Liver failure after major hepatic resection, a persistent clinical conundrum

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INTRODUCTION: Post-hepatectomy liver failure (PHLF) is a significant complication which consumes considerable resource, principally due to the need for intensive care involvement during an extensive and prolonged post-operative recovery. The incidence of PHLF varies from 0.7% to 34% and remains the primary cause of mortality following liver resection. The associated mortality rate varies from 0 to 5% and it remains a contributory factor in 18-75% of fatal cases.

METHODS: This is a narrative review of the current literature focusing on the epidemiology, definition, risk factors, pathophysiology, prediction, prevention and management of PHLF.

RESULTS: In patients with an increased risk of developing PHLF etiological factors are related to the patients' co-morbidity and/or the surgical procedure. Patient risk factors include cirrhosis, steatosis, chemotherapy associated steatohepatitis (CASH), sinusoidal injury, cholestasis and cholangitis. Surgical risk factors include the extent of liver resection, the regenerative capacity of the future liver remnant (FLR), sepsis, ischemia reperfusion injury and 'small for size syndrome' (SFSS). Pre-operative work up including clinical scoring criteria, volumetric analysis and measurement of hepatocyte uptake and elimination are reviewed.

DISCUSSION: PHLF remains a challenging clinical condition which is difficult to treat, and prevention and early recognition remains vitally important. The lack of a single accepted definition hinders the study of PHLF due to the difficulty of cross-comparison. Improved pre-operative planning and the early recognition and treatment of PHLF will improve patient care, morbidity and ultimately the mortality from this complex postoperative complication.

Key Words: *Post-hepatectomy liver failure; Recognition; Preoperative planning*

Hepatic resection remains the gold standard for the treatment of liver tumours (1). Balancing the excision of all clinically detectable disease with adequate clear margins and the necessity to retain adequate future liver remnant remains a significant challenge. In the majority of patient's substantial resections can be safely performed however in those who require very extensive resections, or where there is impaired hepatic parenchymal function and regenerative capacity, surgery is associated with a significant morbidity and mortality.

LITERATURE REVIEW

Post-hepatectomy liver failure (PHLF) is a significant complication which consumes considerable resource, principally due to the need for intensive care involvement during an extensive and prolonged post-operative recovery. With the increasing incidence of parenchymal disease PHLF remains a sequela of liver resection which necessitates further study (2). This review will discuss the epidemiology, definition, risk factors, pathophysiology, prediction, prevention and management of PHLF.

EPIDEMIOLOGY

The incidence of PHLF varies from 0.7 to 34%, although the majority of studies suggest an incidence between 5 and 10% (3-8). The lack of a universally accepted definition has resulted in other pathologies being described as PHLF. This coupled with a heterogeneous patient population makes comparisons between studies problematic (2,9). PHLF remains the primary cause of mortality post hepatic resection, with a mortality rate between 0 and 5% (2,9) and contributes to mortality in 18-75% of fatal cases (10-12).

DEFINITION

A universally accepted definition for PHLF does not exist. Rahbari defined PHLF as 'a post-operative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which are characterised by and increased International normalised ratio (INR) and concomitant hyperbilirubinaemia on or after post-operative day 5' (13,14). Attempts have been made to assign numerical values to the abnormalities of liver function and a serum bilirubin above 50umol/l and a prothrombin time (PT) less than 50% below the patient's baseline value (or and INR greater than 1.7) on day 5 post-hepatectomy have been suggested (2,15).

Balzan referred to this as the '50-50 criteria' and when these criteria are met, patients have a 59% mortality risk compared to 1.2% when they are not met (15). In a study by Mullen in 2007, these criteria were shown to have a sensitivity of 50% and a specificity of 96.6% for PHLF as a cause of death for patients without underlying parenchymal disease (16).

RISK FACTORS

In patients with an increased risk of developing PHLF aetiological factors are related to the patients' co-morbidity and/or the surgical procedure.

