Impact of Intermittent Pringle Maneuver on Long-Term Survival After Hepatectomy for Hepatocellular Carcinoma: Result from Two Combined Randomized Controlled Trials

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Abstract

Background Hepatectomy remains an important curative treatment for hepatocellular carcinoma (HCC). Intermittent Pringle maneuver (IPM) is commonly applied during hepatectomy for control of bleeding. Whether the ischemia/reperfusion injury brought by IPM adversely affects the operative outcomes is controversial. This study aims to examine whether the application of IPM during hepatectomy affects the long-term outcomes.

Methods Two randomized controlled trials (RCT) have been carried out previously to evaluate the short-term outcomes of IPM. The present study represented a post hoc analysis on the HCC patients from the first RCT and all patients from the second RCT, and the long-term outcomes were evaluated.

Results There were 88 patients each in the IPM group and the no-Pringle-maneuver (NPM) group. The patient demographics, type and extent of liver resection and histopathological findings were comparable between the two groups. The 1-, 3-, 5-year overall survival in the IPM and NPM groups was 92.0%, 82.0%, 72.1% and 93.2%, 68.8%, 58.1%, respectively ($P = 0.030$). The 1-, 3-, 5-year disease-free survival in the IPM and NPM groups was 73.6%, 56.2%, 49.7% and 71.6%, 49.4%, 40.3%, respectively ($P = 0.366$). On multivariable analysis, IPM was a favorable factor for overall survival ($P = 0.035$). Subgroup analysis showed that a clamp time of 16–30 min ($P = 0.024$) and cirrhotic patients with IPM ($P = 0.009$) had better overall survival.

Conclusion IPM provided a better overall survival after hepatectomy for patients with HCC. Such survival benefit was noted in cirrhotic patients, and the beneficial duration of clamp was 16–30 min.

Trial registration NCT00730743 and NCT01759901 (http://www.clinicaltrials.gov).

Introduction

Hepatectomy remains the most effective curative treatment for hepatocellular carcinoma (HCC) [1]. Hepatic pedicle clamping or Pringle maneuver (PM) is commonly applied to reduce blood loss during liver resection [2-4]. Among various ways of applying PM, the commonly used method is to apply clamping of hepatoduodenal ligament for 15 min followed by unclamping for 5 min or the intermittent Pringle maneuver (IPM) [5]. Controversy still exists in regard to the efficacy of IPM to reduce blood loss and possible damage to the liver due to ischemia/reperfusion injury [6-8].

Two randomized controlled trials on IPM were carried out in our center previously [9, 10]. The first one was done in the period 2008–2011 to assess the efficacy of IPM to reduce blood loss during hepatectomy for various indications [9]. The second one was done in the period 2013–2016 to assess the postoperative complication rate with or without applying IPM during hepatectomy for HCC

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[10]. The results of both studies have been reported previously.

Another controversial issue on PM is its long-term effect on tumor recurrence and survival. While some studies showed that PM might increase tumor recurrence and jeopardize the long-term survival [11, 12], other studies revealed no adverse effect of PM at all [13, 14]. The pattern of survival curves from our second study [10] suggested that there might be some difference in survival between IPM and NPM groups. In order to address the relationship between IPM and survival, the current study represented a post hoc analysis of HCC patients from the first trial and all patients from the second trial.

Methods

The present study combined two previous prospective randomized studies on IPM from our group. The first trial included 63 patients each in the IPM and the no-Pringle-maneuver (NPM) group. Thirty-eight patients from each group had histologically confirmed HCC [9]. In the second trial, there were 50 patients each in the IPM and NPM groups, all with histological confirmed HCC [10]. By combining all HCC patients from both studies, there were 88 patients each in the IPM and NPM groups. Both previous studies were approved by the Clinical Research Ethics Committee of the Joint Chinese University of Hong Kong – New Territories East Cluster, and both were registered at Clinicaltrials.gov (Registration number NCT00730743 and NCT01759901).

