Ischemic Preconditioning Improves Postoperative Outcome after Liver Resections: A Randomized Controlled Study

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Abstract

Background: Clamping of the portal triad (Pringle maneuver) prevents blood loss during liver resection, but leads to liver injury upon reperfusion. Ischemic preconditioning (IP) has been shown to protect the liver against prolonged ischemic injury in animal models. However, the clinical value of this procedure has not yet been established.

Methods: 61 Patients undergoing hepatic resection under inflow occlusion were randomized to either to receive (Group-A n = 30) or not to receive (Group-B n = 31) an IP (10 minutes of ischemia followed 10 minutes of reperfusion).

Results: Mean (± SD)/ Group-A vs. Group-B. Pringle time of 34 ± 14 and 33 ± 12 minutes and the extent of resected liver tissue (2.7 ± 1.3 vs. 2.7 ± 1.1 segments) were comparable in both groups. Complications, including death, severe liver dysfunction and biliary leakage occurred in 6 patients of Group-A vs. 14 patients of Group-B (p<0.05). Intraoperative blood loss was significantly lower in Group-A (1.28 ± 0.91 l vs. 1.94 ± 0.76 l; p<0.001) with 5 vs. 15 patients requiring transfusions (p<0.01). In a multivariate analysis the duration of the Pringle maneuver (p<0.05) and the absence of preconditioning (p<0.05) were independent predictors for the occurrence of postoperative complications.

Conclusions: IP protects against reperfusion injury, reduces the incidence of complications after hepatic resection under inflow occlusion and is simple to use in clinical practice.

Introduction

Intraoperative blood loss is still a problem in human liver resection [1, 2]. Substantial bleeding during surgery is closely associated with higher postoperative complication rates [3] and, moreover, the need for autologous blood transfusion correlates well with earlier recurrence of malignancies [4]. The most common strategy to minimize bleeding during parenchymal transection consists of temporary clamping of the portal triad, i.e. inflow occlusion by the Pringle maneuver [5]. The duration of the ischemic period correlates with the release of liver enzymes after hepatectomy6, indicating substantial hepatocellular injury caused by the Pringle maneuver [7]. After declamping of the portal triad reperfusion of the remnant liver causes additional damage to parenchymal and non-parenchymal cells [8] which may cause the loss of functional integrity and consecutive hepatic failure. Although some liver resections can be performed without a Pringle maneuver, prolonged normothermic ischemia during human liver resection is frequently unavoidable to achieve radical tumor resection and may thus be responsible for enhanced postoperative morbidity and mortality [6, 9].

Though various strategies against the deleterious ischemia- reperfusion (I/R)- induced complications were suggested [10, 11], they have not been introduced in the field of hepatic surgery in humans. A successful experimental approach to reduce I/R- related injury in the myocardium was presented by Murry and co-workers [12]. In this landmark study the authors referred to "ischemic preconditioning" (IP) as an adaptation of the myocardium to ischemic stress induced by repetitive short periods of ischemia and reperfusion. Meanwhile, the findings of an intrinsic protective property of the myocardium have been confirmed in other organs, including the liver [13, 14]. In the animal liver, brief periods of ischemia and reperfusion (5-10 minutes) protected parenchymal and non- parenchymal cells after sustained warm ischemia [15] or hypothermic preservation [16]. Therefore, ischemic preconditioning appears to induce powerful protective mechanisms with potential benefit for patients undergoing hepatic resection.

To test this hypothesis, we conducted a prospective randomized study to evaluate the protective potential of ischemic preconditioning with regard to its feasibility in clinical routine and the outcome of patients, i.e. ischemia- related morbidity and mortality.

