

ASSOCIATING LIVER PARTITION AND PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY (ALPPS): THE BRAZILIAN EXPERIENCE

Ligadura da veia porta associada à bipartição do fígado para hepatectomia em dois estágios (ALPPS): experiência Brasileira

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ABSTRACT – Background - Postoperative liver failure consequent to insufficiency of remnant liver is a feared complication in patients who underwent extensive liver resections. To induce rapid and significant hepatic hypertrophy, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been recently developed for patients which tumor is previously considered unresectable. **Aim** – To present the Brazilian experience with ALPPS approach. **Method** – Were analyzed 39 patients who underwent hepatic resection using ALPPS in nine hospitals. The procedure was performed in two steps. The first operation was portal vein ligation and in situ splitting. In the second operation the right hepatic artery, right bile duct and the right hepatic vein were isolated and ligated. The extended right lobe was removed. There were 22 male (56.4%) and 17 female (43.6%). At the time of the first operation, the median age was 57.3 years (range: 20-83 years). **Results** - The most common indication was liver metastasis in 32 patients (82.0%), followed by cholangiocarcinoma in three (7.7%). Two patients died (5.2%) during this period and did not undergo the second operation. The mean interval between the first and the second operation was 14.1 days (range: 5-30 days). The volume of the left lateral segment of the liver increased 83% (range 47-211.9%). Significant morbidity after ALPPS was seen in 23 patients (59.0%). The mortality rate was 12.8% (five patients). **Conclusion** – The ALPPS approach can enable resection in patients with lesions previously considered unresectable. It induces rapid liver hypertrophy avoiding liver failure in most patients. However still has high morbidity and mortality.

HEADINGS - Hepatectomy. Neoplasm metastasis. Portal Vein.

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Financial source: none
Conflicts of interest: none

Received for publication: 29/08/2012
Accepted for publication: 12/12/2012

DESCRITORES - Hepatectomia. Metástase neoplásica. Veia Porta.

RESUMO – Racional – Insuficiência hepática pós-operatória devido à remanescente hepático pequeno tem sido complicação temida em pacientes que são submetidos à ressecção hepática extensa. A ligadura da veia porta associada à bipartição do fígado para hepatectomia em dois estágios (ALPPS) foi desenvolvida recentemente com a finalidade de induzir rápida e significante regeneração do fígado para pacientes em que o tumor é previamente considerado irresssecável. **Objetivo** – Apresentar a experiência brasileira com o ALPPS. **Método** – Foram analisados 39 pacientes submetidos ao procedimento ALPPS em nove hospitais. Ele foi realizado em duas etapas. A primeira operação consistiu em ligadura do ramo direito da veia porta e bipartição hepática. Na segunda, os ramos direito da artéria hepática, via biliar e veia hepática foram ligados e o lobo hepático direito estendido foi removido. Foram 22 pacientes do sexo masculino (56,4%) e 17 do feminino (43,6%). A média de idade foi 57,3 anos (variando de 20 a 83 anos). **Resultados** – A indicação mais comum foi metástase hepática em 32 pacientes (82,0%), seguida por colangiocarcinoma em três pacientes (7,7%). Dois morreram neste intervalo e não foram submetidos à segunda operação. O intervalo médio da primeira para a segunda operação foi de 14,1 dias (variando de 5-30 dias). O volume do segmento lateral esquerdo apresentou aumento de 83% (variando de 47-211,9%). Morbidade significativa foi observada em 23 pacientes (59,0%). A mortalidade foi de 12,8% (cinco pacientes). **Conclusão** – O procedimento ALPPS permite ressecção hepática em pacientes com lesões consideradas previamente irresssecáveis por induzir rápida hipertrofia do fígado evitando a insuficiência hepática na maioria dos pacientes. Porém ainda apresenta elevada morbidade e mortalidade.

INTRODUCTION

In patients with primary or metastatic hepatic disease, resection is the only potentially curative therapeutic option. The remaining liver volume is one very important limiting factor to perform major liver resections. Postoperative hepatic insufficiency is a serious complication in these patients who underwent extensive hepatic resections. Avoiding this lethal complication remains a challenge for hepatobiliary surgeons^{5,20,22}.

For patients with normal liver, the future liver remnant to prevent postoperative liver failure should be at least 25% of total liver volume. In patients with hepatic dysfunction or earlier liver injury due to chemotherapy, a higher future liver remnant is recommended^{18,20,21,22}.

Some strategies have been developed to increase resectability in patients undergoing major hepatic resection. The induction of liver hypertrophy by occlusion of portal vein can be done through embolization by radiology or surgically. This approach is able to induce atrophy of the tumor-bearing lobe with subsequent hypertrophy in the contralateral lobe by diverting the portal venous flow. Portal vein occlusion is able to increase the future liver remnant up to 40% within three to eight weeks. In some patients however, sufficient hypertrophy is not always achieved, and there is still concern about the potential for faster growth of the tumor during the period prior to resection^{2,3,4,7,11}.

