

Hemihepatic *versus* total hepatic inflow occlusion during hepatectomy: A systematic review and meta-analysis

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Abstract

AIM: To evaluate the clinical outcomes of patients undergoing hepatectomy with hemihepatic vascular occlusion (HHO) compared with total hepatic inflow occlusion (THO).

METHODS: Randomized controlled trials (RCTs) comparing hemihepatic vascular occlusion and total hepatic inflow occlusion were included by a systematic literature search. Two authors independently assessed the trials for inclusion and extracted the data. A meta-analysis was conducted to estimate blood loss, transfusion requirement, and liver injury based on the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Either the fixed effects model or random effects model was used.

RESULTS: Four RCTs including 338 patients met the predefined inclusion criteria. A total of 167 patients were treated with THO and 171 with HHO. Meta-

analysis of AST levels on postoperative day 1 indicated higher levels in the THO group with weighted mean difference (WMD) 342.27; 95% confidence intervals (CI) 217.28-467.26; $P = 0.00001$; $I^2 = 16\%$. Meta-analysis showed no significant difference between THO group and HHO group on blood loss, transfusion requirement, mortality, morbidity, operating time, ischemic duration, hospital stay, ALT levels on postoperative day 1, 3 and 7 and AST levels on postoperative day 3 and 7.

CONCLUSION: Hemihepatic vascular occlusion does not offer satisfying benefit to the patients undergoing hepatic resection. However, they have less liver injury after liver resections.

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Key words: Inflow occlusion; Hemihepatic; Vascular occlusion; Hepatectomy; Pringle maneuver

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INTRODUCTION

Liver resection is performed mainly for benign and malignant liver tumors, especially for hepatocellular carcinoma. It is a potential curative treatment option in patients with early stage carcinoma^[1]. Intraoperative bleeding is a main concern during liver resections, and mortality and morbidity are clearly correlated with the amount of blood loss

and the subsequent blood transfusions^[2]. Many methods of hepatic vascular control have been introduced to control intraoperative blood loss. In 1908, Pringle applied inflow vascular occlusion technique (the Pringle maneuver) at the hepatic hilar for the first time. It is a technique of total compression of the hepatoduodenal ligament and the most commonly used and relatively easy method for controlling afferent blood flow^[3]. However, the Pringle maneuver also carries the risk of global ischemic damage to the liver and intestinal congestion, especially in patients with chronic liver diseases, the degree of which is likely to be accentuated by a prolonged period of vascular inflow occlusion^[4,5]. In 1987, Bismuth and Makuuchi proposed a hemihepatic vascular occlusion (HHO) technique to reduce the severity of visceral congestion and total liver ischemia, especially for the remaining liver^[6,7]. By this method, visceral congestion is considered to be limited, because considerable portal blood flow is preserved and only portions of the liver are rendered anoxic^[8]. The technique with occlusion of vessels supplying the hemiliver containing the tumor, has been suggested to reduce intraoperative bleeding and postoperative liver functional disturbances because of the interruption of blood flow to the liver^[9]. But, portal vein and artery dissection to perform selective clamping is time consuming and may result in another blood loss^[10]. Many prospective randomized controlled trials (RCTs) and retrospective clinical trials have evaluated the feasibility, safety and efficacy of HHO and total hepatic inflow occlusion (THO), however, the clinical significance between the two vascular control methods remain inconsistent. So, the optimal method of vascular control during hepatic resection continues to be debated.

Up to now, a meta-analysis including all available RCTs is still insufficient. We conducted a systematic review and meta-analysis to evaluate the feasibility, safety and efficacy of HHO and THO in patients undergoing hepatectomy.

MATERIALS AND METHODS

Systematic literature search

A systematic literature search was independently conducted by two authors. They systematically searched the Medline, Embase, Science Citation Index, PubMed and CNKI (China National Knowledge Infrastructure Whole Article Database). The following keywords were used: hemihepatic vascular occlusion, hemihepatic occlusion, selective inflow occlusion, selective clamping or selective portal clamping. The literature search was performed with restriction in languages of English or Chinese and types of randomized controlled trial or controlled clinical trial. The last search was done on November 2, 2010.

Inclusion and exclusion criteria

Type of studies: Only RCTs were considered for this review. Quasi-randomized studies, cohort studies, and case-control studies were excluded.