Methods

Patients and Randomization

From June 1999 to June 2000 a total of 116 patients underwent hepatic resection at our institution (Fig.1). Of these, 68 patients were randomly assigned to this
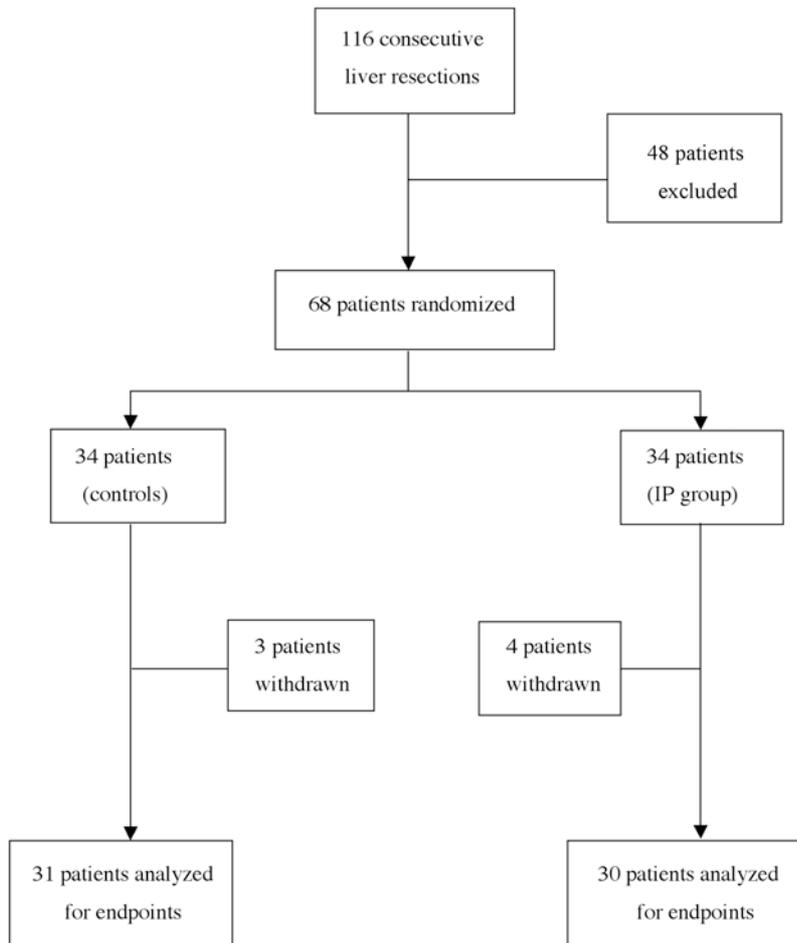
Fig. 1. Study profile (Details see text).

study. Eligibility criteria included major hepatectomies defined as the removal of more than one segment. Forty eight patients were excluded from randomization because of the following reasons: (I) extent of liver resection less than one segment according to Couinaud [17] (16 patients); (II) anticipated necessity of total vascular exclusion, i.e. clamping of the portal triad as well as of the venous outflow of the liver (8 patients); (III) necessity of additional surgical procedures such as bilio-enteric anastomosis or associated gastrointestinal procedures (3 patients); (IV) laparoscopic liver resection (10 patients); (V) underlying liver cirrhosis (9 patients); (VI) emergency surgery (2 patients). Of the 68 randomized patients 7 patients were withdrawn from analysis because of intraoperative detection of inoperability due to generalized liver metastasis (4 patients) or peritoneal carcinosis (3 patients). In these patients surgery was terminated without performing a hepatectomy. 61 Patients undergoing hepatic resection under continuous inflow occlusion (Pringle maneuver) were randomized to receive ischemic preconditioning Group-A (n = 30) or not to receive Group-B (n = 31). Ischemic preconditioning was performed through an inflow occlusion followed by 10 minutes of reperfusion prior to prolonged ischemia and transection of the liver. The study was approved by the local Ethics committee and written informed consent was obtained from each patient before randomization using sealed-envelope method.

STUDY DESIGN

The primary endpoint was the occurrence of ischemia-related complications during the hospital stay including postoperative death. The study had 80 % power to detect differences in complications of 50 %, with p ≤0.05. Secondary endpoints were intraoperative blood loss, serum levels of alanin- aminotransferase (ALT) and bilirubin concentrations on postoperative day 1.

All operations were performed under general anaesthesia according to a standardized protocol. After placement of an epidural catheter for peri- and postoperative analgesia with bupivacain patients were normoventilated with an air / oxygen mixture (FiO$_2$ 0.5) as well as the inhalative anaesthetic Desfluran (4-6 Vol%) following induction of anaesthesia with thiopental, cis-atracurium and fentanyl. Intraoperative blood loss was adequately substituted by infusion of crystalloid and colloidal solutions as well as by autotransfusion using a cell-saver device (CATS, Fresenius, Germany). Transfusion of red packed cells (RPC) was indicated either by hematocrit levels of < 0.25, or by online ST- segment analysis of the ECG, indicating the risk of myocardial ischemia. Decision for transfusion was made independently by the anaesthesiologist. Fresh frozen plasma (FFP) and platelets were only administered when haemostasis was severely disturbed. Body temperature was kept between 36.0 °C and 37.0 °C by continuous warming with a warm touch device.

