
On January 4, 2016, the authors of the article entitled “A systematic review and meta-analysis of feasibility, safety and efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH)” (PMID: 26559020) contacted the Editor-in-Chief of Bioscience Trends regarding an oversight in their methodology. ALPPS is a surgical procedure that was first introduced in 2012. In its early stages, the procedure had several names, and a handful of researchers referred to ALPPS as “in situ liver transection with portal vein ligation.” However, this term was not included as a search term in the article comparing ALPPS and TSH. Once the authors became aware of this oversight, they contacted the Editor-in-Chief of Bioscience Trends to retract their paper. The Editor-in-Chief thoroughly examined the article and made the decision to retract the paper as the authors requested. The reason for this retraction is because the described meta-analysis lacked certain key search terms. The article is meaningful, but this oversight in methodology might undermine the findings of the meta-analysis.

Jianjun GAO, Managing Editor

Reference

A systematic review and meta-analysis of feasibility, safety and efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH)

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Summary

This meta-analysis aimed to review the regeneration rate of future liver remnant (FLR) and perioperative outcomes after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and two-stage hepatectomy (TSH). A web search was performed in "MEDLINE", "EMBASE", and "SCIENCE DIRECT" databases using both subject headings (MeSH) and truncated word to identify all the articles published that related to this topic. Pooled risk ratios were calculated for categorical variables and mean differences for continuous variables using the fixed-effects and random-effects models for meta-analysis. Three studies involved 282 patients, of whom 234 were in the TSH group and 48 in the ALPPS group. Morbidity was experienced in 56.3% patients in the ALPPS group and 36.1% in the TSH group. There was a statistical difference (RR = 1.08; Z = 3.24; 95% CI, p = 0.001). Second surgeries were performed successfully in 79.1% patients in the portal vein embolization (PVE) group and 100% in the ALPPS group. There was a statistical difference (Z = 2.48; 95% CI, p = 0.01). The mean regeneration rate of FLR in the ALPPS group was 56.4% compared with 52.8% in the TSH group. There was no statistical difference (95% CI, p = 0.34). So from the outcome of this meta-analysis, TSH had a similar remnant liver regeneration ability compared to ALPPS while the morbidity and mortality rates were relatively low. Cancer progression while waiting for the staged liver resection after portal vein embolization was a drawback for TSH.

Keywords: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), portal vein embolization (PVE), two-staged Hepatectomy (TSH), liver regeneration

1. Introduction

During the period of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) surgery promotion, there were always comparisons with conventional Two-Stage Hepatectomy (portal vein embolization and staged hepatectomy, TSH), which don't need laparotomy and liver parenchyma partition in the first surgery. Some researchers found that TSH had a similar remnant liver regenerative effect compared to ALPPS while the morbidity and mortality rates were relatively low (1-3). There were already 3 randomized control trials comparing the two surgeries up to now that we have summarized as follows.

The major difference between ALPPS and TSH is the extra liver parenchyma partition in ALLPS, which may result in fast remnant liver regeneration. The procedure of cancer-bearing liver partition may also reduce the chance of tumor invasion to the remnant liver (4). The major deficit of conventional two-stage hepatectomy is that the speed of future remnant liver
(FLR) regeneration is not very high. It’s rarely over 50% for 4–8 weeks. About 1/10 patients who underwent portal vein embolization as the first surgery of TSH lost the second hepatic resection surgery opportunity while waiting for FLR regeneration. So conventional TSH now is widely used for hilar cholangiocarcinoma, which grows slowly compared with hepatic cancer. The purpose of this systematic review and meta-analysis was to compare ALPPS with TSH to evaluate feasibility, safety and efficacy.

2. Materials and Methods

2.1. Procedure of data collection

The databases of "MEDLINE", "EMBASE", and "SCIENCE DIRECT" were searched for articles published up to the date of Oct 15th, 2015 using the medical subject headings (MeSH) terms "portal vein ligation", "PVE", "staged hepatectomy", "staged liver resection", "liver resection", "two-stage hepatectomy", "TSH", "associating liver partition and portal vein ligation for staged hepatectomy" and "ALPPS" (Figure 1). There were no language restrictions. Relevant articles were reviewed and duplicates were removed. Articles unrelated to ALPPS, TSH as well as abstracts were excluded. Full-text articles were assessed for eligibility. Editorials and commentary articles as well as case reports were excluded. Studies reporting on up to three patients were classified as case reports. Patients were carefully screened for double reporting, after exclusion of those patients, a quantitative synthesis and meta-analysis was performed.

