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Management of early complications of hepatic artery post living donor liver transplantations in adults

Hussien Kamal Eldin Hussein
Professor of General & Vascular Surgery, Faculty of Medicine – Cairo University

Mostafa A. EL-Shazly
Professor of General & Hepatobiliary Surgery, Faculty of Medicine – Cairo University, Egypt.

Omar A. EL-Azeez
Professor of Radiodiagnosis, Faculty of Medicine –Cairo University, Egypt

Karim Adel Hosny
Professor of General & Vascular Surgery, Faculty of Medicine – Cairo University, Egypt

Alaa Eldin Mahmoud Amin
Lecturer of Vascular Surgery, Faculty of Medicine – Cairo University, Egypt
Corresponding Author email: alaa301089@cu.edu.eg
ORCID ID: 0000-0002-6850-3339

Mamdouh Abd El Salam Mabrouk
M.B., B.Ch., M.Sc.

***Abstract*---**Background: Liver transplantation has rightly gained recognition as an established therapy for end stage liver disease and acute liver failure. Liver transplantation in humans has come a very long way in a short period of time. The aim were to identify the causes and the risk factors of early complications of hepatic artery post LDLT in adults. Methods: This is a retrospective & prospective analysis study, which was carried out in Orthopedic Surgery This study was conducted on a retrospective review of 20 recipient patients who underwent LDLT and suffering from an early hepatic artery complications at Cairo University Hospitals and Dar Al Foad Hospital from starting the program till 2016. Results. Risk factors were examined as predictors of success including age, sex, history of HCV +/- HCC and any co-morbidity (DM, HTN), the Child-Pugh score, MELD score, identification of potential risk factors (trans-arterial

chemo embolization (TACE) & Hyper-coaglable states), careful preoperative evaluations (Donor & Recipient). Conclusion: Early HA complications remain a major cause of morbidity and mortality after LDLT. Urgent revascularization is necessary to avoid graft loss. Endovascular approach, including IAT and PTA is emerging as a less invasive alternative to open surgery in the management of early HAT and can be used in conjunction.

***Keywords*---**early complications, hepatic artery, liver transplantations.

Introduction

The liver is the largest solid organ in the human body. It has a unique structure with a dual blood supply, being approximately one-third from hepatic artery and two-thirds from portal vein. Within the liver substance blood flows through sinusoids between plates of hepatocytes to drain into central veins, which in turn join the hepatic veins draining into the vena cava[1]. The main causes of severe liver damage that lead to people needing a transplant are: cirrhosis, hepatitis, metabolic conditions, paracetamol poisoning and others[2].

Liver transplantation: Challenging controversies and topics grew out of a need perceived within the fields of transplant hepatology and liver transplantation. Liver transplantation has rightly gained recognition as an established therapy for end stage liver disease and acute liver failure. Few would argue that liver transplantation is one of the few truly lifesaving and life-altering treatments within medicine and surgery[3]

Liver transplantation in humans has come a very long way in a short period of time. First studies of liver transplantation in animals began in 1958 when showed that such a procedure was technically possible. Identified three key challenges: the need to preserve the liver between retrieval and implantation, the need to preserve the recipient in hemodynamic stability and the need to prevent rejection[4].

Living donor liver transplantation (LDLT) is probably the most high-profile of all surgical enterprises. At the same time, it is an amazing act of altruism. It requires hard work of dedicated multidisciplinary medical teams coupled with the courage of the patients and their families. The concept of LDLT is based on the following two factors: (1) the remarkable regenerative capacity of the liver, and (2) the shortage of cadaveric organs. LDLT has become an acceptable alternative for patients in need of liver transplantation (LT) who are not likely to receive a deceased donor liver transplant (DDLT) in a timely fashion[5].