Patient related risk factors

Pre-existing liver parenchymal disease is a significant risk factor and includes cirrhosis, steatosis, chemotherapy associated steatohepatitis (CASH), sinusoidal injury, cholestasis and cholangitis. Cirrhotic patients are known to have a significantly higher mortality rate following resection and studies report mortality rates between 5% and 20% (17-19). In patients with cirrhosis, resection of up to 50% is considered safe in the absence of functional impairment or portal hypertension. However, in Child-Pugh grade B or C, any significant resection can result in PHLF (20,21). Cirrhotic livers demonstrate reduced levels of hepatocyte growth factor (22) and reduced transcription factors (23), meaning that in patients with cirrhosis capacity for regeneration is affected (24) with impaired function post-operatively and reduced functional reserve (25). CASH and sinusoidal injury are increasingly prevalent conditions as more patients with colorectal liver metastases are treated with neoadjuvant chemotherapy (2). Sinusoidal injury has been demonstrated with oxaliplatin chemotherapy which is partially reversible on cessation of treatment (26). CASH is associated with 5-flurouracil and irinotecan treatment which reduces the regenerative capacity of the liver remnant and increases post-resection liver dysfunction (26,27).

Cholestasis

Cholestasis also reduces the regenerative capacity of the liver (28) and increases the likelihood of post-hepatic liver dysfunction (29). Some centres advocate pre-operative biliary drainage which is believed to improve remnant

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function (30) although there is no proven survival benefit and a significant increased risk of morbidity from sepsis (31). Drainage can either be performed by means of external biliary drain or internal stenting. Cholestasis reduces portal venous flow because the bile duct, portal vein and hepatic artery are enclosed within the Glissonian capsule with a finite amount of available space, referred to as the space of Mall (32). As the biliary tract dilates, the space of Mall is reduced with a concomitant reduction of portal venous flow (33). This reduction in portal venous flow is further exacerbated by hepatectomy and this may contribute to an impaired regenerative capacity (Baer). Hepatic regeneration is also impaired by reduced expression of transcription factors such as cyclin E (34) and cytokines such as interleukin six (IL-6) and epidermal growth factor (28,34-37). Elevated levels of bile salts have also been shown to induce hepatocyte apoptosis (38), and the absence of bile salts within small bowel lumen means their protective activity against bacterial translocation is lost (39).

Other patient related risk factors

Men are twice as likely to develop PHLF and post resection morbidity compared to females (16,40) which is in part due to the immunosuppressive effect of testosterones and oestrogen. The regenerative capacity of the liver has also been shown to reduce with age in animal models (41-44) and some studies report an increase in morbidity (16) and mortality (15) with advanced age, particularly after hepatic resection (45,46). Conversely a number of other studies have reported safe hepatic resection in the elderly (47) with no increased morbidity, mortality (48) or the development of PHLF (49,50). Diabetes is known to increase PHLF and the consequent morbidity and mortality following hepatic resection (51). This is thought to be due to an immune dysfunction and the impaired regenerative capacity of the liver resulting from the absence of insulin or insulin resistance (52). The likelihood of developing PHLF increases two-fold with diabetes as an independent prognostic factor (53). Hepatic atrophy has also been demonstrated in insulin deficient animal models (54). Patients with two or more metabolic disorders undergoing right hepatectomy (diabetes mellitus, obesity, hypertension and dyslipidaemia) have been shown to have a perioperative mortality of 30% (55). Malnutrition is noted in 65-90% of patients with advanced liver disease (56) and 20-55% of colorectal cancer patients (57) and optimizing nutrition has been shown to reduce post-operative liver dysfunction and morbidity. Studies have demonstrated that malnutrition impairs the immune response (58,59) reduces hepatic protein synthesis and increases the risk of developing PHLF. This is possibly the result of impaired regenerative capacity (58,60) and/or secondary to disordered mitochondrial function (61).