Patient selection

Patient selection was similar in both studies. Patients above the age 18 years who were scheduled for open hepatectomy were recruited. Patients were excluded if there was portal vein thrombosis, portal vein tumor thrombus or previous portal vein embolization. Patients with hepatic artery thrombosis or previous transarterial therapy were also excluded. Other exclusion criteria included cases of emergency hepatectomy, hepatectomy for ruptured HCC, anticipated portal vein resection or concomitant bowel or bile duct resection.

Randomization

Randomization was done in the operating room after laparotomy confirmed liver resection could proceed. Patients would be excluded if there were adhesions or any anatomical variations that might preclude safe application of IPM. Randomization was stratified according to the presence or absence of liver cirrhosis as judged by operating surgeons. Block randomization was used. Block size of 2 and 4 was randomly assigned to generate the randomization sequence. The computer-generated numbers were prepared and kept inside sealed envelopes by a research assistant who was not physically present in the operating room.

Operative technique

This was described in our previous two studies [9, 10]. IPM was done by encircling the hepaticoduodenal ligament and applying a vascular clamp in an intermittent manner: 15-min clamping followed by unclamping for 5 min till end of liver transection. The central venous pressure was kept below 5 mmHg during transection if possible. Liver resections were classified according to Brisbane 2000 terminology and was defined as a major when three or more liver segments were removed [15].

Outcome measurement

Operative outcomes including operative blood loss, need for transfusion, operative time and postoperative hospital stay were all recorded. Complications were graded according to the Clavien–Dindo classification [16]. Any death within 90 days after surgery was defined as operative mortality. After surgery, patients were followed up in outpatient clinics 3 monthly within first year and then half yearly afterward. Ultrasound or computed tomography was offered 3 monthly in first year and then half yearly afterward. Chest X-ray would be done half yearly. Alpha-feto protein (AFP) would be checked before each follow-up. Overall survival (OS) was calculated from time of hepatectomy to date of death or last available follow-up. Disease-free survival (DFS) was calculated from time of hepatectomy to date of diagnosis of first recurrence or last available follow-up.

Statistical analysis

All data were prospectively collected by a research assistant and kept in a computer database. Data were presented as median (range) unless specified otherwise. Statistical analysis was performed by Chi-square test or Fisher's exact test to compare categorical variables and Mann–Whitney U test to compare continuous variables. The Kaplan–Meier method was used to estimate the survival rates, and the survival curves were compared by the log-rank test. Univariate and multivariable analyses were done by Cox regression. $P < 0.05$ was taken as the level of statistical significance. All statistical data analyses were performed using SPSS version 21.0 (IBM Corp 2012).

Results

There were 88 patients each in the IPM and the NPM groups. The two groups were comparable in age, sex, body mass index, number of comorbidities and American Society of Anesthesiologists (ASA) score (Table 1). All patients in this study were of Child's grade A liver function. Most of the patients were hepatitis B carriers (75–80%). The two groups did not differ in preoperative complete blood counts, liver function, renal function, clotting profile and AFP value. Indocyanine green (ICG) test was performed for all patients, and there was no difference in retention rate at 15 min (R15) between the two groups (Table 1).

The proportion of major hepatectomy was similar between the two groups (39–42%) (Table 2). There was no difference in types of liver resection between the two groups. The operative time, blood loss and blood transfusion rate were similar. There was one operative mortality in each group. Complication rate and severity of complication according to Clavien–Dindo classification were similar except pleural effusion was significantly more in the IPM group (13.6% vs 3.4%, $P = 0.015$). Length of postoperative hospital stay was similar (Table 2).

Concerning the histopathological findings, there was no difference between the two groups in terms of American Joint Committee on Cancer (AJCC) staging, number of tumors, size of largest tumor, resection margin and incidence of vascular invasion (Table 3).