Abdeldayem *et al.* reported unplanned adult-to-child LDLT using right liver. In this particular case, the operative procedure was changed from left to right hepatectomy because of unfavorable anatomy of the left hepatic artery[5]

The characteristics of the living donor and the liver graft determine not only the safety of the donor but also the operative outcome of the recipient. The objectives

of the process of donor selection and evaluation include ensuring true voluntarism without coercion or inducement, assessing the donor's operative risk by screening for underlying medical illness, blood group matching and detecting occult liver disease and transmissible disease, determination of the type of liver graft to be used, and defining anatomic variations that can be of consequence if unrecognized[6]

No surgical intervention is completely safe, and death may complicate any intervention. We know that liver donation puts the donor at risk of medical and surgical complications and even death. When death occurs in a healthy donor, there are exceptional consequences. A donor death will have a devastating effect not only on the families and friends of the donor and recipient but also on all the clinical staff involved in the procedure. The impact of the death may spread to other potential donors and recipients, and brings negative publicity and potential economic damage to the transplant center[7,]

Hepatic artery stenosis and thrombosis are common complications in liver transplant patients, after primary non function (PNF). Hepatic artery thrombosis (HAT) is the second main cause of liver graft failure. Moreover, HAT is the most common arterial complication in orthotopic liver transplantation (OLT). It is associated with a marked increase in morbidity, being the leading cause of graft loss (53%) and mortality (33%) during the immediate postoperative period[8] Vascular complications after orthotopic liver transplantation (OLT) ranges from (2% to 25%) in most publications. The most frequent complications involve the hepatic artery (2% to 12%) in adults[9].

Depending on its time of onset, it can be classified as early or late HAT. There is a wide range of criteria that define these entities making comparative studies difficult. The definition of early HAT ranges from day zero up to 40 days[10]. The incidence of early hepatic artery complications following LDLT is reportedly (4.2–16.3%) for adults and (1.7-10%) for children[11].

Early hepatic artery complications after living donor liver transplantation (LDLT), including hepatic artery thrombosis, stenosis, spasm, kinks, and aneurysms can directly affect both the graft and recipient outcomes. For this reason, early diagnosis and treatment are essential when dealing with these complications[12]. The complications of hepatic artery are usually associated with technical, hemodynamic, immunological and infectious factors which may result in biliary tract complications or sepsis and even a re-transplantation may be required[11].

The aim of this study were to identify the causes and the risk factors of early complications of hepatic artery post LDLT in adults. The ultimate goal of this study is prevention of hepatic artery complications following LDLT in adults. To review different lines of treatment (endovascular or laparotomy) of 20 patients having hepatic artery complications post LDLT in adults. Early diagnosis of hepatic artery complications post LDLT in adults. To discuss morbidity and mortality of cases with hepatic artery complications post LDLT in adults.

Patients and Methods

This study was conducted on a retrospective review of 20 recipient patients who underwent LDLT and suffering from an early hepatic artery complications at Cairo University Hospitals and Dar Al Foad Hospital from starting the program till 2016. Analysis of results, outcome and comparison to literature, to detect the percentage of successfully treated cases with maintained patency of hepatic artery with good flow of oxygenated blood supply to liver graft and survival of graft. The management procedures, possible complications, benefits, risks and alternative between methods were all explained to the patients.

Patients

From starting Cairo University Liver Transplantation Team Program till now, sex hundred (600) patients underwent primary LDLT at Cairo University Hospitals and Dar Al Foad Hospital. Thirty-one patients who developed with hepatic artery complications, twenty patients with early hepatic artery complications post LDLT in adults were included, The criteria of patients are as following:

Inclusion Criteria: Age (adults)**.** Living donor liver transplantations in adults. Early complications of hepatic artery (from day 0 to 40 days). Any hepatic artery complications even if affected on liver function or not.
Exclusion criteria: Liver transplantations in children Late complications of hepatic artery after 40 days. The patients underwent clinical, laboratory and radiological evaluation up to two years follow up to early detection recurrence or any another events.