Type of participants: Patients who were about to undergo selective liver resection for benign or malignant liver

tumor were included, irrespective of age, gender, cirrhosis, tumor size and nodule numbers. Trials in which patients required contralateral hepatic resection or had distant metastasis or synchronous malignancy in other organs were excluded in the study.

Types of interventions: We included trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion in hepatectomy, irrespective of ischemic preconditioning before vascular occlusion. Trials only comparing other types of vascular occlusion were excluded.

Type of outcome measures: Primary outcomes: Operative blood loss, biochemical markers of liver injury, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and transfusion requirement. Secondary outcomes: Peri-operative mortality, peri-operative morbidity, operating time, ischemic duration and hospital stay.

Selection of studies

Two authors identified and evaluated independently the trials for inclusion in form of abstracts or full text if necessary. Any disagreement in study selection and data extraction was resolved by discussion.

Data extraction

Two authors extracted the data on a standard form that included population characteristics (sex, age, percentage of major liver resections, methods of ischemic preconditioning and the presence of chronic liver disease) the co-interventions and information on the outcome measures in each trial.

Quality assessment

We assessed the methodological quality of the trials independently. The assessment was made based on sample size calculation; sequence generation; allocation concealment; whether blinding method was adopted for the participants of patients and those who performed the trial and evaluate the outcome; efficacy of randomization; deviations, withdrawals and dropouts; and definition of outcome parameters^[11,12].

Statistical analysis

We pooled the synchronized extraction results as estimates of overall therapeutic effects in a meta-analysis using Review Manager Version 5.0 for Windows. The estimated effect measures were odds ratio (OR) for dichotomous data and weighted mean difference (WMD) for continuous data, both reported with 95% confidence intervals (CI). We checked all results for clinical and statistical heterogeneity. Clinical heterogeneity was evaluated based on the study populations and interventions, definition of outcome measures, concomitant treatment, and perioperative management. Heterogeneity was determined by Chi-squared test. P value of 0.10 was considered significant difference and I^2 values were used for the evaluation of statistical heterogeneity (I^2 of 50% or more indicating presence of heterogeneity)^[13]. We used a fixed-effects model to synthesize

Table 1 Characteristics of randomized controlled trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion

Author (yr)	Design	Sample size (n)	THO (n)	HHO (n)	Journal	Comparison
Figueras <i>et al</i> (2005)	RCT	80	39	41	<i>Annals of Surgery</i>	Complete vs selective portal triad clamping
Wu <i>et al</i> (2002)	RCT	58	28	30	<i>Arch Surg</i>	Hemihepatic vs total hepatic occlusion techniques
Yuan <i>et al</i> (2010)	RCT	120	60	60	<i>The American Journal of Surgery</i>	Pringle maneuver vs hemihepatic vascular occlusion
Liang <i>et al</i> (2009)	RCT	80	40	40	<i>Hepato-Gastroen-terology</i>	Continuous hemihepatic with intermittent total hepatic inflow occlusion
Total	--	338	167	171	--	--

THO: Total hepatic inflow occlusion; HHO: Hemihepatic vascular occlusion; RCT: Randomized controlled trials.

Table 2 Characteristics of patients in randomized controlled trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion

Author (yr)	Age (mean yr)	Sex (male:female)	Cirrhosis (n:N)	Ischaemic preconditioning	Resection margin (≤ 1 segments: ≥ 2 segments)	Diseases HCC: Others
	THO/HHO	THO/HHO	THO/HHO		THO/HHO	THO/HHO
Figueras <i>et al</i> (2005)	61.8/62	31:8/28:13	18:39/21:41	IC	25:14/29:12	16:23/17:24
Wu <i>et al</i> (2002)	57.5/53.2	23:5/25:5	28:28/30:30	IC	5:23/7:23	25:3/26:4
Yuan <i>et al</i> (2010)	48.6/49.3	46:14/41:19	39:60/35:60	IC if transaction time > 30 min or CC	5:55/5:55	44:16/43:17
Liang <i>et al</i> (2009)	49.4/49.55	27:13/31:9	17:40/19:40	IC or CC	6:34/10:30	20:20/21:19
Total	--	127:40/125:46	102:167/105:171	--	41:126/51:120	105:62/107:64

IC: Intermittent clamping; CC: Continuous clamping; HCC: Hepatocellular carcinoma; N: The number of all patients in one trial; n: The number of patients with cirrhosis; THO: Total hepatic inflow occlusion; HHO: Hemihepatic vascular occlusion.