The median follow-up period for the IPM group and the NPM group was 48.7 months and 39.9 months, respectively. There was no difference in the rate of tumor recurrence, intrahepatic recurrence and extrahepatic recurrence (Table 4). There was no difference in non-disease-related deaths. Besides, types of treatment for recurrent disease did not differ between the two groups. The 1-,

Table 1 Patent demographics and preoperative investigation results

	IPM ($n = 88$)	NPM ($n = 88$)
Sex		
Male	75 (85.2%)	75 (85.2%)
Female	13 (14.8%)	13 (14.8%)
Age	58.0 (38.0–84.0)	60.5 (27.0–81.0)
Body mass index (BMI)	23.1 (16.5–36.0)	24.0 (16.5–31.6)
American Society of Anesthesiologists (ASA) score		
I	8 (9.1%)	6 (6.8%)
II	69 (78.4%)	72 (81.8%)
III	11 (12.5%)	10 (11.4%)
No. of comorbidities	1 (0–6)	1 (0–7)
Hepatitis B status		
Positive	66 (75.0%)	70 (79.5%)
Negative	22 (25.0%)	18 (20.5%)
Hepatitis C status		
Positive	12 (13.6%)	5 (5.7%)
Negative	66 (75.0%)	71 (80.7%)
Unknown	10 (11.4%)	12 (13.6%)
Child's grading: A	88 (100.0%)	88 (100.0%)
ICG (R15) (%)*	4.3 (0.4–28.5)	3.4 (0.2–39.5)
Alpha-feto protein (AFP) (μg/L)	28.0 (1.0–191,009.0)	25.0 (1.0–16,246.0)
Hemoglobin (g/dl)	14.2 (8.2–17.7)	14.3 (9.7–16.5)
Platelet ($\times 10^9$/L)	157 (89–391)	164 (75–354)
White cell count ($\times 10^9$/L)	5.6 (3.2–14.2)	6.0 (2.8–10.0)
International normalized ratio (INR)	1.04 (0.84–1.29)	1.04 (0.84–1.36)
Albumin (g/L)	43.0 (35.0–50.0)	43.0 (33.0–48.0)
Bilirubin (μmol/L)	9.0 (3.0–27.0)	10.0 (4.0–23.0)
Alkaline phosphatase (IU/L)	83.5 (39.0–251.0)	77.5 (37.0–350.0)
Alanine aminotransferase (IU/L)	37.0 (10.0–207.0)	37.0 (11.0–283.0)
Creatinine (μmol/L)	79.5 (5.0–213.0)	88.0 (46.0–147.0)

*ICG (R15): Percentage retention rate of indocyanine green at 15 min

Table 2 Perioperative outcomes

	IPM (*n* = 88)	NPM (*n* = 88)	*P* value
Magnitude of hepatectomy			0.645
Minor	51 (58.0%)	54 (61.4%)	
Major	37 (42.0%)	34 (38.6%)	
Types of resection			
Wedge resection/segmentectomy	43 (48.9%)	49 (55.7%)	0.451
Bisegmentectomy	3 (3.4%)	0 (0.0%)	0.246
Central lobe hepatectomy	3 (3.4%)	1 (1.1%)	0.621
Left lateral sectionectomy	2 (2.3%)	3 (3.4%)	>0.999
Right posterior sectionectomy	0 (0.0%)	1 (1.1%)	>0.999
Left or extended left hepatectomy	9 (10.2%)	15 (17.0%)	0.188
Right or extended right hepatectomy	28 (31.8%)	19 (21.6%)	0.125
Concomitant procedure	60 (68.2%)	57 (64.8%)	0.632
Clamp time (min)	45.0 (15.0–87.0)	NA	NA
Operation time (min)	230.0 (120.0–560.0)	230.0 (110.0–448.0)	0.930
Blood loss (ml)	331.5 (50.0–3600.0)	310.0 (50.0–3160.0)	0.771
Perioperative blood transfusion	6 (6.8%)	3 (3.4%)	0.496
Complication	34 (38.6%)	22 (25.0%)	0.052
Ascites	8 (9.1%)	4 (4.5%)	0.232
Intra-abdominal collection	7 (8.0%)	4 (4.5%)	0.350
Bile leak	0 (0.0%)	1 (1.1%)	>0.999
Pleural effusion	12 (13.6%)	3 (3.4%)	0.015*
Wound infection	8 (9.1%)	5 (5.7%)	0.387
Atrial fibrillation	2 (2.3%)	2 (2.3%)	>0.999
Myocardial infarction	2 (2.3%)	1 (1.1%)	>0.999
Intestinal obstruction	2 (2.3%)	0 (0.0%)	0.497
Ileus	1 (1.1%)	0 (0.0%)	>0.999
Retention of urine	1 (1.1%)	0 (0.0%)	>0.999
Pneumonia	1 (1.1%)	3 (3.4%)	0.621
Exacerbation of obstructive airway disease	1 (1.1%)	0 (0.0%)	>0.999
Septicemia	1 (1.1%)	0 (0.0%)	>0.999
Atelectasis	0 (0.0%)	1 (1.1%)	> 0.999
Supraventricular tachycardia	0 (0.0%)	1 (1.1%)	>0.999
Urinary tract infection	0 (0.0%)	1 (1.1%)	>0.999
Liver failure	4 (4.5%)	0 (0.0%)	0.121
Respiratory failure	1 (1.1%)	1 (1.1%)	>0.999
Renal failure	1 (1.0%)	0 (0.0%)	>0.999
The Clavien–Dindo classification of complication			
1	16 (18.2%)	12 (13.6%)	0.410
2	2 (2.3%)	1 (1.1%)	>0.999
3	13 (14.8%)	7 (8.0%)	0.154
4	2 (2.3%)	1 (1.1%)	>0.99
5	1 (1.1%)	1 (1.1%)	>0.999
Complication			
>2	16 (18.2%)	9 (10.2%)	0.131
Postoperative hospital stay (days)	7 (4–55)	7 (4–39)	0.189
Operative mortality	1 (1.1%)	1 (1.1%)	>0.999