Consent & Ethical committee Agreement

Approval of this study was obtained from the Research ethical committee and informed consent was obtained from all patients including approval of the protocol of treatment and the anonymous use of the data for research purposes.

Methodology

1. Study design:

We studied retrospectively 20 cases were developed early hepatic artery complications in patients who underwent LDLT in adults at Cairo University Hospitals and Dar Al Foad Hospital.
Early complications of hepatic artery which detected from day 0 to 40 days post-surgery of transplantation and this complications may be thrombosis, stenosis, spasm, kinks, and aneurysms and how they were detected early by clinically, laboratory and radiological modalities (it was performed using Doppler, CT angiography, and digital subtraction angiography).
Any hepatic artery complications even if affected on liver function or not.

1- Recipient of living donor liver transplantation in adult's assessment by a history (age, DM, HTN and history of HCV +/- HCC and). Physical examination (The Child-Pugh score and MELD score)

2- Identification of potential risk factors (trans-arterial chemo-embolization (TACE) & Hyper-coaglable states)
3- Careful preoperative evaluations and intra-operative microsurgical technique for hepatic artery reconstructions end to end**.**
4- Postoperative follow up (duplex u/s, liver function every 12h & anti-coagulant & MDCT if detect any abnormalities and if available.

2. Treatment protocol:

Careful preoperative evaluations and intra-operative microsurgical technique for hepatic artery reconstructions are the keys in prevention of hepatic artery complications after LDLT. A multidisciplinary team including micro surgeons, transplant surgeons, interventional radiologists, and hepatologists decided the protocol of management.

Results

The study population comprised 20 males. The indication for transplantation was liver cirrhosis secondary to HCV in all cases with or without hepatocellular carcinoma on top of cirrhosis and received right lobe graft from a living donor. In our study 16 cases in the 1st week (80%) and four cases in the 2nd week (20%), ranging 1–12 days, mean 6.5 day. At the time of diagnosis, shooting of the liver enzymes was noticed in eight cases (40%), being stable in six cases (30%) and mildly elevated in six cases (30%). The mean age in our patient series was 51±13 years; ranging from 38 to 64 years. There was no significant difference in age between the different causes of HA complications post LDLT. According to the preoperative evaluation among all 20 cases suffering from HCV, were classified Child-Pugh score as Child B nine cases (45%) and Child C eleven cases (55%) and according to MELD score all cases more than MELD 12.

Careful preoperative evaluations for recipient and donor (clinically, laboratory and radiologically) use MDCT for both before LT operation and intraoperative microsurgical technique for hepatic artery reconstructions were done for all patients and selection of recipient artery according to donor artery size so we use RT HA in eight cases & LT HA in eleven cases and proper HA in one cases Table (1). In our study, HAC according to type of complication are two cases suffering from mismatching size and of them associated with HA kink, one case suffering from steal with HAS, one case suffering from spasm with HAT, six cases suffering from significant stenosis (HAS) and ten cases suffering from primary thrombosis (HAT) according to the selection criteria and were included in our study Table (2).

Angioplasty Procedure

Percutaneous transluminal angioplasty (PTA) was considered in 18 out of 20 cases (90%) and two cases were considered to surgery direct without PTA (10%) because unavailable some Endovascular equipment. PTA was complete successful in fourteen patients from 18 patients (77.8%) and failed to complete management in four cases (22.2%) so the main benefit of PTA in this cases as a diagnostic and detect the cause. IAT was attempted in 18/20 cases. Streptokinase was used in 15 cases and tPA used in three cases. Initial successful IAT was achieved in

15/18 cases (83.33%). Successful recanalization was achieved after the bolus dose in 13/15 cases (11 cases using streptokinase and two cases using tPA), whereas two cases required continuous infusion of tPA for 8 h and streptokinase for 12 h to recanalize. IAT failed in 3/18 cases (16.7%). Successful IAT revealed underlying hepatic artery stenosis (HAS) in 4/15 cases (26.67%), significant steal with HAS in 1/15 (6.67%), spasm associated with HAT in 1/15 cases (6.67%) and did not reveal underlying anatomical defect with thrombosis only in 9/15 cases (60%). After successful recanalization, rebound thrombosis developed in 4/18 cases (22.2%).