Table 3 Outcomes of randomized controlled trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion

Author (yr)	Operative time (min)	Ischemic duration (min)	Blood loss (mL)	Transfusion requirements	Complications total (n)	In-hospital stay (d)	In-hospital death (n)
	THO/HHO	THO/HHO	THO/HHO	THO/HHO	THO/HHO	THO/HHO	THO/HHO
Figueras <i>et al</i> (2005)	207 ± 48/219 ± 45	41 ± 14/47 ± 18	671 ± 533/735 ± 397	4:39/6:41	15:39/ 12:41	9.38 ± 4.9/8.15 ± 3.8	0:39/1:41
Wu <i>et al</i> (2002)	409 ± 19.2/399 ± 15.6	96.0 ± 10.9/94.2 ± 9.9	1685 ± 170/1159 ± 221	12:28/5:30	8:28/10:30	14.8 ± 1.4/16.4 ± 1.4	0:28/0:30
Yuan <i>et al</i> (2010)	114.2 ± 37.2/133.5 ± 44.6	16.6 ± 8.7/14.9 ± 4.5	339.5 ± 205.1/354.4 ± 240.3	6:60/4:60	19:60/12:60	13.7 ± 5.2/10.2 ± 4.1	1:60/0:60
Liang <i>et al</i> (2009)	203.98 ± 38.36/236.15 ± 49.2	40.17 ± 13.30/42.38 ± 12.79	569.8 ± 285.56/649.35 ± 279.05	14:40/15:40	8:40/9:40	9.85 ± 3.55/10.12 ± 2.41	0:40/0:40
Total	--	--	--	36:167/30:171	50:167/43:171	--	1:167/1:171

THO: Total hepatic inflow occlusion; HHO: Hemihepatic vascular occlusion.

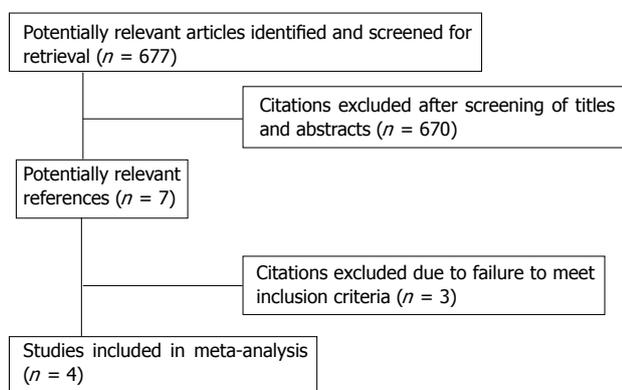


Figure 1 Reference flow chart.

data when heterogeneity was absent, otherwise a random-effects model would be used. Data were presented as forest plot and funnel plot was used to assess publication bias.

RESULTS

We searched a total of 677 references published between 2002 and 2010. Four RCTs^[14-17] including 338 patients met the predefined inclusion criteria (Figure 1). All the trials (Table 1) compared HHO (n = 171) with THO (n = 167). Three trials enrolled cirrhotic and non-cirrhotic patients^[14,16,17] and one trial enrolled only cirrhotic patients^[15]. In all trials, both major (> 2 segments) and minor (≤ 1 segments) hepatic resections were performed, but one trial exclusively included patients undergoing complex central liver resections. Tables 2-4 summarize the baseline characteristics and outcomes of the trials. The potential bias of included trials are shown in Table 5. Only one of the trials reported the blinding methods used and the generation of allocation sequence^[16].