NA not applicable

*Statistically significant

Table 3 Histopathological findings

	IPM ($n = 88$)	NPM ($n = 88$)	P value
Differentiation of tumor			0.400
Well	10 (11.4%)	5 (5.7%)	
Moderate	73 (83.0%)	78 (88.6%)	
Poor	5 (5.7%)	5 (5.7%)	
AJCC staging			0.693
1	54 (61.4%)	53 (60.2%)	
2	20 (22.7%)	24 (27.3%)	
3	14 (15.9%)	11 (12.5%)	
Number of tumor			0.486
Solitary	64 (72.7%)	68 (77.3%)	
Multinodular	24 (27.3%)	20 (22.7%)	
Size of largest tumor (cm)	3.9 (1.0–12.3)	3.5 (1.0–18.0)	0.719
Resection margin (cm)	1.0 (0.0–5.8)	1.0 (0.0–5.0)	0.745
Involved margin	3 (3.4%)	1 (1.1%)	0.621
Cirrhosis	53 (60.2%)	50 (56.8%)	0.646
Vascular invasion	19 (21.6%)	26 (29.5%)	0.226

AJCC American Joint Committee on Cancer

3-, 5-year OS in the IPM and the NPM group was 92.0%, 82.0%, 72.1% and 93.2%, 68.8%, 58.1%, respectively. The 1-, 3-, 5-year DFS in the IPM and NPM groups were 73.6%, 56.2%, 49.7% and 71.6%, 49.4%, 40.3%, respectively. Log-rank test revealed a significant better OS ($P = 0.030$) but not DFS ($P = 0.366$) in the IPM group (Fig. 1).

Subgroup analysis in cirrhotic patients revealed IPM had a significant better OS ($P = 0.009$) than NPM, but DFS was similar. In the non-cirrhotic patients, both the OS and DFS were similar between the two groups (Table 5). Subgroup analysis was also performed in major and minor hepatectomy patients, and in patients with or without vascular invasion, no difference in both the OS and DFS was found between IPM and NPM in these subgroups.