- One case had adherent thrombus at the anastomotic site so subtotal thrombolysis was done and for follow up but thrombosis reinformed and was developed after 4 h, for which successful surgical reconstruction was performed.
- In the 2nd case, IAT was performed significant kink and size mismatch between the recipient and donor arteries, for which successful surgical reconstruction was performed but rebound thrombosis and splenic steal after 72 h and graft failure so the patient was scheduled to retransplant. The patient died after 2 months.
- The 3rd case, rebound HAT developed after 72 h from successful IAT and stent placement. This was associated with portal vein thrombosis. Successful surgical revascularization (PV thrombectomy and saphenous graft of the HA) was performed. This patient died after 2 months of persistent graft failure after successful revascularization.
- In the 4th case, IAT was performed after failed surgical revascularization in the 1st day, PTA was not attempted and rebound thrombosis developed after 72 h. The patient died after 1 week of graft failure.

Laparotomy Procedure:

Case No. 1 of them reanastomosis of HA due to tight stenosis affecting HA flow and HAT day 1 PO, the diagnosis confirmed with MDCTA, The recipient was scheduled to urgent laparotomy direct without PTA because the anastomosis was recently done and there was not stent positioning because the stenosis over estimation.

Intra operative we remove anastomotic stitches and thrombectomy was don, refreshment of the edges of the HA and make inter position graft of saphenous vein, micro vascular reanastomosis after thrombectomy and injection of heparin proximal and distal ends of HA. Intraoperative Duplex excluded any stenosis pre, at and post both anastomosis. This patient suffered from biliary leakage after 4 weeks.

Case No. 2 suffering from HA thrombosis on top of HAS in day 2 PO, the diagnosis confirmed with MDCTA, so patient was scheduled to laparotomy and thrombectomy done and revision of the HA anastomosis. Patient was survived but complicated with biliary structure and IHBRD after one year.

Case No. 3 suffering from re-thrombosis on top of HA kink and mismatching, the diagnosis confirmed with MDCTA and PTA.

Patient was scheduled to laparotomy and thrombectomy done and revision and refashioning of the HA anastomosis. Patient post-surgery suffered from re-thrombosis again associated with splenic steal, Surgical ligation of the splenic

artery was performed and complicated by splenic abscess and underwent splenectomy so patient was scheduled for re-transplantation and died after 2 months.

Case No. 4 IAT was then attempted and was initially successful In this case suffering from re-thrombosis post PTA, so patient was scheduled to urgent laparotomy and thrombectomy done and revision of the HA anastomosis, the intra-operative biopsy revealed acute rejection and the patient died after one week of graft failure**.**

Case No. 5 suffering from total HAT and extended thrombus so PTA failed to complete thrombolysis (make partial recanalized) so patient was scheduled for laparotomy and thrombectomy was done to avoid high risk of recurrence, microvascular for closure of arterotomy after complete thrombectomy and injection of heparin proximal and distal part of HA. Graft and patient were survived.

Case No. 6 rebound HAT developed after 72 h from successful IAT and stent placement. This was associated with portal vein thrombosis. Successful surgical revascularization (PV thrombectomy and saphenous graft of the HA) was performed. This patient died after 2 months of persistent graft failure after successful revascularization Table (3).

Clinical improvement:

Major complications means prolonged hospital stay or mortality. The results of surgical and endovascular revascularization of HAT are summarized in Tables (4).