Effects of interventions

Blood loss. Information on intraoperative blood loss was

Table 4 Postoperative aspartate aminotransferase and alanine aminotransferase levels of patients in randomized controlled trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion

Author (yr)	AST (U/L) Day 1 THO/HHO	AST (U/L) Day 3 THO/HHO	AST (U/L) Day 7 THO/HHO	ALT (U/L) Day 1 THO/HHO	ALT (U/L) Day 3 THO/HHO	ALT (U/L) Day 7 THO/HHO
Wu <i>et al</i> (2002)	420 ± 790/290 ± 770	180 ± 320/190 ± 510	50 ± 40/30 ± 20	370 ± 490/480 ± 510	330 ± 320/320 ± 270	90 ± 20/70 ± 20
Yuan <i>et al</i> (2010)	812.6 ± 475.3/ 447.6 ± 210.3	423.7 ± 265.4/ 207.5 ± 79.3	143.6 ± 87.5/ 64.2 ± 29.4	1013.6 ± 654.4/ 369.4 ± 347.2	592.2 ± 416.4/ 218.4 ± 185.3	172.4 ± 125.8/ 79.6 ± 55.3
Figueras <i>et al</i> (2005)	NS	NS	NS	402 ± 258/372 ± 234	NS	NS

THO: Total hepatic inflow occlusion; HHO: Hemihepatic vascular occlusion.

Table 5 Assessment the methodological quality of included studies

Author (yr)	Sample size calculation	Generation of allocation sequence	Allocation concealment	Deviations, withdrawals and dropouts	Efficacy of randomization	Blinding	Definition of outcome parameters
Figueras <i>et al</i> (2005)	Yes	No description	Sealed envelope	Yes	Yes	No description	Yes
Wu <i>et al</i> (2002)	No description	No description	Sealed envelope	No description	Yes	No description	Yes
Yuan <i>et al</i> (2010)	Yes	Yes	Sealed envelope	Yes	Yes	Single-blinded	No description
Liang <i>et al</i> (2009)	No description	No description	No description	Yes	Yes	No description	Yes

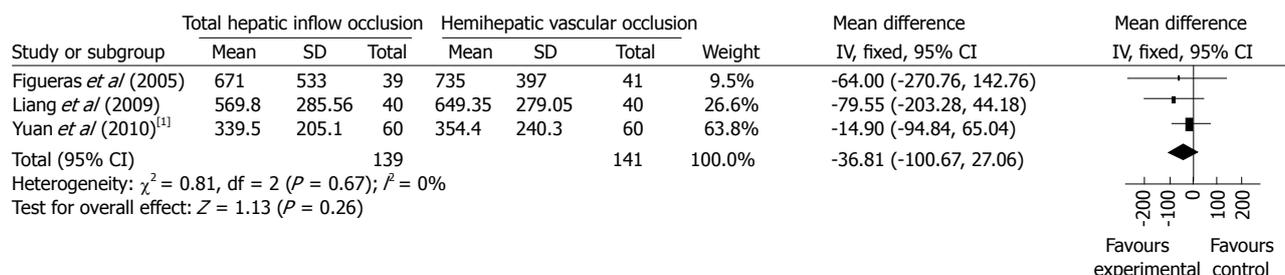


Figure 2 Meta-analysis of blood loss in randomized controlled trials comparing total hepatic inflow occlusion with hemihepatic vascular occlusion. ¹Blood loss.

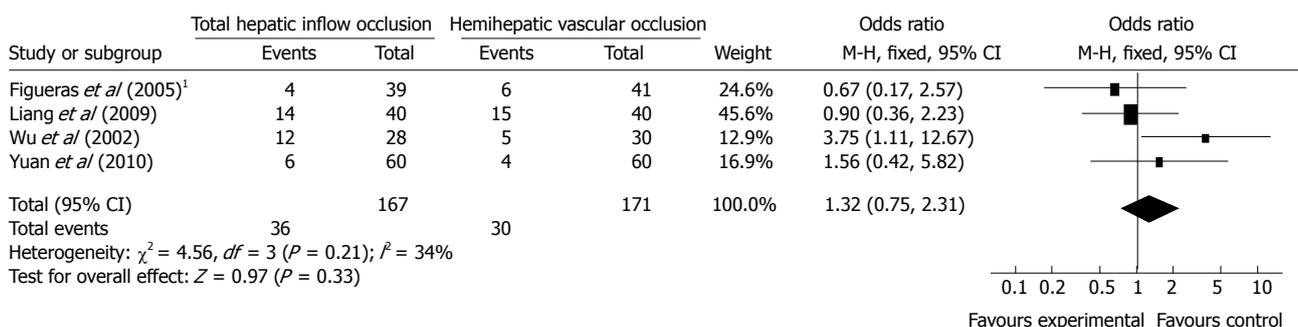


Figure 3 Meta-analysis of aspartate aminotransferase levels on postoperative 1st d. ¹Transfusion requirements (n).