The total clamp time was categorized into four different groups (4 patients ≤ 15 min, 9 patients 16–30 min, 56 patients 31–45 min and 19 patients > 45 min) to compare with 88 patients in the NPM group. When the overall survival of the NPM group was compared with the overall survival of the four different clamp time groups individually by log-rank test, the P values were 0.296, 0.024, 0.066 and 0.422, respectively. Hence, only the group with clamp time 16–30 min had significantly better overall survival than the NPM group. For DFS, there was no difference in the NPM group compared with all the four different clamp time groups.
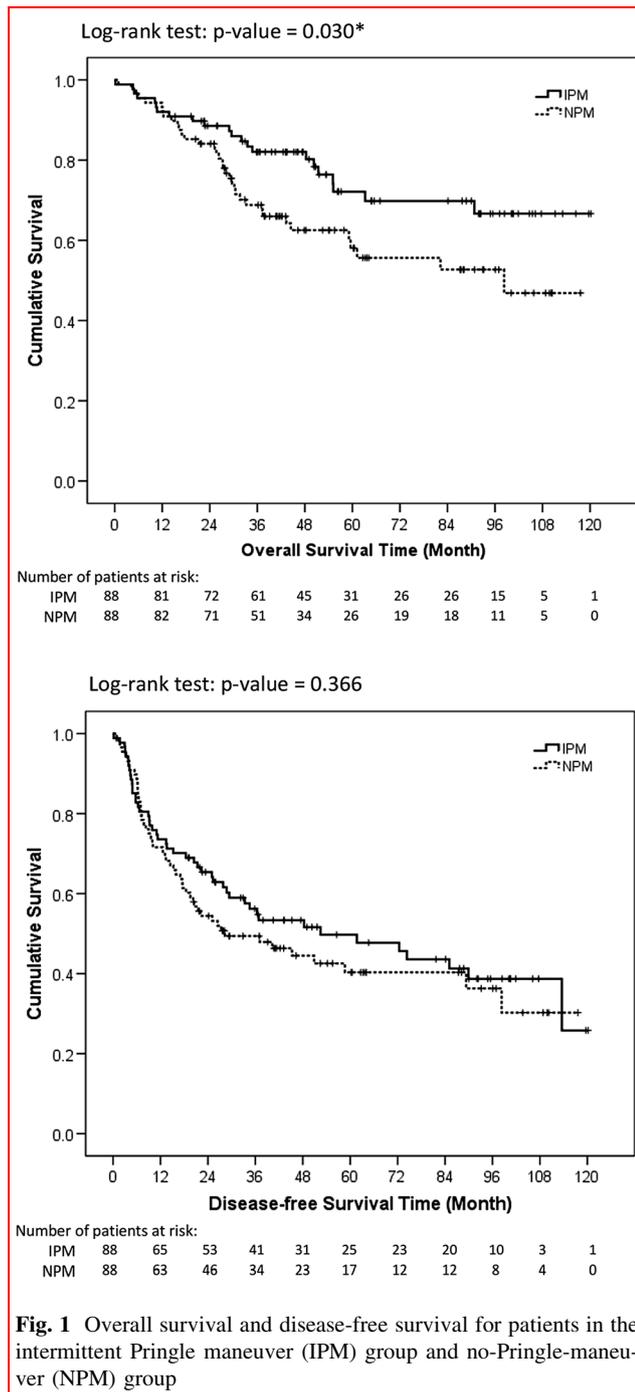
Univariate and multivariable analyses were done to determine the factors affecting OS and DFS. For OS,

Table 4 Long-term outcomes

	IPM ($n = 88$)	NPM ($n = 88$)	P value
Follow-up period (month)	48.7 (0.2–120.2)	39.9 (1.0–117.6)	0.092
Recurrence	44 (50.0%)	48 (54.5%)	0.546
Intrahepatic recurrence	41 (46.6%)	44 (50.0%)	0.651
Extrahepatic recurrence	11 (12.5%)	17 (19.3%)	0.216
Time to recurrence			0.317
1-year	75.7%	72.4%	
3-year	58.4%	50.8%	
5-year	53.6%	41.5%	
Treatment for recurrence			
Re-hepatectomy	16 (18.2%)	11 (12.5%)	0.296
Radiofrequency/ microwave ablation	4 (4.5%)	9 (10.2%)	0.150
Transarterial therapy	15 (17.0%)	14 (15.9%)	0.839
Chemotherapy/target therapy	4 (4.5%)	6 (6.8%)	0.515
Palliative	3 (3.4%)	8 (9.1%)	0.120
Overall survival			0.030*
1-year	92.0%	93.2%	
3-year	82.0%	68.8%	
5-year	72.1%	58.1%	
Disease-free survival			0.366
1-year	73.6%	71.6%	
3-year	56.2%	49.4%	
5-year	49.7%	40.3%	
Cause of death			
Diseases progression	19 (21.6%)	31 (35.2%)	0.045*
Postoperative complication	1 (1.1%)	2 (2.3%)	>0.999
Not liver cancer related	2 (2.3%)	2 (2.3%)	>0.999

