Review Article

Associating liver partition and portal vein ligation for staged hepatectomy: the current role and development

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BACKGROUND: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been developed to induce rapid liver hypertrophy and reduce post-hepatectomy liver failure in patients with insufficient future liver remnant (FLR). ALPPS is still considered to be in an early developmental phase because surgical indications and techniques have not been standardized. This article aimed to review the current role and future developments of ALPPS.

DATA SOURCES: Studies were identified by searching MEDLINE and PubMed for articles from January 2007 to October 2016 using the keywords "associating liver partition and portal vein ligation for staged hepatectomy" and "ALPPS". Additional papers were identified by a manual search of references from key articles.

RESULTS: ALPPS induces more hypertrophy of the FLR in less time than portal vein embolization or portal vein ligation. The benefits of ALPPS include rapid hypertrophy 47%-110% of the liver over a median of 6-16.4 days, and 95%-100% completion rate of the second stage of ALPPS. The main criticisms of ALPPS are centered on its high morbidity and mortality rates. Morbidity rates after ALPPS have been reported to be 15.3%-100%, with ≥ the Clavien-Dindo grade III morbidity of 13.6%-44%. Mortality rates have been reported to be 0%-29%. The important questions to ask even if oncologic long-term results are acceptable are: whether the gain in quality and quantity of life can be off balance by the substantial risks of morbidity and mortality, and whether stimulation of rapid liver hypertrophy also accelerates rapid tumor progression and spread. Up till now, the documentations of the ALPPS procedure come mainly from case series, and most of these series include heterogeneous groups of malignancies. The numbers are also too small to separately evaluate survival for different tumor etiologies.

CONCLUSIONS: Currently, knowledge on ALPPS is limited, and prospective randomized studies are lacking. From the reported preliminary results, safety of the ALPPS procedure remains questionable. ALPPS should only be used in experienced, high-volume hepatobiliary centers.

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KEY WORDS: associating liver partition and portal vein ligation for staged hepatectomy; portal vein embolization; laparoscopy; colorectal liver metastases; hepatocellular carcinoma

Introduction

Liver surgery for malignancy aims at R0 resection with sufficient postoperative liver remnant and functional reserve to provide possible long-term survival. An inadequate volume of future liver remnant (FLR) is associated with an increase risk in postoperative liver failure. There are two effective methods to increase the volume of the FLR: portal vein ligation (PVL)/percutaneous portal vein embolization (PVE), and two-stage hepatectomy. These strategies, however, carry a considerable failure rate because a significant proportion of patients eventually drop out from subsequent curative resection due to tumor progression in the waiting interval between the two stages, or because of failure of the FLR to adequately grow. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been developed to induce rapid liver hypertrophy so as to reduce post-hepatectomy liver failure. Schlitt first performed this technique in 2007[1-3]. He originally

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planned to perform an extended right hepatectomy in a patient with hilar cholangiocarcinoma. During surgery, he realized that the FLR was too small for the patient to survive so he quickly made an intraoperative decision to carry out a hepaticojejunal bypass operation. For optimal exposure and positioning of the hepaticojejunostomy, he performed an *in situ* split of the liver parenchyma along the right border of the falciform ligament. He then ligated the right portal vein to induce hypertrophy of liver segments 2 and 3. Out of curiosity he performed a computed tomography (CT) scan on postoperative day 8 and found the left lateral section of the liver had hypertrophied rapidly. He then decided to carry out the original planned liver resection and the patient recovered well. This novel approach was formally presented in 2011 by Baumgart and colleagues in the 9th European-African Hepato-Pancreatico-Biliary Association Congress in Cape Town, South Africa.[1] In the same year, de Santibañes and his colleagues reported their data on 3 patients [colorectal liver metastases (CRLM), *n*=2 and hilar cholangiocarcinoma, *n*=1].[2] Schnitzbauer and his colleagues reported the technique of "right portal vein ligation combined with *in situ* splitting" on 25 patients [hepatocellular carcinoma (HCC), *n*=3, intrahepatic cholangiocarcinoma, *n*=2, extrahepatic cholangiocarcinoma, *n*=2, malignant epithelioid hemangioendothelioma, *n*=1, gallbladder cancer, *n*=1, CRLM, *n*=14, ovarian cancer with liver metastasis, *n*=1, gastric cancer with liver metastasis, *n*=1). After a median of 9 days (range 5-28), the median preoperative volume of the left lateral liver section increased from 310 mL (range 197-444) to 536 mL (range 273-881), representing a median volume increase of 74% (range 21%-192%).[3] The description by Schnitzbauer et al, together with reports from regions around the world were then published with overwhelming enthusiasm. In 2012, de Santibañes and Clavien proposed the acronym for this procedure as associating liver partition and portal vein ligation for staged hepatectomy, or ALPPS in short.[4] ALPPS is still considered to be in an early developmental phase and its surgical indications and techniques have not yet been standardized. This article aimed to review the current role and development of ALPPS.

Methods

Studies were identified by searching MEDLINE and PubMed for articles published from January 2007 to October 2016 using the keywords "associating liver partition and portal vein ligation for staged hepatectomy" and "ALPPS". Additional papers were identified by a manual search of references from key articles.

Results and discussion

Pathophysiology

The pathophysiological mechanism of ALPPS in enhancing rapid liver hypertrophy remains unclear. In addition to disrupting the main portal vein supply to the two parts of the partitioned liver and blocking the portal venous supply to a part of the liver, ALPPS also divides any venous collaterals within the liver parenchyma. It is hypothesized that liver grows faster when total portal blood flow redistributes to the FLR. Animal studies showed that the hypertrophic effects of ALPPS are more complicated. Apart from increased blood flow, hepatocyte proliferation is part of the reason of liver volume increase. Liver damage at the first stage of ALPPS triggers inflammatory response and plays an important role in inducing hepatocyte proliferation.

Hepatocyte cellular and molecular changes associated with liver hypertrophy during ALPPS have been studied in experimental models. de Santibañes et al[5] found that proliferating cell nuclear antigen (PCNA) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) ratio, an proliferative index, was significantly increased from -3.78 cells/mm^2 in stage 1 to 2.32 cells/mm^2 in stage 2. The median FLR hypertrophy was 104% in 6 days, with a significant mean difference between the preoperative and postoperative volumes of 361 mL. The mean hepatocyte number significantly increased from 52.7 cells/mm^2 in stage 1 to 89.6 cells/mm^2 in stage 2. The PCNA expression increased by 190% between the 2 stages with a linear correlation (r=0.58) with macroscopic hypertrophy. The results of this study indicated the rapid FLR volumetric increase in ALPPS being accompanied by histological and molecular evidences of hepatocyte cell proliferation. Shi et al in animal study found that the regeneration rate in the FLR after ALPPS was 2 times relative to those after PVL, whereas rats with parenchymal transection alone showed minimal volume increase.[6] The expression levels of Ki-67 and PCNA were about ten-fold higher after ALPPS compared with rats which underwent transection or left lateral section resection, and four-fold higher compared with rats after PVL. The levels of TNF-α, IL-6 and HGF in the regenerating liver remnant were about three-fold higher after ALPPS compared with controls. There were more significant activations of NF-κB p65, STAT3 and Yap after ALPPS, suggesting synergistic activation of the pathways by PVL and transection, which might play an important role in liver regeneration after ALPPS.

An experimental model using mice by Schlegel et al gave important information about the mechanism of accelerated hypertrophy in ALPPS.[7] The ALPPS group received 90% PVL combined with liver parenchymal