Surgery related risk factors

The extent of hepatic resection correlates with PHLF and perioperative mortality with 80% of deaths occurring when more than 50% of the liver is resected (15,16,18,61-70). A minimum liver remnant volume (LRV) in patients with normal liver parenchyma is generally considered to be between 20-30% of total liver volume (4,19,21,40,70). In the presence of parenchymal disease without portal hypertension or hepatic insufficiency the minimum LRV is considered to be between 40-50% (4,21,71,72). Where liver dysfunction occurs as a result of extensive resection this is termed 'small for size' liver remnant (9). Intraoperative blood loss of greater than 1-1.2L and the need for blood transfusion have also been shown to be associated with PHLF and sepsis (3,18,73-75). Significant intraoperative haemorrhage results in large fluid shifts, coagulopathy and bacterial translocation, with a significant immunosuppressive action (76-78). Vascular reconstruction following hepatic and inferior vena cava resection is also associated with PHLF (79,80) while biliary reconstruction is associated with increased morbidity and mortality, although is not generally considered an independent risk factor for the development of PHLF (18,29,75).

PATHOPHYSIOLOGY

Liver failure following excessive resection is usually characterised by coagulopathy, hyperbiliruninaemia and encephalopathy and accompanied by sepsis and/or multi-organ failure (32). PHLF is multi factorial and the extent of liver resection and the regenerative capacity of the future liver remnant (FLR) are the crucial factors which increase the risk of developing PHLR, while sepsis, ischaemia reperfusion injury and 'small for size syndrome' (SFSS) are important secondary factors. It has been postulated that the lack of regeneration demonstrated in failing livers may be a consequence of excessive resection rather the cause of failure (32), a theory that is supported by significant apoptosis and hepatocyte loss in animal models following hepatectomy (81). To avoid PHLF the liver must not only limit hepatocyte death but also resist metabolic stress and provide sufficient synthetic function (52,82,83).

Post-operative portal flow

Post operatively, there is a significant reduction in portal venous flow, with an increase in hepatic arterial resistance and an increase in portal venous pressure (32,84). The resultant congestion of liver sinusoids produces parenchymal stress which is similarly exhibited in SFSS seen after liver transplantation (85). The parenchymal congestion causes an increase in shear stress and is a important factor in initiating regeneration (32).

Shear stress and liver damage

Despite being an important initiating factor in liver regeneration, excessive shear stress can lead to hepatocyte loss and collapse of the hepatic microcirculation (86). Approaches to reducing portal venous pressure include splenectomy and porto-systemic shunting (87). Normalising portal pressure has been demonstrated to produce a survival benefit in animal studies (38,88). While portocaval shunting has been shown to reduce hepatocyte necrosis, this comes at the cost of a delay in liver regeneration (88,89), possibly due to an over reduction of shear stress and a diversion of hepatotrophic factors into the systemic circulation (32). Mesocaval shunting may be a suitable compromise (90) and pharmacological control can be useful in the short-term post operatively (32).

Intra-operative and post-operative ischaemia

Ischaemia both intra and post-operatively can significantly influence the development of PHLF. Many techniques have been described to limit intraoperative blood loss and the Pringle manoeuvre is commonly used either continuously or intermittently to limit intraoperative blood loss. This does not prevent hepatic venous bleeding, and some centres advocate total vascular exclusion (TVE), where the Pringle manoeuvre is accompanied by clamping of the supra and infra-hepatic vena cava (32). Ischaemic preconditioning (IP) has been shown to reduce the risk of ischaemia reperfusion injury (IRI) in a rat model (91) and improve survival rates (92). It involves short periods of ischaemia followed by longer periods of reperfusion, after which the Pringle manoeuvre can be continuously or intermittently applied. This promotes liver regeneration through the up regulation of cytokines such as IL-6 and tumour necrosis factor alpha (TNF), coupled with down regulation of transforming growth factor beta (TGF) (93). IRI is characterised by persistent post-operative parenchymal damage (2) and ischaemia activates the complement cascade and leads to Kupffer cell activation, endothelial cell damage and the generation of reactive oxygen species (ROS)2, Excessive IL-6, TNF and nuclear factor beta exacerbate micro vascular injury, Kupffer cell mediated inflammation and ultimately hepatocyte death (94,95).

