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Original Article

Clinical effect of ischemic preconditioning prior to hepatectomy

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Abstract: Objective: This study evaluated the effect and clinical value of hepatic ischemic preconditioning (IP) prior to hepatectomy. Methods: 458 patients who underwent liver resection from 2001 to 2014 at Xijing Hospital were retrospectively analyzed. The patients were divided into two groups. From 2001 to 2005, the Pringle maneuver was primarily used for hepatic inflow occlusion, and 223 patients were assigned to the Pringle group, which served as the Control Group. From 2006 to 2014, IP was performed instead of the Pringle maneuver, and 235 patients were assigned to the IP Group. The liver function, duration of hepatic inflow occlusion, blood loss and transfusion volume during the operation; the duration of hospital stay; and complications were compared. Results: At postoperative days 1, 3, 5, and 7, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (TBIL) were significantly lower in the IP Group compared with the Control Group ($P<0.05$). The albumin (ALB) in the IP Group was also higher, but there was a significant difference only at the 1st and 7th days. Additionally, a shorter inflow occlusion time and hospital stay duration, less bleeding, and fewer transfusions were observed in the IP Group. No significant differences in complications were observed between the groups. Conclusions: Performing hepatic inflow occlusion prior to hepatectomy could significantly extend the duration of hepatic ischemic tolerance. The procedure could also maintain the consistency of the surgery, reduce blood loss, alleviate reperfusion injury, and promote liver function recovery.

Keywords: Hepatic ischemic preconditioning, hepatectomy, liver function

Introduction

Bleeding and the control of bleeding are the primary problems during liver surgery, and inflow occlusion of the first hepatic portal (Pringle maneuver) is a simple and effective procedure. However, the ischemic tolerance time is limited, and reperfusion may induce liver injury. In particular, the ischemic tolerance time is a type of time range. During this time range, ischemia may cause liver injury; however, the liver injury can recover automatically and reversibly in the period of time after the surgery. Hepatic ischemic preconditioning (IP) is a procedure in which a short period of ischemia increases the tolerance of the liver to a subsequent period of prolonged ischemia and the resulting ischemia/reperfusion injury [1]. Vascular exclusion of the liver prevents intraoperative hemorrhage by suppressing both inflow and outflow bleeding. Vascular exclusion of the liver is followed by more severe ischemia/reperfusion injury [2, 3], and diseased liver parenchyma may facilitate worse injury [4, 5]. Although several studies concerning IP of the liver, including basic research studies, studies of animal models and clinical series, have already been performed, our study aimed to compare the recovery of liver function following performance of the two methods during liver resection. The sample size was more than 400 patients, and the data are available for reference. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) and albumin (ALB), which are indicators of liver function, allow assessment of the degree of injury. In addition, the duration of hospital stay and complications can reflect the recovery condition of patients. Therefore, we carried out a retrospective study by comparing the above indexes between patients who underwent the Pringle maneuver and patients who underwent IP to assess the

Table 1. General patient characteristic in the two groups

Variables	Control Group (n=223)	IP Group (n=235)	*P* value
Age (years)	44.6±13.8	46.8±11.4	0.0630
Gender (male/female)	132/91	146/89	0.5843
Child-Pugh class (A/B)	95/128	110/125	0.4173
Max diameter of tumor (cm)	9.6±3.5	9.5±3.7	0.7668
Range of hepatectomy (irregular/right half/left half)	186/14/23	190/21/24	0.5542/0.3039/0.9716
Diagnosis			
Liver tumor/Liver tumor with cirrhosis	79/63	84/68	0.6941/0.9532
Hemangioma	74	78	0.9986
Hepatolithiasis/Hepatolithiasis with cirrhosis	50/6	51/5	0.9419/0.9299
Hepatic echinococcosis	6	7	0.8528
Hepatapostema	4	8	0.3833
Hepatic tuberculosis	3	5	0.7249
Metastatic tumor from digestive tract	4	7	0.5454

Statistical analyses were performed by t test and chi-square test. There are no significant differences between IP Group and Control Group.

Table 2A. ALT levels in the two groups pre- and post-operation

Time	Control Group (n=223)	IP Group (n=235)	*P* value
Pre-operation	48.6±20.3	42.8±18.6	0.0015*
1 day post-operation	398.6±291.7	189.8±196.6	0.0001*
3 days post-operation	516.3±310.5	211.8±132.6	0.0001*
5 days post-operation	362.4±286.3	152.8±67.6	0.0001*
7 days post-operation	92.6±40.6	50.8±35.6	0.0001*

Statistical analyses were performed by t test. *P<0.05 means there is significant statistical difference between IP Group and Control Group.