Schnitzbauer et al.¹⁷ in Germany developed a new two-step technique consisting on the combination of partition of liver parenchyma with portal vein ligation in order to improve resectability. De Santibanes and Clavien have proposed to rename it "associating liver partition and portal vein ligation for staged hepatectomy" (ALPPS). This technique has been used around the world with excellent results^{14,15,16,17}.

The aim of this study is to present the Brazilian experience with ALPPS for the treatment of patients with initially unresectable primary and metastatic liver tumors.

METHOD

The clinical records of all patients who underwent hepatic resection using ALPPS procedure in nine hospitals were reviewed. In the period between July 2011 and October 2012, 39 patients underwent liver resection with ALPPS technique in nine different hospitals in Brazil. Before resection all patients underwent radiologic evaluation with a 3-phase intravenous contrast CT scan of the abdomen and were considered unresectable or marginally resectable.

The surgical technique has been previously reported and was performed in two steps¹⁹. After

exploratory laparotomy, intraoperative ultrasound was carried out in most patients to assess the proximity and position of the tumor in relation to major remaining vessels and confirm a tumor-free left lateral lobe. The first operation was portal vein ligation and in situ splitting. The right branch of portal vein was dissected and ligated. Portal, arterial and biliary segment IV branches were identified and divided. Total or nearly total parenchymal dissection along the falciform ligament was performed using bipolar forceps and continuous irrigation with saline solution. The middle hepatic vein was divided during the parenchymal transection. After in situ splitting, the abdomen was drained and closed. During the second operation, the right artery, right bile duct and the right hepatic vein were ligated. Remaining parenchymal bridges of liver tissue with vena cava and diaphragm, if present, were divided. The liver resection was then completed.

There were 22 male (56.4%) and 17 female (43.6%). At the time of the first operation, the median age was 57.3 years (range: 20-83 years). The most common indication was liver metastasis in 32 patients (82.0%), followed by cholangiocarcinoma in three patients (7.7%), sarcoma in two patients (5.1%) and liver cystic disease and hepatocellular carcinoma (one patient each, 5.2%). All patients were noncirrhotic. Preoperative volumetry was performed in 28 patients (71.7%) and all patients had normal liver function before resection. In patients who have undergone chemotherapy, the chemotherapeutic agent was discontinued at least four weeks before surgery.

RESULTS

The first operation (PVL and ISS) was performed in 39 patients. However two patients died (5.2%) during this period and did not undergo the second operation. An 83 years old male developed severe inflammatory response and died twelve days later. The second patient with angiosarcoma had multiples metastasis in the interval between the first and the second operation and died six days later. In this same period 262 liver resections were carried out in these medical institutions (11.4% was ALPPS).

The mean interval between the first and the second operation was 14.1 days (range: 5-30 days). The preoperative volumetry was performed in 28 patients (71.7%). In those patients who had preoperative volumetry, the mean volume of the left lateral segment of the liver had increased 83% (range 47-211.9%). In one patient was not performed the liver transection (ISS) during the first operation, just two lines of radiofrequency ablation along the falciform ligament.

Fibrin sealant was used on the raw surface after in situ splitting in 18 patients (46.1%) and plastic

bag in eight patients (20.5%). In two patients (5.1%) the ALPPS was performed totally laparoscopic. Was performed at the same time in the first operation a pancreaticoduodenectomy in one patient and a transverse colectomy in another. During the second operation was also performed a rectosigmoidectomy in one patient. Nine patients (23.0%) received intra-operative blood transfusion (1-4 units).

Significant morbidity after ALPPS was seen in 23 patients (59.0%). Minor complications occurred in some patients. Most patients had more than one complication. Complications such as hepatic artery thrombosis, acute liver failure, acute renal failure and sepsis were responsible for mortality (Table 1).

TABLE 1 - Complications after ALPPS approach

Complications	n	%
Surgical site infection	8	20.5
Ascites	5	12.8
Biliary fistula	4	10.2
Pneumonia	4	10.2
Abdominal hernia	4	10.2
Sepsis	3	7.7
Acute renal failure	2	5.1
Bile duct injury	1	2.5
Hepatic artery thrombosis	1	2.5
Acute liver failure	1	2.5
Others	9	23.0

The average length of stay in the intensive care unit was nine days. The mortality rate was 12.8% (five patients) including two patients who did not perform the second operation. One patient developed acute liver failure after hepatic artery thrombosis. The second patient developed acute renal failure followed by sepsis and the third patient presented with postoperative biliary fistula. This was followed by peritonitis and sepsis. All of them died of multi-organ failure. The total length of stay was 17.8 days (range: 13-40 days).