Sepsis

Sepsis has been reported to occur in up to 50% of patients following hepatic resection (70). Sepsis affects post-operative liver function and regenerative capacity and can be both a consequence of, and precipitate PHLF. Sepsis induced hypotension can prolong post-operative ischaemia leading to Kupffer cell dysfunction and hepatotoxic levels of circulating cytokines (32). Although a relative increase in endotoxin delivery to the liver can stimulate regeneration, excessive or prolonged endotoxinaemia can have an inhibitory effect on hepatocyte proliferation (96,97) by impairing mitochondrial function and bile salt excretion (98-100). Kupffer cell activation is instrumental in initiating liver regeneration and its interaction with leukocytes through an intracellular adhesion molecule ICAM-1 leads to a cytokine mediated pro-inflammatory response promoting hepatocyte proliferation (32). Mice deficient in ICAM-1 demonstrated an impaired capacity of the liver to regenerate following a 70% liver resection (101). It has also been shown that after a significant hepatic resection there is a reduction in the number of Kupffer cells, impairing the liver's ability to eliminate bacteria from the blood which may persist for up to 2 weeks (102). TNF normally induces hepatocyte proliferation at physiological blood levels but during sepsis excess levels occur and can initiate apoptosis largely due to its activation of NF-kappaB (103).

PREDICTION

Clinical scoring systems

The Child-Pugh score and the model for end-stage liver disease (MELD) score are systems that are now widely used to predict the risk of hepatic resection in cirrhotic patients (104-109). The Child-Pugh score was originally designed to predict mortality in cirrhotic patients undergoing shunting procedures (110), and incorporates five parameters; serum albumin, bilirubin, INR, clinical evidence of ascites and hepatic encephalopathy. The majority of hepatic resections are performed in Child-Pugh A patients; however an increasing number are being undertaken in Child Pugh B patients. The majority of

centres do not advocate hepatic resection in Child-Pugh C, although a small number are beginning to be performed in selected cases (111). The MELD score is calculated using serum creatinine, bilirubin and INR and has the benefit of incorporating renal function. Some studies have suggested it's superiority to the classically used Child-Pugh (14,109,112). In the absence of cirrhosis, neither scoring system can be utilised resulting in the use of clinical and radiological assessment for patient selection (1).

Volume measurement

Establishing the LRV is of vital importance in operative planning. This is accomplished by pre-operative radiological assessment using computed tomography (CT) or magnetic resonance imaging (MRI) (113). Cross-sectional imaging also permits the calculation of LRV to total functioning liver volume ratio (40,114,115) and can assist in the diagnosis of underlying parenchymal disease (4,40,115-120). Advanced CT volumetric analysis is increasingly accessible with software such as PhotoshopTM and ImageJTM demonstrating good correlation with predicted and actual volume of liver resection (116,121). However, cross sectional imaging provides inadequate information when predicting the functioning hepatocyte mass post resection.

Measurement of hepatocyte uptake and elimination

Pre-operative assessment of liver function is crucial when planning hepatic resection and predicting the risk of PHLF and several techniques have been developed.

Indocyanine green retention rate

Indocyanine green (ICG) binds to albumin in plasma and is water soluble (1). It is a fluorescent dye which is selectively taken up by hepatocytes but importantly not by the enterohepatic circulation and it is also not metabolised by the liver (9,122). Following intravenous injection, ICG retention rate at 15 minutes (ICG-15) is a commonly used measurement to determine an index of functional hepatocyte mass, liver perfusion and energy reserve (25,123,124). It has demonstrated a greater predictive accuracy when compared to the Child-Pugh (125) and MELD scores (126). There is no definitive cut off for a "safe" resection, although patients with an ICG-15 of above 10-20% are considered to have impaired hepatic reserve (127), and require an adequate liver remnant volume to avoid PHLF (68,128,129). Those with ICG-15 between 10-20% may benefit from preoperative volume manipulation (20,21) As ICG absorption and emission spectrum are in the near infrared range, measurements can be taken non-invasively meaning ICG uptake can be monitored intra and post-operatively (8,124,130-136). One large series reported only 1 mortality in 1429 hepatic resections (73), although it can be argued that cases with a with a borderline ICG-15 who may have safely tolerated surgery were possibly excluded (1).

