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ORIGINAL ARTICLE

Ischemic preconditioning provides no additive clinical value in liver resection of cirrhotic and non-cirrhotic patients under portal triad clamping: A prospective randomized controlled trial



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Summary

Background and objective: The clinical value of ischemic preconditioning (IP) on patients undergoing hepatectomy under portal triad clamping (PTC) is uncertain, especially for patients with liver cirrhosis. Hence, we conducted a prospective randomized controlled trial to test whether IP could protect liver against ischemic reperfusion (IR) injury after hepatectomy under PTC.

Method: One hundred patients, including 67 with cirrhosis, undergoing hepatectomy with PTC were randomly divided into IP and control groups. Liver function tests at postoperative days 1, 3, and 7 as well as postoperative morbidity, mortality, and duration of hospitalization were compared between the two groups.

Results: The general clinical characteristics between both groups were comparable. The duration of the operation, the amount of intraoperative blood loss, and the need and amount of perioperative blood transfusion were similar in both groups. The postoperative levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and albumin were not statistically different between the two groups. In addition, the morbidity and mortality rates and the duration of hospitalization were similar in both groups.

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Conclusions: IP did not improve liver tolerance to IR injury after hepatectomy under PTC. Therefore, the clinical use of IP cannot be recommended as a standard procedure before PTC.
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Introduction

Due to the advances in surgical techniques and perioperative care, the amounts of intraoperative blood loss during hepatectomy have been greatly reduced within the past two decades, and mortality rates are now less than 5% in centers with highly experienced personnel [1–3]. Although these advances permit hepatectomy with limited blood loss even without portal triad clamping (PTC) [4,5], PTC is still considered as an effective and simple technique to limit bleeding during hepatic parenchymal transection, and remains widely used during hepatectomies [6–9]. However, PTC can also cause ischemic and subsequent reperfusion injury to the remnant liver, especially in patients with severe underlying liver disease [10,11]. It is generally accepted that the cirrhotic liver is particularly sensitive to ischemic reperfusion (IR) injury [12,13]. Therefore, therapeutic modalities to ameliorate IR injury are critically important in liver surgery [14–16].

Several studies have confirmed that intermittent PTC is the only clinically established protective strategy against liver injury due to prolonged ischemia, and it is particularly indicated in patients with chronic liver diseases, such as steatosis, fibrosis, or cirrhosis, which are most susceptible to IR injury [17,18]. Ischemic preconditioning (IP) effectively decreases IR injury in animal models, but the results of human studies on IP during hepatectomy under PTC are controversial [19–30]. The routine use of IP in liver surgery is not recommended based on meta-analysis studies [31–33]. In addition, up until now, IP data have mostly focused on noncirrhotic cases [19–28]. In China and other Asian countries, more than 80% of hepatocellular carcinoma (HCC) patients have underlying cirrhosis or hepatitis due to hepatitis B virus infection [10,15]. All identified studies of IP excluded patients with cirrhosis, with the exception of two studies [29,30]. One study exclusively recruited cirrhotic patients and reported the significantly positive impact of IP on postoperative morbidity and aminotransferase levels [29], but its sample size was small and the PTC duration was less than 25 min. In the other study [30], Hahn et al. compared IP plus continuous PTC and intermittent PTC in 160 patients, including 60 with cirrhosis, and the results showed that cirrhotic patients with IP had significantly lower morbidity rates and shorter intensive care unit (ICU) durations and hospital stays. However, this favorable result could not demonstrate that IP directly alleviated IR injury, since the IP group had less blood loss than those treated with intermittent PTC [30].

Despite the benefit of IP in experimental studies, clinical trials have shown no significant clinical benefit and the availability of human studies of IP in cirrhotic patients is limited. Hence, we conducted this prospective randomized

controlled trial on unselected patients, either cirrhotic or not, to test whether IP could protect the liver against IR injury after hepatectomy under PTC. IR injury (primary end point of the study), liver function, morbidity, and mortality after hepatectomy were compared in control and preconditioned patients.

Patients and methods

Patients and study design

From January 2005 to January 2008, all patients requiring major or minor hepatectomy with PTC were included in the study. Patients were excluded if they were aged 17 years or younger or if they had obstructive jaundice. Patients were randomized into two groups, the IP and control groups. The characteristics of the two patient groups are shown in Table 1. In the IP group, liver resections were performed with PTC after IP. IP was performed as described previously [29], using the Pringle maneuver for 5 min followed by reperfusion for 5 min before PTC. In the control group, liver resections were performed using PTC without IP. Because most patients in our study had liver cirrhosis, intermittent PTC was performed by cycles of 15-min inflow occlusion followed by 5-min reperfusion for the patients whose duration of clamping was expected to exceed 20 min, in order to avoid irreversible IR injury [17]. The protocol was approved by the local ethics committee. Written informed consent was obtained from all patients. No patient dropout occurred after randomization.

Surgical procedure

After laparotomy, the liver was mobilized and the hilar structures were prepared. Randomization was performed intraoperatively using sealed envelopes (50 control group and 50 IP group), after an indication for hepatectomy under PTC was confirmed by inspection and intraoperative ultrasonography. The PTC was performed by placing a clamp on the hepatic artery and portal vein. The PTC was maintained until the liver resection was finished (control group). In the IP group, PTC was preceded by a brief period of ischemia (5 min) followed by 5 min of reperfusion. When a left hepatic artery arising from the left gastric artery was present, it was clamped during IP and PTC. Clamping of the infrahepatic inferior vena cava was performed when the tumor involved the major hepatic veins and inferior vena cava. Efforts were made to avoid fluid overload and to maintain low central venous pressure on unclamping. The parenchymal transection was initiated with the Kelly clamp crushing technique under vascular inflow occlusion. Small vessels or bile ducts

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