*Statistically significant

factors which were significant on univariate analysis were ASA score, ICG (R15), preoperative albumin and alkaline phosphatase, use of IPM, blood loss, multiplicity of tumor, tumor size and vascular invasion. Only IPM or NPM, blood loss (> 320 ml or ≤ 320 ml) and solitary/multinodular tumor were significant factors on multivariable analysis (Table 6). For DFS, significant factors on univariate analysis were ASA score, preoperative albumin and alkaline phosphatase, type of hepatectomy, multiplicity of tumor, tumor size and vascular invasion. Only preoperative albumin, type of hepatectomy, tumor size and vascular invasion were significant factors on multivariable analysis (Table 6).

Fig. 1 Overall survival and disease-free survival for patients in the intermittent Pringle maneuver (IPM) group and no-Pringle-maneuver (NPM) group

Discussion

IPM is still commonly used by many liver surgeons during hepatectomy in an attempt to reduce intra-operative blood loss. Though initial randomized controlled trials showed that it was effective in reducing blood loss [6, 7], subsequent trials did not confirm this effect [8-10]. The other concern for IPM is its ischemia/reperfusion injury [17]. Use of IPM may increase chance of postoperative liver

failure and surgical complications. Our previous trial revealed no increase in complications or liver, failure but there was an increase in subclinical ascites and pleural effusion [10]. Even more worrying issue about the use of IPM is its long-term effect. In animal studies, ischemia/reperfusion injury might negatively impact the oncological outcomes by accelerating tumor growth and promoting metastases [18-20]. In a survey among European hepato-biliary surgeons, 71% of surgeons indicated that they applied PM when it was deemed appropriate and, when applied, 65% applied it intermittently [21]. According to a national survey from Japan, PM was performed in 93.5% of the hospitals (routinely in 25%) [22]. Thus an understanding of IPM on the impact of long-term outcomes after hepatectomy is crucial for the liver surgeons to adopt the technique or not.

Retrospective studies have yielded controversial results surrounding the impact of PM on long-term outcomes after hepatectomy for HCC. While some studies showed that there was no effect [13, 14, 23], other studies revealed a negative impact on long-term survival and disease recurrence [11, 12, 24-26]. Similarly, retrospective studies on the impact of IPM on the long-term outcomes of hepatectomy for colorectal liver metastasis (CRM) revealed controversial results [27-30]. One meta-analysis [31] and one

Table 5 Subgroup analysis: a) cirrhotic patients, b) non-cirrhotic patients

	IPM (*n* = 53)	NPM (*n* = 50)	*P* value
(a)			
Overall survival			0.009*
1-year	92.5%	90.0%	
3-year	82.5%	58.3%	
5-year	76.1%	50.2%	
Disease-free survival			0.326
1-year	69.3%	64.0%	
3-year	55.0%	43.8%	
5-year	44.9%	33.1%	
	IPM (*n* = 35)	NPM (*n* = 38)	*P* value
(b)			
Overall survival			0.842
1-year	91.4%	97.4%	
3-year	80.7%	83.5%	
5-year	65.7%	68.5%	
Disease-free survival			0.733
1-year	80.0%	81.6%	
3-year	58.1%	56.9%	
5-year	58.1%	50.6%	

*Statistically significant

Table 6 Univariate and multivariable analyses for overall and disease-free survival