available in all analyzed trials. The trial by Wu *et al*^[15] reported significantly more blood loss in patients of both groups. Statistical heterogeneity was presented and $P = 0.000001$. Funnel plot to evaluate publication bias for outcome of blood loss demonstrated a strong asymmetry, suggesting the existence of severe publication bias. Clinical heterogeneity analysis found that complex central liver resections were performed on cirrhotic patients, and the cut surface area was wider and would increase intraoperative blood loss. Meta-analysis of the other three trials showed no significant difference between THO group

and HHO group (WMD -36.81; 95% CI -100.67 to 27.06, $P = 0.26$, $I^2 = 0\%$) (Figure 2).

Transfusion requirement. All trials reported the number of patients who needed transfusion in both groups. Funnel plot did not demonstrate a strong asymmetry. Meta-analysis (Figure 3) indicated no difference in postoperative transfusion requirement between the groups (OR 1.32 95% CI 0.75-2.31, $P = 0.33$, $I^2 = 34\%$). Since there was no uniform definition of the average transfusion volume in the trials, we did not compare the transfusion volume in the study.

Biochemical markers of liver injury. All the four tri-

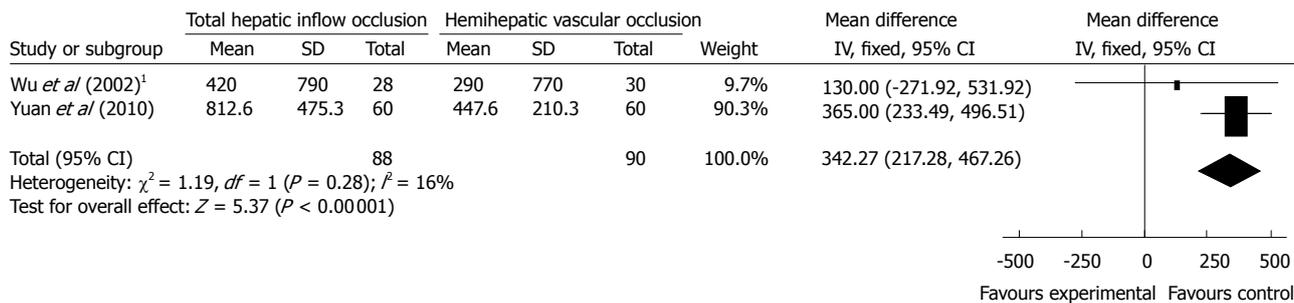


Figure 4 Meta-analysis of aspartate aminotransferase levels on postoperative Day 1. ¹Aspartate aminotransferase (D1).

als provided AST and ALT levels on postoperative days. However, data on AST and ALT were available in only two studies. We did not draw funnel plots to examine the potential publication bias in this review, because the number of the included trials was small. Wu *et al.*¹⁵ provided the data of ALT and AST levels on postoperative days 1, 3, 5 and 7, and Yuan *et al.*¹⁶ gave the information on postoperative days 1, 3 and 7. The ALT levels on postoperative day 1 in Figueras’s study¹⁴ were also available. Meta-analysis of ALT levels on postoperative days 1, 3 and 7 showed no significant difference between the two groups (WMD on day 1/191.03, 95% CI -239.04 to 621.10, $P = 0.38$, $I^2 = 94\%$; WMD on day 3/192.86, 95% CI -163.66 to 549.37, $P = 0.29$, $I^2 = 94\%$, and WMD on day 7/54.43, 95% CI -16.81 to 125.67, $P = 0.13$, $I^2 = 94\%$). Meta-analysis of AST levels on postoperative days 3 and 7 in the two studies showed no significant difference between THO group and HHO group (WMD on day 3/127.52, 95% CI -88.92 to 343.96, $P = 0.25$, $I^2 = 73\%$; WMD on day 7/49.10, 95% CI -9.1 to 107.3, $P = 0.10$, $I^2 = 94\%$). Meta-analysis of AST levels on postoperative day 1 indicated higher postoperative AST levels in the THO group (WMD 342.27; 95% CI 217.28 to 467.26; $P = 0.00001$, $I^2 = 16\%$) (Figure 4).