All patients underwent surgery by an abdominal approach. Clamping of the portal triad (Pringle maneuver) was performed without affecting the bile duct. Transection was started immediately after inducing the Pringle maneuver which was maintained until the transection was finished. Parenchymal transection was performed by use of a water jet cutter [Saphir Medical, Lyon, France]. Haemostasis was secured by clipping of small vessels and bile ducts, major vascular structures were ligated with 4-0 monofil sutures. Minor bleedings from the liver cut surface were coagulated with the argon beam [Erbe, Tuebingen, Germany] and the transection area was covered with collagen fleece [TachoComb®, Germany]. The volume of blood loss was determined from the blood collected by the cell saver device as well as from the suction apparatus of the water jet. Blood- soaked gauze was wrung out and collected by the cell saver. The volume of irrigation fluid of the water jet was deducted accordingly. The volume of the resected liver was determined by the quantity of displaced fluid in a pre- filled trough. Operations were performed by four experienced abdominal surgeons.

Laboratory parameters of hepatocellular injury (ALT) and liver function (bilirubin) were obtained obligatory before operation and on postoperative days 1, 2 and 7. Nontumorous liver tissue which was adjacent to hepatic pathologies served as specimen for determination of the degree of steatosis and fibrosis of the liver. Severe hepatic dysfunction was defined as bilirubin levels >5 mg/dL and/or prothrombin activity <40% for at least 3 postoperative days. Fatal liver failure was defined as death from irreversible hepatic dysfunction (hepatic coma, massive detorioration of blood coagulation, progressive hyperbilirubinemia) in the absence of other causes, such as sepsis.

The diagnosis of biliary leakage was based on the postoperative findings of (1) drainage of bile from the abdominal wound or drain, (2) intraabdominal collection of bile confirmed at the time of re-operation or percutaneous drainage or (3) cholangiography. Leakage requiring intervention, such as puncture / drainage or reoperation was considered as major, leakage which spontaneously ceased as minor biliary complication.

STATISTICAL ANALYSIS

Numerical values are provided as mean and standard deviation unless otherwise noted. All significance tests were two- sided and a p- value of less than 0.05 was considered statistically significant. Data analysis was performed using SPSS 10.0 (SPSS Inc., Chicago, USA). Comparison between the two groups (with / without preconditioning) was performed using the Mann- Whitney- U- test, the chi- square test or the exact Fisher test, as appropriate. To analyze factors predicting blood loss multiple linear regression was applied. Multivariate analysis of complications was performed by means of logistic regression (backward selection). A multivariate analysis was performed by entering factors that appeared to be of significance on univariate analysis (P<0.2) into a COX proportional hazard model to test for significant effects while adjusting for multiple factors simultaneously.

RESULTS

BASELINE DATA

There were no differences of demographic data, intraoperative parameters and liver histology in both groups (Table 1).

INTRAOPERATIVE PARAMETERS AND POSTOPERATIVE COURSE

Intraoperative blood loss as well as the need for autologous transfusion were significantly lower in the Group-A with 17% of patients receiving blood transfusion versus 48% in the Group-B (p<0.006) (Table 2).

The postoperative course was uneventful in 24/30 patients in Group-A but only in 17/31 patients in Group-B (p<0.05) (Table 2). Two patients of the Group-B died due to progressive liver failure on postoperative days 12 and 25, respectively. Severe, but reversible liver dysfunction as previously defined occurred in one patient of the Group-A and in two patients of the Group-B (Table 2). There were no additional major complications in these patients and the laboratory parameters returned towards normal within 10 days following hepatectomy.