Hepatobiliary Scintigraphy/Single positron emission CT (SPET-CT)

The uptake of various radiolabelled compounds allows for the assessment of hepatic anatomy and functional mass. Physiologically, asialoglycoproteins are exclusively taken up by receptors on hepatic sinusoidal membranes (137) and a decrease in number of receptors has been noted in chronic liver disease (1). Technetium-99m-diethylenetriamine-pentacetic acid-galactosyl-human serum albumin 99 Tc-GSA is a compound that binds to asialoglyoprotein receptors allowing for volumetric assessment of the functional hepatocyte mass (1). SPET-CT allows measurement of radiotracer-labelled compounds such as 99 Tc-GSA in combination with standard CT assessment and is considered superior to scintigraphy, which only uses a gamma camera (138,139).

Lidocaine metabolism (MEGX)

The 'MEGX test' refers to the conversion rate of lidocaine to monoethylglycinexylidide (MEGX) in hepatocytes by the cytochrome p4503A system (140). This test is inconsistent when patients are taking medications which are also metabolised by the cytochrome system. MEGX levels are measured at intervals after administration of 1 mg/kg of 2% lidocaine (141) and MEGX correlates with the extent of cirrhosis and predicts prognosis in cirrhosis (142). Although there is little evidence to support the use of post-operative MEGX testing, it has been shown pre-operatively to predict the risk of developing PHLF in non-cirrhotic patients, particularly when combined with resection volume (143).

Galactose elimination capacity (GEC)

Another means of measuring hepatic metabolism is by galactose elimination. Following intravenous administration the serial measurement of galactose in serum and urine allows for the calculation of galactose elimination. GEC is predictive of post-operative liver dysfunction and long-term survival after hepatic resection (144) although it is resource intensive requiring serial sampling.

PREVENTION

Patient optimisation

Prior to surgery it is important to improve any modifiable co-morbidity. In patients with biopsy proven steatosis, weight reduction of 5% has been shown to improve the steatosis (145,146) but no concomitant improvement in post-operative recovery has been demonstrated (147). Patients are often malnourished pre-operatively (57) and improving their nutritional status has been shown to reduce complications particularly in cirrhotic patients (58,148). However, these studies have failed to demonstrate a link between malnutrition and PHLF (3) and importantly there is no evidence to support delaying surgery while nutritional status is addressed unless the patient is significantly malnourished (18,149,150). Pre-operative screening for diabetes mellitus is essential and oral carbohydrate loading should be considered to limit post-operative insulin resitance (151). Studies have failed to show a benefit from pre-operative percutaneous transhepatic drainage (PTD) in the setting of cholestasis. However, complication rates are significant and PTD has been shown to prolong hospital stay (31,152,153). PTD is only advocated to reduce morbidity when cholestasis is accompanied by segmental cholangitis in patients with a biliary carcinoma (154).

Improve FLR

Portal vein embolization (PVE) is a percutaneous procedure that occludes a branch of the portal vein. This induces apoptosis of the ipsilateral lobe and stimulates growth of the contralateral lobe, thus increasing FLR volume (155). It is indicated in patients with normal liver function and a FLR volume of less than 25-30% (4), or where liver function is impaired (ICG-15 of 15-20%) when FLR volume is less than 40-45% (155-157). PVE can offer a FLR volume increase of between 20-46% and this is dependent on the patient's comorbidity and extent of hepatic parenchymal disease with peak growth at 2-4 weeks post treatment (155,157-159). Patients who do not demonstrate a significant increase in liver volume after PVE are likely to have impaired regenerative capacity and therefore are unlikely to tolerate extensive resection (159.) However, there is some evidence to suggest that PVE can cause a tumour flare in the ipsilateral lobe resulting from an increase in hepatic arterial flow to that lobe (160,161). To combat this, neoadjuvant chemotherapy can be used to reduce tumour growth prior to resection (162,163). Portal vein ligation (PVL) is occasionally preferred to PVE especially when bi-lobar tumour invasion occurs, necessitating a two-stage resection to maintain an adequate FLR (164,165). In this approach, the contralateral portal vein is ligated during the initial surgery followed by interval of between 3-6 weeks, after which the second, and often more extensive resection is performed (9). PVE and PVL were shown to be comparable in a meta-analysis that demonstrated no significant difference in FLR volume achieved by either technique (166). There is evidence that, in selected cases, two-stage hepatectomy in combination with PVE, PVL or neoadjuvant radiotherapy can increase FLR and overall survival rates (21,164,167,168).