Table 2B. AST levels in the two groups pre- and post-operation

Time	Control Group (n=223)	IP Group (n=235)	*P* value
Pre-operation	44.5±24.2	46.5±20.6	0.3406
1 day post-operation	343.3±275.1	256.1±189.6	0.0001*
3 days post-operation	467.8±268.5	168.1±135.6	0.0001*
5 days post-operation	310.3±196.6	102.1±98.6	0.0001*
7 days post-operation	85.6±45.4	59.1±40.6	0.0001*

Statistical analyses were performed by t test. *P<0.05 means there is significant statistical difference between IP Group and Control Group.

protective effect of the two procedures on the liver.

Patients and methods

Patients inclusion

From January 2001 to October 2014, approximately 700 patients who underwent liver resection at Xijing Hospital were retrospectively analyzed, and 458 were included in the study according to the inclusion criteria. From January 2001 to December 2005, the Pringle maneuver was primarily used for hepatic inflow occlusion, and 223 patients were assigned to the Pringle Group, which served as the Control Group. From January 2006 to October 2014, IP was performed instead of the Pringle maneuver in our department, and 235 patients were assigned to the IP Group. The inclusion criteria were as follows: The patients were diagnosed with primary hepatic carcinoma by pathology, radiography, and/or serum alpha fetoprotein (AFP), and several were also diagnosed with giant hemangioma, hepatolithiasis complicated by cirrhosis, or nodular cirrhosis by pathology/radiography.

The diameter of every tumor was greater than or equal to 5 cm because 5 cm tumors are likely to deteriorate the liver function of patients. Therefore, this tumor size could provide a good comparative condition for liver function recovery.

The liver cancer was not treated previously.

The Child-Pugh liver function scores were all Child A or Child B.

Liver function and other clinical indexes (including blood/urine routine, renal function, pulmo-

Table 3. TBIL between the two groups pre- and post-operation

Time	Control Group (n=223)	IP Group (n=235)	*P* value
Pre-operation	18.7±7.3	17.5±6.1	0.054
1 day post-operation	35.0±6.7	21.8±7.8	0.0001*
3 days post-operation	37.0±8.1	23.2±0.2	0.0001*
5 days post-operation	42.0±9.6	22.8±3.6	0.0001*
7 days post-operation	36.6±6.6	21.8±9.8	0.0001*

Statistical analyses were performed by t test. *P<0.05 means there is significant statistical difference between IP Group and Control Group.

Table 4. ALB between the two groups pre- and post-operation

Time	Control Group (n=223)	IP Group (n=235)	*P* value
Pre-operation	31.8±4.7	31.5±2.6	0.3953
1 day post-operation	31.4±5.1	30.5±4.5	0.0456*
3 days post-operation	31.2±4.5	30.4±4.4	0.0550
5 days post-operation	29.4±8.1	28.4±6.6	0.1473
7 days post-operation	31.5±5.1	30.1±7.6	0.0218*

Statistical analyses were performed by t test and chi-square test. *P<0.05 means there is statistical difference between IP Group and Control Group.

nary function, and EKG) were nearly complete. These indexes revealed no abnormalities.

Pringle maneuver (intermittent pringle occlusion): control group

After the abdomen was opened, the peritoneal cavity and liver were examined to ensure that there was no contraindication. The hepatic ligaments were cut as required to expose the view for surgery. Inflow occlusion was then performed via the Pringle maneuver for less than 20 minutes each time, followed by unclamping for 5 to 10 minutes. Approximately 1 to 4 occlusion/release periods were needed to complete the liver resection. As soon as the first hepatic portal was occluded, the surgery started. In all cases, liver resection was performed with an ultrasonic dissector, and bleeding was primarily stopped by electrocoagulation and clamp/ligation methods. Electrocoagulation, suture/ligation, and fibrin glue painting were used on the transection to ensure that there were no active bleeding points. The occlusion was then released.

Ischemic preconditioning: IP group

After the abdomen was opened, the peritoneal cavity and liver were examined to ensure that there was no contraindication. The surrounding and tightening method, in which the first hepatic portal was surrounded by a soft plastic tube, followed by tightening of the tube to occlude the inflow into the liver, was performed for the first hepatic portal occlusion. The occlusion lasted for 10 minutes, and the hepatic portal occlusion was then released for 10 minutes. Thus, the hepatic ligaments could be cut as required to expose the view for surgery for 20 minutes. The long-term occlusion was then completed. If the surgery could not be completed in 30 minutes, the first hepatic portal occlusion was released for 10 minutes prior to the second occlusion. Most surgeries were completed during the first or second occlusion. Electrocoagulation, suturing/ligation, and fibrin glue painting were used on the transection to ensure that there were no active bleeding points. The occlusion was subsequently released.