Table (1): Patients demographics and co-morbidity and history

Patients	Mean age (years)	38-64	51±13
demographics			
	Gender	M:F	20-0
	DM	12	60%
	HTN	4	20%
	HCV	20	100%
Co-morbidity	HCC	6	30%
and history			
	Child-Pugh score	A-B-C	0-9-11
	MELD score	> 12	
	Potential risk factors	2	10%

Table (2): Types of HAC and methods of management

Type of complication	No. of cases	%	Angioplasty method	Laparotomy method	Both methods
HA tight stenosis with mismatching	1	5%	-	1	-
HA kink and mismatching size	1	5%	-	-	1
HA steal + stenosis	1	5%	1	-	-
HA stenosis	6	30%	3	1	2
HA thrombosis	10	50%	9	-	1
Spasm + HAT	1	5%	1	-	-

Table (3): Rate of complications of every method

Angioplasty Method	Laparotomy post PTA		Laparotomy method	Laparotomy complications
18	4		6	3

Table (4): Different complications of all cases

Degree of complications		No.	%
Without any complications		12	60%
Major complications	Early	4	20%
	Late	4	20%

Early complications are bleeding, sepsis, retransplantation and acute rejection. Late complications are biliary complications (structure or leakage) and chronic rejection.

Discussion

Potential risk factors have been identified in many series. It may be surgical (technical) or nonsurgical. We encountered underlying HAS in 6/20 cases (30%) that developed HAT. The arterial anatomy of both recipient and donor/graft can affect the incidence of HAT. The smaller the arteries, the higher the incidence[13]. One common problem is the discrepancy in size between the graft and recipient arteries. Different techniques have been described for an anastomosis in such cases. Funnelization is our preferred technique. In two cases that developed HAT, there was significant kinks and size mismatch between the recipient and graft arteries (>2:1). However, they were considered as contributing factors as one case were treated by IAT with no further intervention and another case with surgery, Also, kinks and size mismatch contributed to the splenic artery steal in one case.

In our study, 30 cases with Cairo University Liver Transplantation Team Program, the hepatic artery reconstruction was performed using magnifying loop, the incidence of HAT was 4/30 (13.3%) and the most of cases the hepatic artery reconstructions were performed by a micro-surgeon using the operative microscope, the incidence of HAT improved to 4.5% (26/570 cases). Non-surgical potential risk factors, include hypercoagulable disorders (thrombophilias) in recipient and donor, cytomegalovirus mismatch, ABO incompatibility, and the arterial reperfusion time. Prolonged operation times are also suggested. In our study no case of 20 cases hade this medical problems. Regarding etiology of Early Complications of Hepatic Artery Post Living Donor Liver Transplantations in Adults are:
The incidence of steal syndrome is 3% to 7%; if left untreated, it represents a significant potential risk for postoperative morbidity and graft loss[15], in our study we have two cases suffering from steal which increased and become significant with HAS so managed with stent of HAS and another case associated mismatching and kink.

Hepatic arterial thrombosis (HAT) is the most common arterial complication of liver transplantation. HAT represents 58% of arterial complications with adult liver transplant recipients. HAT occurred in 4- 11% of adult transplants[16] in this study we have 11 cases suffering from HAT, this number means 51% of cases suffering from early HA complications post LTX one of them associated with spasm.

Predisposing factors can be classified based on lesion location. It should be noted that one of the major predisposing factors for the development of HAT is an underlying anatomical defect such as HAS or HAK Saad and coworkers demonstrated that 65% of liver transplant recipients developed HAT within six months from the angiographic diagnosis of a significant HAS[16]. HAK occur in 0.4% of transplant recipients and represents 6% of abnormal arteriograms and 13 to 19% of arterial anatomical defects[16]. In addition, 7% of HAS cases can be associated with HAK (range, 0-19% of cases). Hepatic arterial kinks (HAK) are usually caused by redundancy of the donor or recipient hepatic arteries. In this study we have one case suffering from HAK associated with HAS (5%).