Operative considerations

As previously discussed, excessive blood loss is a risk factor for PHLF and surgery should be performed with a central venous pressure (CVP) of less than 5mmHg limits bleeding without affecting renal function (169-171). Ischaemic preconditioning (IP) reduces hepatic parenchymal damage and is used prior to either intermittent or continuous portal triad clamping to reduce intra-operative blood loss. Intermittent clamping is preferred to continuous clamping typically in a 15-minute clamp to 5-minute unclamp ratio (94,172,173). Intermittent portal triad clamping is preferable to total vascular exclusion, which has been shown to induce more haemodynamic instability and a higher complication rate (154).

MANAGEMENT

Post-operatively, patients should be monitored for clinical or biochemical evidence of liver failure, particularly ascites, hepatic encephalopathy, coagulopathy and hyperbilirubinaemia. Close attention must also be paid to nutrition, haemodynamic status, renal function and early signs of infection should warrant a low threshold for treatment (174,175). Sepsis can exacerbate PHLF and bacterial infection is present in 80% of patients with PHLF (70). Sepsis should always be considered in any acute deterioration and should be managed with microbiology involvement (176). Antibiotic prophylaxis has not been demonstrated to reduce the incidence of sepsis or PHLF (177), however antibiotics may be of benefit once PHLF is established (178,179).

Current practice for the management of PHLF largely mimics that of acute liver failure with a focus on goal-directed therapy and end organ support in an intensive care setting (180,181). As gastrointestinal bleeding is a recognized complication of PHLF, proton pump inhibitors or H_2-receptor antagonists are routinely administered in mechanically ventilated patients (182,183).

Extracorporeal Liver Support (ELS)

ELS devices detoxify existing plasma or replace it with fresh frozen plasma, allowing the administration of plasma components such as albumin and clotting factors while removing toxic compounds such as ammonium which is water soluble and when in excess results in hepatic encephalopathy. ELS has been shown to improve clinical condition but not survival (184,185).

Molecular Absorbent Recirculating System (MARS®)

MARS® is an extracorporeal system which dialyses plasma albumin and albumin bound toxins against an albumin enriched dialysate (186,187). Although MARS® has provided promising results for the treatment of acute liver failure, (188) it is yet to demonstrate a survival benefit for PHLF (189-192).

Modified fractionated plasma separation and adsorption (Prometheus®)

Like MARS®, Prometheus® utilises fractionated plasma separation and albumin dialysate to remove albumin-bound toxins through a semi-permeable membrane, after which the detoxified albumin is returned to the patient (186,187). Although the detoxifying ability of Prometheus® appears superior to that of MARS® there is a lack of evidence to suggest any advantage in the management for PHLF (193).

Liver transplantation

Rescue hepatectomy and emergency liver transplantation is a last resort when supportive methods have failed. Many patients with PHLF are not candidates for further major surgery and there is a lack of criteria directing the selection of patients for transplantation. Van den Broek proposed that patients with favourable tumour characteristics without significant comorbidities limiting life expectancy should be considered (3).

DISCUSSION AND CONCLUSION

PHLF is still a challenging clinical condition that is difficult to treat. The prevention and early recognition remain the mainstays of management. The lack of a universally accepted definition hinders the study of PHLF owing to the difficulty of cross-comparison. With the increasing prevalence of parenchymal disease such as cirrhosis, non-alcoholic fatty liver disease and CASH, it is becoming an increasing health and economic burden and further studies are required to help identify those patients at risk, methods of pre-operative optimisation and the effective management of PHLF. This will improve patient care, morbidity and ultimately mortality from this complex post-operative complication.

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