Variable	Overall survival				Disease-free survival			
	Univariate		Multivariable		Univariate		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Trial								
1	1.28 (0.74, 2.24)	0.380			0.95 (0.63, 1.45)	0.814		
2	–				–			
Sex								
Male	1.75 (0.70, 4.38)	0.232			1.35 (0.74, 2.48)	0.327		
Female	–				–			
Age	1.02 (0.99, 1.04)	0.282			1.00 (0.98, 1.02)	0.880		
Body mass index (BMI)	0.94 (0.87, 1.03)	0.171			0.95 (0.90, 1.02)	0.139		
American Society of Anesthesiologists score (ASA)								
I	0.48 (0.19, 1.22)	0.124	0.57 (0.19, 1.67)	0.304	0.56 (0.25, 1.29)	0.176	1.05 (0.45, 2.46)	0.920
II	0.28 (0.15, 0.52)	< 0.001*	0.47 (0.22, 1.03)	0.058	0.45 (0.26, 0.77)	0.004*	0.76 (0.43, 1.36)	0.353
III	–		–		–		–	
Hepatitis B carrier	0.94 (0.50, 1.78)	0.845			0.87 (0.54, 1.39)	0.553		
Hepatitis C carrier	0.78 (0.28, 2.17)	0.639			1.27 (0.67, 2.39)	0.465		
Pre-op ICG (R15) (%)	1.04 (1.00, 1.09)	0.047*	1.01 (0.95, 1.08)	0.674	1.02 (0.98, 1.06)	0.389		
Pre-op alpha-feto protein (AFP) (μg/L)								
>27	1.45 (0.86, 2.44)	0.167			1.27 (0.85, 1.89)	0.241		
≤ 27	–				–			
Pre-op platelet	1.00 (1.00, 1.01)	0.172			1.00 (0.99, 1.00)	0.695		
Pre-op albumin	0.86 (0.80, 0.93)	< 0.001*	0.94 (0.86, 1.04)	0.224	0.90 (0.85, 0.96)	0.001*	0.93 (0.87, 0.99)	0.025*
Pre-op bilirubin	1.03 (0.98, 1.09)	0.216			0.99 (0.95, 1.03)	0.655		
Pre-op alkaline phosphatase (ALP)	1.01 (1.00, 1.01)	0.021*	1.00 (1.00, 1.01)	0.381	1.01 (1.00, 1.01)	0.027*	1.00 (1.00, 1.01)	0.389
Pre-op alanine aminotransferase (ALT)	1.00 (0.99, 1.01)	0.849			1.00 (0.99, 1.00)	0.590		
Hepatectomy type								
Major	0.73 (0.42, 1.26)	0.258			0.64 (0.42, 0.98)	0.039*	0.38 (0.23, 0.63)	<0.001*
Minor	–				–		–	
Clamp								
IPM	0.56 (0.33, 0.95)	0.033*	0.53 (0.29, 0.96)	0.035*	0.83 (0.56, 1.24)	0.367		
NPM	–		–		–			
Operation time (min)								
>235	1.23 (0.73, 2.06)	0.445			1.04 (0.70, 1.56)	0.834		
≤235	–				–			
Blood loss (ml)								
>320	2.06 (1.20, 3.55)	0.009*	1.95 (1.05, 3.61)	0.035*	1.33 (0.89, 1.98)	0.162		
≤320	–		–		–			
Tumor differentiation								
Well	2.11 (0.44, 10.19)	0.352			3.77 (0.82, 17.55)	0.089		
Moderate	1.42 (0.34, 5.85)	0.631			3.30 (0.81, 13.44)	0.095		
Poor	–				–			
Solitary tumor	0.39 (0.23, 0.67)	0.001*	0.41 (0.22, 0.77)	0.006*	0.56 (0.37, 0.86)	0.008*	0.70 (0.45, 1.09)	0.117
Tumor size (cm)	1.15 (1.08, 1.22)	< 0.001*	1.04 (0.95, 1.14)	0.356	1.12 (1.05, 1.19)	< 0.001*	1.13 (1.04, 1.22)	0.003*
Vascular invasion	3.02 (1.76, 5.19)	< 0.001*	1.51 (0.74, 3.09)	0.261	2.51 (1.63, 3.86)	< 0.001*	1.84 (1.14, 2.98)	0.013*
Cirrhosis	1.44 (0.83, 2.49)	0.199			1.51 (0.99, 2.29)	0.054		
Involved margin	0.05 (0.00, 131.54)	0.452			0.86 (0.21, 3.48)	0.828		

*Statistically significant

randomized controlled trial [32] reached the same conclusion that IPM did not seem to affect the survival of patients with CRM.