Intraoperative assessment

The peripheral blood pressure, central venous pressure (CVP), pulse oxygen saturation, and heart rate were routinely monitored. Blood loss (based on the volume in the suction apparatus and the weight of the gauze) was also recorded, as well as the transfusion volume of plasma and the number of red blood cell units transfused.

Postoperative management

Oxygen uptake was regularly applied in every patient for 48 hours. Supportive treatment, such as antibiotics, hemostasis, protection of liver function, and liquid supplementation, was administered as normal. Abdominal closed-suction draining was also routinely performed on each patient after hepatectomy. The color, trait, and volume of the drainage were observed. The temperature and peripheral hematologic index were additionally measured. Liver biochemistry was performed on postoperative days 1, 3, 5, and 7 to evaluate the injury and recovery of hepatic cells. The postoperative duration of hospital stay and complications were also recorded.

Table 5. Blood loss and transfusion volumes in the two groups during surgery

	Control Group (n=223)	IP Group (n=235)	*P* value
Blood loss (ml)	680±320.6	420±120.8	0.0001*
Transfusion of RBCs (u)	5.2±3.5	3.5±2.3	0.0001*
Occlusion time (minutes)	38±21	30±15	0.0001*

Statistical analyses were performed by t test. *P<0.05 means there is significant statistical difference between IP Group and Control Group.

Table 6. Complications and hospital stay duration between the two groups post-operation

	Control Group (n=223)	IP Group (n=235)	*P* value
Pulmonary infection	29	22	0.2757
Pleural effusion	26	29	0.9359
Sub-diaphragmatic effusion	21	18	0.6128
Biliary fistula	15	13	0.7352
Incision infection	9	10	0.9063
Death during surgery	0	0	-
Death post-operation	0	0	-
Hospital stay post-operation	16.2±3.5	15.5±3.6	0.0356*

Statistical analyses were performed by chi-square test and t test. *P<0.05 means there is significant statistical difference between IP Group and Control Group.

Statistical analysis

All calculations were performed with SPSS 10.0 software. The results are mostly expressed as medians and standard deviation. The chi-square test and t test were used to compare variables between groups. Statistical significance was defined as a *P* value less than 0.05.

The study was approved by the ethical committee of Xijing Hospital.

Results

There were no differences in general characteristics between the IP Group (n=223) and the Control Group (n=235) (**Table 1**).

On postoperative days 1, 3, 5, and 7, both the AST and ALT levels in the patients in the IP Group were significantly lower than in the Control Group (P<0.05) (**Table 2A** and **2B**). The TBIL levels had the same tendency (**Table 3**). Additionally, the ALB in the IP Group was higher than that in the Control Group, but there was a significant difference only at the 1st and 7th days; the difference was not significant at the 3rd and 5th days (**Table 4**).

The mean hepatic portal occlusion time for the patients in the IP Group was 30±15 minutes, with a maximum occlusion time of 45 minutes, and the mean volume of blood loss was 420±120.8 ml. For the patients in the Control Group, the mean hepatic portal occlusion time was 40±16 minutes, with a maximum occlusion time of 60 minutes, and the mean volume of blood loss in the Control Group was 680±320.6 ml (**Table 5**). No significant differences with respect to complications were observed between the groups, but the hospital stay duration were significant different (16.2±3.5 days versus 15.5±3.6 days) (**Table 6**).

Discussion

The control of bleeding during liver surgery contributes to the surgery's success, the safety of the patient, and recovery from the illness. The following methods are widely used to control bleeding during surgery: 1. The Pringle maneuver; 2. Intermittent occlusion of the first hepatic portal; 3. Total hepatic vascular occlusion (simultaneous inflow and outflow occlusion); 4. Selective inflow occlusion; 5. CVP control during liver resection (proper decrease in the CVP to reduce blood loss).

Of these methods, the third method is the most effective method to control bleeding during liver resection. However, this method may cause hemodynamic disorders in the liver or even the whole body and may also result in a high likelihood of complications and high mortality [5]. Therefore, this method is only suitable for a few patients who are in good hepatic and physical condition. The fourth method can protect the blood supply and function of the remaining part of the liver, but the first hepatic portal and its branch (the left and right hepatic arteries and the portal vein), and occasionally even the second or third hepatic portal, must be dissected when performing this method, which may increase the operative time and difficulty. This approach can also increase the volume of blood loss when the vessels are dissected prior to liver resection and hepatectomy. Finally, the fifth method must be coordinated with other bleeding control methods. Therefore,

due to its simplicity, effectiveness, and little influence on the hemodynamics of the liver and the patient, the first method, known as the Pringle maneuver, remains the most common technique with which to control bleeding during liver surgery [6].