Peri-operative mortality and morbidity. Four studies provided data on peri-operative mortality and morbidity. In total, two patients died in the four trials. Both died from liver failure, one in THO group and the other in HHO group. Meta-analysis of these studies revealed neither of the two groups showed superiority in overall morbidity (OR 1.28, 95% CI 0.79-2.07, $P = 0.31$, $I^2 = 0\%$) and mortality (OR 1.03, 95% CI 0.14-7.44, $P = 0.98$, $I^2 = 0\%$). Meta-analysis of bile leak (OR 0.92, 95% CI 0.35 -2.44, $P = 0.87$, $I^2 = 0\%$) and hepatic insufficiency (OR 1.02, 95% CI 0.29 - 3.60, $P = 0.97$, $I^2 = 35\%$) showed no statistically significant difference.

Operating time, ischemic duration and hospital stay. There was no statistically significant difference in operating time (WMD -12.44, 95% CI -32.88 to 8.00, $P = 0.23$, $I^2 = 86\%$) between the two groups, also in hospital stay (WMD 0.63, 95% CI -1.60 to 2.85, $P = 0.58$, $I^2 = 91\%$) and in ischemic duration (WMD 0.61, 95% CI -1.40 to 2.61, $P = 0.55$, $I^2 = 43\%$)

DISCUSSION

The key points in hepatectomy are to control intraopera-

tive bleeding and prevent postoperative complications such as liver failure and bile leakage¹⁸. Intraoperative blood loss has been shown to significantly influence the short-term prognosis of patients undergoing liver resection^{19,20}. Hemihepatic vascular clamping selectively interrupts the arterial and venous inflow to the right or left hemiliver and therefore avoids both splanchnic blood stasis and ischemia or ischemia-reperfusion injury to the whole liver^{9,21}. A retrospective study²² indicated that the average bleeding volume and transfusion requirements were less in hemihepatic vascular occlusion group compared with Pringle maneuver group. But, other retrospective studies^{8,23} showed no difference between the two groups. Our meta-analysis showed no significant difference in blood loss and transfusion requirements between the two groups. Three^{14,16,17} of the four trials in the review showed no difference in the amount of hemorrhage and blood transfusion requirements, but one study¹⁵ reported that the amount of operative blood loss and the incidence of blood transfusion were significantly higher in group THO patients (1685 mL *vs* 1159 mL, $P = 0.049$) and the volume of blood loss was much higher than in other studies. It could be explained by the fact that the patients in the study had cirrhosis and underwent complex central liver resections, while other trials included both cirrhotic and non-cirrhotic patients. The procedures presented herein were more difficult and time-consuming than conventional major hepatectomy and transected plane was also wider^{15,24-26}. Both factors induced massive bleeding and difficulties in hemostasia.

Liver injury due to ischemia and subsequent reperfusion are major concerns in inflow vascular occlusion²⁷⁻²⁹ and are usually monitored after surgery by measuring aminotransferase levels³⁰. We found no significant difference on ALT levels on postoperative days 1, 3 and 7 in the two groups, also on AST levels on postoperative days 3 and 7. Three RCTs^{14,15,17} and one retrospective study¹⁸ drew the same conclusion. Theoretically, the blood flow in one lobe of the liver in group HHO is preserved and the liver function damage may be less than that in group THO³¹. Yuan *et al.*¹⁶ indicated that the Pringle maneuver group was associated with a significantly higher peak in ALT and AST levels ($P = 0.01$). Meta-analysis showed that AST levels on postoperative day 1 were also higher in the THO group (WMD 342.27, 95% CI 217.28-467.26, $P = 0.00001$, $I^2 = 16\%$). Chau *et al.*²³ concluded that patients subjected to HHO responded better than those subjected to the Prin-

gle maneuver in terms of earlier recovery of postoperative liver function. Therefore, HHO resulted in less liver injury and was advantageous in the recovery of postoperative liver function.