Diagnosis of HAC post LDLT in adults:
The liver enzymes were stable at that time. This phenomenon (no diastole) was also encountered in other patients with high portal flow and cases of small-for-size grafts[19]. In these equivocal cases, HAT should be ruled out by MDCTA or DSA. Although DSA is the gold standard, MDCTA has emerged as a noninvasive imaging modality for the diagnosis of HAT. A sensitivity rate of 100% with a specificity rate of 89% and accuracy of 95% has been demonstrated. Conventional catheter angiography can be used as a next step possibly if any interventional treatment is contemplated[20]. We encountered false positive results using Doppler US in 5/600 cases when MDCTA was not performed and DSA revealed patent HA.

Management of HAC:
In general, there are three different treatment modalities for HAC: Re-transplantation, surgical revascularization and endovascular re-vascularization[21]. Our criteria for management of HAT depend on many factors: The timing of thrombosis, the possible underlying cause, the graft function, and the opinion of the surgeon who performed the anastomosis. If the onset is within the first 3 days PO, we prefer surgical revascularization as the underlying cause is probably technical and the exposure is relatively easy as adhesions have not developed yet. Also, we do not recommend thrombolysis that early after surgery, especially if the drain output signifies early ongoing bleeding. In addition, the endovascular approach may carry an increasing risk of complications as spasm, dissection, hemorrhage or anastomotic rupture in that early PO period. After the 3rd day PO, the cause of HAT is less likely to be technical error and may be related to hemodynamic or immunological abnormality, so we prefer to attempt IAT. In addition, surgical re-exploration after the 3rd day PO is more difficult and carries the risk of dislodgment of the biliary stents or injury to the vascular pedicle that by now had formed adhesions around them.

Finally, in our protocol of management, cases that failed arterial revascularization or had successful revascularization after a prolonged interval of ischemia with clinical and laboratory manifestations of graft failure are considered candidates for re-transplantation. In Egypt, deceased donor liver transplantation is not available therefore surgical or endovascular revascularization remain the primary options because of difficulties of finding a suitable donor in an emergency setting. In a systematic review by Bekker *et al.*[8] an overall success rate with surgical revascularization of about 50% was reported with similar rates among adults. Recently, HAC has been successfully managed with total endovascular management including IAT, PTA, and stenting. Sixty-nine cases have been reported in 16 studies as both rescue and definitive therapy. Sixty-three patients (91%) underwent IAT following deceased donor LT and only six patients have been reported following LDLT[16,9]. Successful IAT was achieved in 47 cases (68%). The initial success rate of IAT in our study (partial or total recanalization) was 94.4% (17/18 cases) and definite endovascular treatment rate of 66.6% (12/18 cases).

Majority of studies indicated the preferred use of urokinase. We had to use streptokinase in 9/11 cases, as it was available on shelf. There is no consensus on the optimal technique for catheter-directed delivery of any thrombolytic agent as they have been successfully used as continuous infusion or bolus form[21,]. We agree with the termination of thrombolysis, if there is a residual thrombus or

persistent HAT. We allowed continuous infusion of streptokinase for max 12 h to avoid the potential risk of hemorrhage.

Hemorrhage was the most common reported complication of thrombolysis seen in about 20% of the patients[21]. Fatal hemorrhage was reported in three patients. In this study, 3/20 cases (15%) developed serious intra-abdominal bleeding after 8 h of continuous infusion of tPA and after 8h, 12h of continuous infusion of streptokinase. All of them required blood transfusion and survived the bleeding episode.

Conclusion

Early HA complications remain a major cause of morbidity and mortality after LDLT. Urgent revascularization is necessary to avoid graft loss. Endovascular approach, including IAT and PTA is emerging as a less invasive alternative to open surgery in the management of early HAT and can be used in conjunction. The choice of therapy depends on a variety of factors, including the timing of thrombosis, the graft function, the underlying cause, and the availability of organs for re-transplantation: Recipient of living donor liver transplantation in adult's assessment by a history, physical examination. Identification of potential risk factors e.g.: trans-arterial chemo embolization (TACE).

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