All patients who underwent liver resection for malignant tumors in both normal and cirrhotic livers were included. Inclusion criteria for searching were studies evaluating the use of TSH and ALPPS for elective liver resection.

2.2. Types of outcome measures

The morbidity rate, second surgery finish rate, FLR regeneration rate of TSH and ALPPS were measured.

Figure 1. Prisma flowchart of databases searched, strategy used, and exclusions performed for "ALPPS" and "TSH". Randomized and case-controlled studies, irrespective of language, country of origin, hospital, blinding, sample size, or publication status that compared ALPPS and TSH were included in this review. The databases of "MEDLINE", "EMBASE", and "SCIENCE DIRECT" were searched for articles published up to the date of Oct 15th, 2015 using the medical subject headings (MeSH) terms "portal vein ligation", "PVE", "staged hepatectomy", "staged liver resection", "liver resection", "ALPPS", "TSH", "associating liver partition and portal vein ligation for staged hepatectomy" and "Hepatectomy". Relevant articles were reviewed and duplicates were removed. Articles unrelated to ALPPS, TSH as well as abstracts were excluded. Full-text articles were assessed for eligibility. Editorials and commentary articles as well as case reports were excluded. Studies reporting on up to three patients were classified as case reports. Patients were carefully screened for double reporting.
2.3. Statistical analysis

Statistical analysis was performed using Review Manager Version 5.2 software (Cochrane Collaboration). The risk ratio (RR) with 95% confidence interval (CI) was calculated for binary data, and the mean value differences with 95% CI for continuous variables. When median and range were reported instead of mean and variance, the mean and variance were calculated based on the methods described by Hozo et al. (6). Random and fixed effects models were used to calculate the outcomes of both binary and continuous data. In cases of heterogeneity, only the results of the random effects model were reported. Heterogeneity was explored using the Chi-square test, with significance set at \( p < 0.05 \). Low heterogeneity was defined as \( I^2 \leq 33\% \). If the standard deviation was not available, it was calculated according to the guidelines of the Cochrane Collaboration. This process involved assumptions that both groups had the same variance, which may not have been true, and variance was estimated either from the range or from the \( p \) value. Forest plots were used for graphic display of the results. Quality assessment of the included studies was based on the Newcastle-Ottawa scale (7).

3. Results

The strategies of the literature search and the selection of studies are summarized (Figure 1). Three studies comparing ALPPS with TSH procedure met the inclusion criteria (1,2,8). All studies were retrospective. These three studies involved 282 patients, of whom 48 were in the ALPPS group and 234 in the TSH group. Pooled data were analyzed by combining the results of these three studies.

3.1. Comparison of morbidity rate between ALPPS and TSH

There was no heterogeneity among the included studies (\( \text{Chi}^2 = 9.97; \text{df} = 2; p = 0.007; I^2 = 80\% \)). Morbidities were experienced in 56.3% of patients in the ALPPS group and 36.1% in the TSH group. In a random effects model, there was statistical difference (\( \text{RR} = 1.08; Z = 3.24; 95\% \text{ CI}, p = 0.001 \); Figure 2).

3.2. Comparison of second surgery finish rate between ALPPS and TSH

There was no heterogeneity among the included studies (\( \text{Chi}^2 = 1.54; \text{df} = 2; p = 0.46; I^2 = 72\% \)). The staged surgeries were performed successfully in 79.1% of patients in the PVE group and 100% in the ALPPS group. In a random effects model, there was statistical difference (\( Z = 2.48; 95\% \text{ CI}, p = 0.01 \); Figure 3).

3.3. Comparison of FLR regeneration rate after first surgery between ALPPS and TSH

There was no heterogeneity among the included studies (\( \text{Chi}^2 = 1.54; \text{df} = 2; p = 0.46; I^2 = 72\% \)). The staged surgeries were performed successfully in 79.1% of patients in the PVE group and 100% in the ALPPS group. In a random effects model, there was statistical difference (\( Z = 2.48; 95\% \text{ CI}, p = 0.01 \)).

