopressors with minimal PRS hemodynamic instability.

Conflict of Interest

Nothing to disclose

Author's contribution

We hereby declare that the article has not been published or submitted to or accepted for publication in any form in any other journal. I vouch that the authorship of this manuscript will not be contested by anyone whose names are not listed. On acceptance the article will become the copyright of Journal. The manuscript has been read and approved by all the authors.

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