To our knowledge, the present analysis is the first to study data from randomized controlled trials to evaluate the impact of IPM on the long-term outcomes after liver resection for HCC. Although the study was a combination of two separate studies to evaluate the short-term outcomes, the two groups were comparable and the follow-up treatment remained essentially the same throughout the period. Interestingly, patients with IPM had significantly longer overall survival than the NPM group, while the DFS was not different. This is something that cannot be easily explained. An even more interesting finding is that the benefit of improved OS is seen in cirrhotic patients but not in non-cirrhotic patients. This is contrary to the usual belief that pathological liver including cirrhosis tolerate ischemia/ reperfusion poorer. The survival benefit was only seen with total clamp time of 16–30 min. Actually there was also a survival benefit seen in the clamp group 31–45 min group but not reaching statistically significance ($P = 0.066$). This can be due to a Type II error. It seems that a modest duration of clamp 16–45 min is most desirable to get the survival benefit. Theoretically, a clamp time less than 15 min is almost equivalent to the no-clamp group. Prolonged clamp time more than 45 min may reflect a more difficult and lengthy operation with more blood loss. The animal study by van der Bilt et al. showed that the outgrowth of micrometastases in occluded liver for 45 min was accelerated five- to sixfold of the nonoccluded lobe [33]. However, the authors also showed that such accelerated tumor growth was completely prevented by IPM for 3 cycles. A clinical study in human showed that prolonged IPM time more than 60 min had a significantly shorter OS compared with that < 60 min for HCC [11]. Another study on CRM showed that prolonged IPM time more than 45 min was associated with decreased time to hepatic tumor recurrence [27]. Since the median clamp time in the present study was only 45 min, any adverse effect due to prolonged clamping might not show up in the result.

Conversely, a study has reported that use of IPM might actually reduce extrahepatic recurrence in HCC [34]. It was postulated that clamping during liver resection might reduce the risk of tumor cell shedding and dissemination into the portal venous system. In our study, since there is no difference in tumor recurrence rate and DFS rate, it is unlikely that the application of IPM affects the incidence of tumor recurrence. An improved OS but not DSF survival may imply that patients can receive more radical re-treatment. However, on further analysis, there was no difference between the two groups in proportion of radical re-treatment like re-hepatectomy and local ablation (Table 4).

In this study, the use of IPM has been shown to be a positive predictor in multivariable analysis for OS. It was not a predictor for DFS. Improved survival associated with the use of IPM was rarely reported in the literature. One case-matched study involving CRM patients reported that the 5-year recurrence-free survival rate of IPM patients was significantly higher than that of the NPM group [35]. Another recent study showed that AJCC stage IIIB HCC patients (with macrovascular invasion) had better OS and recurrence-free survival with clamp time > 12 min than those with NPM or clamp time < 12 min [36]. The protective effect of IPM in this group of patient was believed to be due to the blockage of tumor cell dissemination in the portal tributaries and into remnant liver. We have performed subgroup analysis for tumor with or without vascular invasion, but no significant difference was seen on OS and DFS. The mechanism for the superior OS in the IPM group in this study is still poorly understood.

Since only retrospective data and pooled samples were used in this study, the results were considered to be preliminary and further studies are needed. However, this analysis gave an insight that IPM might have real positive impact on HCC patients after hepatectomy. Apart from designing a new randomized control trial, a systemic review on randomized control study of IPM and individual patient data (IPD) meta-analysis could help reduce bias between different randomized control trials.

In conclusion, this study suggested that IPM provided a better OS after hepatectomy for HCC. Such survival benefit was noted in cirrhotic patients, and the beneficial duration of clamp was 16–30 min.

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