**Figure 2. Comparison of morbidity rate between ALPPS and TSH.** There studies were included in the analysis. Three was no heterogeneity amongst the included studies (\( \text{Chi}^2 = 9.97; \text{df} = 2; p = 0.007; I^2 = 80\% \)). Morbidity was experienced in 56.3% of patients in the ALPPS group and 36.1% in the TSH group. In a random effects model, there was statistical difference (\( Z = 3.24; 95\% \text{ CI}, p = 0.001 \)).

**Figure 3. Comparison of second surgery finish rate between ALPPS and TSH.** There studies were included in the analysis. Three was no heterogeneity amongst the included studies (\( \text{Chi}^2 = 1.54; \text{df} = 2; p = 0.46; I^2 = 72\% \)). The secondary surgeries were performed successfully in 79.1% of patients in the PVE group and 100% in the ALPPS group. In a random effects model, there was statistical difference (\( Z = 2.48; 95\% \text{ CI}, p = 0.01 \)).
(Chi\(^2\) = 36.12, df = 2; I\(^2\) = 94\%). The mean regeneration rate of FLR in the PVE group was 56.4% compared with 52.8% in the TSH group. In a fixed effects model, there was no difference in the regeneration rate of FLR between ALPPS and TSH (95% CI, p = 0.34; Figure 4).

### 4. Discussion

This meta-analysis shows that about three years after the inaugural publication of the novel ALPPS technique (4), the level of evidence supporting its advantages compared with traditional TSH remains low. Studies confirm the high completion rate of 97% for ALPPS, although with the two common biases of single-center and retrospective design. Perioperative mortality rate was 11% and complications grade IIIa or higher occurred in 44% of all patients (9).

The reasons for the rapid hypertrophy of the FLR observed in ALPPS and the actual functional growth of the FLR are important clinical questions. Although the rapid growth of the FLR after the ALPPS procedure is very impressive, it remains not so clear that it is better compared with a right hemi-liver plus segment 4 PVE. In our meta-analysis there wasn’t any statistical difference between the two types of surgeries in regeneration volume. As reported previously, the hypertrophy of the FLR is negatively correlated with the pre-PVE FLR volume (10). Because hepatic parenchyma transection is usually performed along the umbilical fissure (the segmental border between left lateral lobe and segment 4) in ALPPS procedure (4,11) while PVE is usually performed on right hemi-liver in TSH procedure (12,13). It is incorrect to attribute the reason for the rapid growth of the FLR to hepatic parenchyma partition (8,11). Therefore, more prospective studies about FLR regeneration volume comparison between ALPPS and a right hemi-liver plus segment 4 PVE should be performed.

Second, the mechanism explaining how the in situ splitting facilitates the regeneration of the FLR needs to be clarified. In animal models, there were no differences between TSH and ALPPS for the quantity of effective regenerative liver cells. The comparison for the quantity of effective regenerative liver cells between ALPPS and PVE was performed in rat models. DNA synthesis was assessed by bromodeoxyuridine (BrdU) and proliferating cell nuclear antigen (PCNA) immunohistochemistry staining on paraffin sections. There were no differences in BrdU\(^+\) or PCNA\(^+\) hepatocytes. The liver weights were assessed seven days after surgery. The weights of the remnant livers were not significantly different following PVL and ALPPS (14). Other research (15) also reported similar results that portal vein ligation and portal vein ligation combined with in situ splitting were performed in two groups of mice. The results showed no obvious differences between the two groups were observed at 24 and 48 hours after surgeries.

This systemic review was limited due to the small number of original publications about comparison of ALPPS, which is a very recently introduced technique, with TSH. The reason for this early systematic review was to support the opinion with data about the ongoing debate on the benefits and deficits of ALPPS compared with TSH. At the same time, the quality of studies published currently has not allowed the establishment of solid evidence for safety and efficacy, as shown by this systematic review. More prospective studies about comparison between ALPPS and TSH should be performed to support further assessment of feasibility, safety and oncologic efficacy.

### 5. Conclusion

TSH has similar remnant liver regeneration ability compared with ALPPS while the morbidity and mortality rates are relatively low. Cancer progression while waiting for the second stage hepatectomy after portal vein embolization is a major shortcoming for TSH.

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### References

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