Unfortunately, only two trials in our analysis included data on ALT and AST levels. There were no significant differences in patients' general characteristics, resection margin, and ratio of cirrhotic to non-cirrhotic patients ($P = 0.05$). However, intermittent clamping was used in the trial by Wu *et al.*^[15], whereas Yuan *et al.*^[16] did continuous clamping if transaction time was ≤ 30 min, otherwise intermittent clamping would be used. A RCT^[32] comparing intermittent portal triad clamping with continuous clamping showed no statistically significant differences, although the peak AST level was lower in the intermittent portal triad clamping. Belghiti *et al.*^[33] suggested that in chronic patients, the transaminase levels were significantly higher in the continuous portal triad clamping than in the intermittent portal triad clamping. Cirrhotic liver and pre-existing liver were less able to tolerate ischemia than normal liver in clinical observations or animal experiments^[28,34,35]. The proportion of chronic patients in the two RCTs were 100% and 61.7% respectively, which may influence the ALT and AST levels in HHO and THO groups and account for the lack of difference between the two groups on postoperative days 3 and 7. Due to the limited number and non-available data in the trials, no subgroup analysis was performed in patients with cirrhosis, which is known to increase the sensitivity of the livers to ischemia^[30].

There was one death in Figueras' trials^[14] in HHO group as a result of hepatic insufficiency in a patient with hepatitis C virus (HCV) cirrhosis. His blood loss during the operation was 2120 mL and 5 units of red blood cell transfusion were required. Yuan *et al.*^[16] reported one patient in the Pringle maneuver group who died of liver failure on the 26th d after a right hepatectomy. The total mortality was 0.51% and total peri-operative morbidity was 27.51%. But no statistically significant difference was found in the peri-operative mortality, peri-operative morbidity, operating time, ischemic duration and hospital stay. Complications included ascites, bile leak, hepatic insufficiency, portal thrombosis, pleural effusion, wound infection, hemorrhage and so on. Meta-analysis of bile leak and hepatic insufficiency showed no significant difference between THO group and HHO group.

This review has some limitations. First, our literature search might have not detected all relevant evidences and the number of RCTs included in this review is small. Second, incomplete reporting of important methodological issues, such as sample size calculation, randomization process and blinding assessment of trial quality, might raise doubts on the adequate power of these studies^[36]. Third, the heterogeneity of the patients in the included trials may influence the conclusions as some trials included major and complex central liver resections and some included normal and cirrhotic livers.

In conclusion, the current evidence shows no advantage of hemihepatic vascular occlusion over the total he-

patic inflow occlusion in terms of blood loss, transfusion requirement, mortality and morbidity, operating time and hospital stay. However, HHO results in less liver injury after liver resections. Further trials are required to assess optimal technique of hepatic vascular control for the patients hepatectomy especially for the patients with chronic cirrhosis.

COMMENTS

Background

Possibility of life-threatening hemorrhage always exists in patients with liver resection, so liver vascular control to reduce blood loss is important. Since the Pringle maneuver technique was successfully applied by Pringle in 1908, many methods of hepatic vascular control have been introduced to accelerate the development of hepatic surgery. Bismuth and Makuuchi proposed the hemihepatic vascular occlusion technique, which attracted much attention among surgeons.

Research frontiers

Both Pringle maneuver and hemihepatic vascular occlusion techniques can reduce blood loss during transaction of the hepatic parenchyma but Pringle maneuver produces ischemic injury to the remaining liver and intestinal congestion. Hemihepatic vascular occlusion technique has become very popular in recent years, because it is thought to limit visceral congestion and can protect the remaining liver. Many studies including randomized controlled trials (RCTs) have been designed to evaluate the safety, feasibility and efficiency of the two methods.

Innovations and breakthroughs

The authors searched and assessed all the RCTs comparing the two techniques and drew a conclusion by a systematic review and meta-analysis. They found that hemihepatic vascular occlusion did not offer benefit to the patients except for reducing ischemic liver injury after liver resections.

Applications

Hemihepatic vascular occlusion technique should be recommended for hepatectomy to reduce peri-operative blood loss and protect the remaining liver after the surgery.

Terminology

Hemihepatic vascular occlusion is a method which selectively interrupts the arterial and portal inflow to the part of the liver (right or left hemiliver) ipsilateral to the lesion that requires resection. It can be achieved after placing a curved renal pedicle clamp across the right or left portal structures. And Pringle maneuver involves compression of the hepatoduodenal ligament to interrupt all arterial and portal inflow to the whole liver.

Peer review

The manuscript is methodologically well designed and is concise in its data and conclusion. However, it should be subjected to linguistic revision to improve several mistakes in grammar and style.

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