Nearly 100 years ago, Pringle described a new technique to reduce blood loss during liver surgery [7]. Since that time, the Pringle maneuver has become a routine procedure [8] and a preferred method to avoid massive hemorrhage during partial liver resection for a large spectrum of non-malignant and malignant diseases.

Generally, 15 minutes is regarded as the limit for hepatic occlusion during liver surgery, although the longest continuous occlusion time that the first hepatic portal can withstand is 60 minutes under normal hepatic conditions. However, the option to extend the occlusion time during surgery has achieved inconsistent results in certain clinical trials. Beighiti et al [5] reported that several patients with different degrees of cirrhosis died postoperatively due to liver or renal failure because of a continuous hepatic portal occlusion time of more than 30 minutes during hepatic lobectomy. In a series of patients undergoing liver resection, the authors [9] also showed that intermittent clamping of the portal triad was better tolerated than continuous clamping was.

When the blood vessels of portal triad were clamped for periods longer than 10 minutes, which is necessary for institution of the Pringle maneuver, the clamping-induced vascular effects were the same. However, hemodynamic changes occurred as the result of reperfusion after the removal of clamping. The release of vasoactive substances such as prostaglandins (e.g., 6-keto-PGF1-alpha, thromboxane) or adenosine [10] has been proven to be the critical reason for post-reperfusion arterial hypotension. Arterial hypotension may further exacerbate reperfusion injuries because it reduces blood flow to the liver and thereby adversely affects the hepatic microcirculation. Along with the reduced blood flow, the decreasing metabolic ability may promote the development of liver dysfunction.

Because the mortality of traditional long-term hepatic portal occlusion can reach 5%, the resection time must be shortened when the Pringle maneuver is performed during hepatectomy. Therefore, dissection need not be performed carefully to ligate specific vessels. However, when the surgery is performed for large tumors or tumors in certain locations, careful dissection and a long first hepatic portal occlusion time are needed to avoid massive hemorrhage and protect important vessels. Recently, intermittent first hepatic portal occlusion (consisting of alternative sessions of clamping for 15 minutes and unclamping for 5 minutes, repeating until the end of hepatectomy) has been proposed. Using this method, the tolerance to ischemia can be improved, and the duration of the first hepatic portal occlusion can be extended, which can allow sufficient time for surgeons to complete a complicated liver surgery [6, 11]. However, the continuity of surgery must be broken because of the intermittent and repeated unclamping, resulting in longer operative times [12]. Thus, this method may not improve bleeding control during surgery and may even harm recovery after surgery.

Warm IP is performed with short-term occlusion followed by unclamping for short-term reperfusion just prior to complete occlusion of blood flow to the target organ. In the current study, IP was found to confer protection to the liver, as evidenced by decreased serum AST, ALT, and TBIL levels measured 1, 3, 5, and 7 days after surgery. A trend toward higher concentrations of transaminases (AST and ALT) in the IP patients than in the controls was specifically observed, and a similar trend was observed for TBIL. These biochemical indexes are currently the most sensitive markers of ischemic injury to the liver. Studying a variety of markers of injury in an isolated perfused rat liver model, Lu et al [13] demonstrated that AST release best correlates with the degree of ischemic injury. Most clinical studies have used transaminase levels to assess hepatic injury resulting from ischemia [9, 14, 15]. This procedure has been effective in alleviating warm ischemic injury and ischemia/reperfusion injury of the heart, skeletal muscles, and brain [16]. The results are exciting because IP was found to increase liver tolerance to ischemia/reperfusion during liver resection compared with the Pringle maneuver. Therefore, IP is expected to have more beneficial effects during

vascular exclusion of the liver, which is the least well-tolerated type of vascular clamping.