DISCUSSION

For patients with hepatic primary tumor or metastasis from other primary cancers the only chance to obtain long-term survival is complete tumor resection. The remaining liver volume is still one important limiting factor to perform major liver resections. Portal vein embolization or ligation are able to induce liver hypertrophy of 25-40% after three to eight weeks. However, the embolization of segment IV branch requires optimal access, may frequently be incomplete and is not available in many centers. In some patients sufficient hypertrophy of the future liver remnant is not always achieved and there is still concern about the potential for simultaneous tumor progression after portal vein embolization during the period prior to resection^{4,7,13,18}. In ALPPS approach, the portal vein ligation associated with in situ splitting is able to induce enormously accelerated hypertrophy.

The neovascularisation and persistence of interlobar perfusion are prevented by performing parenchymal dissection and complete devascularization of segment IV. The nearly total parenchymal dissection induced a median hypertrophy of 74%, which is markedly above the range that can be achieved by portal vein ligation or portal vein embolization alone^{14,15,16,17}. In the present study we observed hypertrophy up to 200%.

The median time interval to have hypertrophic effect is nine days. De Santibanes et al observed a rapid growth of the future liver remnant up to 83% in only six days. In contrast, hypertrophy using portal vein ligation or portal vein embolization is generally after four weeks and achieved a much lower degree of hypertrophy^{3,7,11,14,15,16}. Although some patients in this study have performed the second operation in 30 days, the mean interval between the first and second operation was 14 days.

An important point to promote accelerated hypertrophy must be attributed to the in situ splitting procedure. This technique leads to complete devascularization of segment IV and also prevents formation of vascular collaterals between the left lateral and the right extended liver lobe. This combination of portal vein ligation and in situ splitting is able to induce a much stronger stimulus leading to rapid and marked hypertrophy of the left lateral lobe. The in situ splitting causes disruption on intrahepatic portal collaterals leading to a portal flow deprivation to the excluded segments and redistribution of hepatotrophic factors^{15,16,17}. In one patient was not performed in situ splitting (ISS) during the first operation, but just two lines of radiofrequency ablation along the falciform ligament. In this patient was observed a hypertrophy of 94.5% in 21 days. The radiofrequency has been used in liver resections¹².

In spite of the excluded liver does not have any portal flow, it acts as an auxiliary liver that contributes to the total liver function until the contralateral lobe has grown enough to tolerate the physiological function like a normal liver^{14,15,16,17}.

The morbidity after this extended liver resection depends on the liver and patient condition at the time of surgery. The extent of resection and underlying disease are also important. Schnitzbauer et al.¹⁷ observed 64% of complications. Fifty percent were classified as grade I or II. We observed a high morbidity and mortality of 12.8% (five patients). Acute liver failure, acute renal failure and infectious complications were those responsible for mortality. Schnitzbauer et al.¹⁷ reported a perioperative mortality rate of 12% (3 patients of 25) which is similar to our study. It is a new procedure and still has high rates of morbidity and mortality. A second operation within a short period of time with a significant inflammatory syndrome has been a concern. Adequate patient selection is important, particularly those younger and

without comorbidities. In hilar cholangiocarcinoma, the jaundice and possible biliary infection cause a negative impact on survival. ALPPS is a safe procedure, but technically complex and should be undertaken by experienced hepatobiliary surgeons^{14,15,16,17}.

The use of fibrin sealant or plastic bag on the raw surface or around the liver to avoid adhesions is another point of interest and concern. Bioactive sealants have the advantage that they do not have to be removed. Wrapping of the whole right lobe cannot be recommended because of the possible undrained fluid collections within the bag. Plastic bag can be hazardous because sometimes the second stage needs to be postponed due to clinical complications or because sufficient hypertrophy of the liver remnant has not been achieved. In some cases, the second stage may never occur and the patient will need a reoperation to remove the bag. One of the authors performed two procedures totally by laparoscopy with minor adhesions based on his previous experience^{8,9,10}.

Simultaneous surgery for primary colorectal tumor with synchronous liver metastasis has been showed to be safe and effective. Likewise, in selected patients, liver resection can also be performed simultaneously with pancreaticoduodenectomy for cholangiocarcinoma. In the patient who will undergo ALPPS, it can be performed simultaneously, without mortality^{1,6}.

This and other experiences should stimulate further basic scientific research to answer some questions related to liver regeneration, tumor molecular biology and biochemical analysis. These studies can have the opportunity in the future to explain these unsolved questions nowadays. The adequate selection of the patient who might benefit from this approach must be taken into account. In this and others studies ALPPS was able to induce much more pronounced and rapid tissue increase in future liver remnant for patients with marginally resectable liver tumors^{14,15,16,17}.

CONCLUSION

The ALPPS approach can enable resection in patients with lesions previously considered unresectable. It induces rapid liver hypertrophy avoiding liver failure in most patients. However still has high morbidity and mortality.

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