IP has mainly been described as a protective measure against hepatic ischemia/reperfusion injury in experimental models [17-19]. A rat model was studied by Figueira et al [20] and the results demonstrated that this experimental model is appropriate to determine the effects of IP on the hemodynamics of the portal vein during liver ischemia/reperfusion and that IP can promote the recovery of the portal vein flow and metabolic profile while lowering the level of liver transaminases. Additionally, the levels of AST and ALT began to decrease in the IP group compared with the control group at 12 hours after reperfusion. Peralta et al [21] showed that hepatic preconditioning preserves energy metabolism during subsequent ischemia and contributes to the maintenance of better anatomic and functional cellular integrity. In 2000, Clavien et al [12] first reported that warm IP prior to anatomical right or left hemihepatectomy could protect against ischemic injury and ischemia/reperfusion injury, decrease the blood loss and transfusion volumes, and alleviate the liver function injury caused by long periods of ischemia. The researchers also showed the clinical effectiveness of liver preconditioning and confirmed that apoptosis plays a central role in mediating cellular death through caspase-3 activation in human beings. These results demonstrated that IP (consisting of 10 minutes of occlusion and 10 minutes of reperfusion, followed by continuous inflow occlusion for exactly 30 minutes) can decrease the volumes of blood loss and transfusion during surgery. The researchers concluded that IP is a simple and effective modality for protecting the liver against subsequent prolonged periods of ischemia. This strategy may be a more attractive technique than intermittent inflow occlusion.

The mechanism involved in the protective effect of IP on target organs remains unclear. However, based on several primary studies and clinical trials, this mechanism is primarily associated with the following elements: 1. The metabolites of arachidonic acid (prostacyclin, thromboxane, and leukotrienes) [22, 23]; 2. Acidosis [24]; 3. The influx of calcium [25]; 4. Oxygen-derived free radicals [26]; 5. The apoptosis of sinusoidal endothelial cells caused by ischemia and ischemia/reperfusion injury. An animal model showed that IP can protect against liver ischemia/reperfusion injury via heme-oxygenase-1-mediated autophagy [27].

The warm IP technique has been comprehensively performed at our hospital since 2005 to extend the duration of the first hepatic portal occlusion. To ensure the safety of the patients in the current study, we preferentially selected patients with Grade A (Child-Pugh) liver function. Warm IP was then performed on these patients. The intraoperative and postoperative statuses of these patients were compared with those of the patients who underwent the Pringle maneuver and who had also had a similar hepatic condition in the past. In patients with Grade A liver function, warm IP (occlusion for 10 minutes, followed by unclamping for 10 minutes) improved ischemic tolerance in both the normal liver and under different pathological conditions of the liver (steatosis, fibrosis, and cirrhosis) and also extended the duration of the first hepatic portal occlusion. The longest occlusion time reached 45 minutes, occurring when irregular hepatic lobectomy was performed on a patient suffering from cirrhosis accompanied by liver cancer. Protective effects against ischemia/reperfusion injury in cirrhotic livers were demonstrated in the IP Group. Liver function damage in the IP Group was decreased compared with that in the Control Group. In particular, the main indexes, namely, AST, ALT, and TBIL, were significantly lower in the IP Group compared with the Control Group. The time to liver function recovery was also shorter. Importantly, the continuity of surgery can be maintained by IP because it allows sufficient time for surgeons to perform the dissection in detail and to ligate/devascularize the vessel system. Therefore, the blood loss and transfusion volumes decrease significantly. If the liver surgery cannot be completed in 45 minutes, the method (unclamping for 10 minutes and occlusion for 30 minutes) can be repeated. Surgery on the 8th segment for a large liver tumor resection occurred in our study, and a first hepatic portal occlusion was performed for 45 minutes. The cycle, consisting of 10 minutes of unclamping and 30 minutes of occlusion, was then repeated twice. The total occlusion time was more than 100 minutes, and the patient had good recovery. Although the results showed that IP could not decrease the complications in the present study, but the shortening of hospital stay duration, the improvement of

transaminase levels and the lower volumes of blood loss and transfusion demonstrated that IP may be beneficial to the recovery of hepatic perfusion and liver function.

Moreover, although the sample size was over 400 patients and the results were meaningful, it should be noted that all of the patients were comparatively selected from a single center. The surgeons' experience and the volume of cases operated on at this particular hospital may have affected the outcome measures to a certain degree, which may inevitably influence the potential generalizability of the results. Furthermore, the fact that the study was retrospective, rather than a randomized trial, poses a potential risk of selection bias. However, the grouping of patients depended on the procedure (IP or Pringle maneuver), rather than the outcomes, which may have decreased the influence of the selection bias.

In conclusion, even with the limitations of a retrospective study, the study indicates that IP provides better intraoperative hemodynamic stability and protection against ischemia/reperfusion injury. The clinical results demonstrate that the IP technique can improve tolerance to hepatic warm ischemia as a simple, effective, and safe method to control bleeding during liver surgery.

Disclosure of conflict of interest

None.

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