Minor biliary leakage ceased spontaneously in 4 of the 6 patients (67%) of the Group-B (Table 2). The other two patients had major biliary complications requiring re-operation and bilio-enteric anastomosis because of quantitative bile secretion from an injured hepatic duct. In the Group-A two patients showed bile secretion via the abdominal tubes for two and three postoperative days, respectively and were classified as minor biliary leakage. One patient required re-operation and bilio-enteric anastomosis. This major complication occurred after extended right hepatectomy and was probably due to injury of an abberant bile duct originating from the right posterior segment draining into the left duct. Furthermore, two patients of the Group-B had wound infection, one patient suffered from prolonged ascites and one patient developed infectious hematoma in the right upper abdomen which required puncture and drainage. One patient of the Group-A needed an immediate operation after 5 uneventful days following extended right hepatectomy because of duodenal ulcer perforation. Because of severe peritonitis this patient died 4 days later with sepsis and multi-organ failure. Another patient of the Group-A suffered from ascites which, however, ceased spontaneously within 10 days of surgery.

LABORATORY PARAMETERS

In the Group-A, markedly but not statistically significant decreased ALT levels on postoperative day 1 were observed when compared to the Group-B (Table 2) which normalized within seven days in both groups (Fig. 2). Serum bilirubin levels in the first seven days were not influenced by ischemic preconditioning (Table 2).

Predictors of intraoperative blood loss and postoperative morbidity

Table 1. Characteristics of the 61 patients with liver resection.

	Group-A With Preconditioning (N = 30)	Group-B Without preconditioning (N = 31)	p- Value

Age – yrs
  Mean
  Range
	
	57 ± 14
	26 - 81
		
		55 ± 13
		28 - 77
			
			0.61

Sex - no. Male / Female	 18 / 12	 19 / 12	 0.92
Tumor - no. Malignant / non Malignant	 26 / 4	 28 / 3	 0.65

Fibrosis of the liver - no.
  None
  Minor ($\mathcal{L}$ 10%)
  Moderate ($\mathcal{L}$ 40%)
	
	10
	15
	5
		
		12
		14
		5
			0.39

Steatosis of the liver - no.
  None
  Minor ($\mathcal{L}$ 25%)
  Moderate ($\mathcal{L}$ 50%)
  Severe ($\geq$ 50%)
	
	8
	16
	5
	1
		
		10
		14
		5
		2
			0.39

Operation time – min
  Mean
  Range
	
	260 ± 63
	170 - 420
		
		271 ± 58
		180 - 420
			
			0.36

Duration of Pringle´s maneuver - min.
  Mean
  Range
	
	34 ± 14
	15 - 82
		
		33 ± 12
		8 - 67
			
			0.70

Time for liver transection
  Mean
  Range
	
	30 ± 10
	10-50
		
		31 ± 11
		15-56
			
			0.83

Volume of resected liver - ml
  Mean
  Range
	
	390 ± 303
	80 - 1400
		
		426 ± 453
		30 - 2000
			
			0.77

Liver segments resected - no.
  Mean
  Range
	81
	2.7 ± 1.3
	1-5
		85
		2.7 ± 1.1
		1-5
			
			0.69

Hemihepatectomy* - no. (%)	9 (30)	10 (32)	0.85

* hemihepatectomies and extended hemihepatectomies

The variables that were significantly related to blood loss during surgery are shown in Table 3. Out of the six investigated parameters only treatment with ischemic preconditioning, the duration of hepatic inflow occlusion and the volume of the resected liver were independent predictors of intraoperative blood loss, suggesting ischemic preconditioning as an effective method to prevent bleeding during liver surgery. Variables which were predictive for the development of postoperative complications are given in Table 4. Of six investigated parameters only the duration of the Pringle maneuver and the procedure of ischemic preconditioning were factors, independently influencing the outcome of patients after hepatic resections.

DISCUSSION

The aim of this study was to investigate the value of ischemic preconditioning in the clinical practice of liver surgery. The main results obtained are that (1) ischemic preconditioning is feasible in clinical routine and (2) this procedure significantly improves the outcome of patients after liver resections under inflow occlusion.

During liver surgery in humans clamping of the portal triad (Pringle maneuver) is widely practiced to minimize intraoperative blood loss but can result in considerable liver damage [6, 8, 18]. Consequently, it has been generally accepted that periods of warm and cold ischemia of the liver should be shortened as

Table 2. Outcome parameters of surgery.

	Group-A With Preconditioning (N=30)	Group-B Without preconditioning (N=31)	p-Value

Intraoperative blood loss - ml
   Mean
   Range
	1280 ± 910
	260 - 5250
		1940 ± 760
		375 - 3375
			0.001

Transfusion of RPC Patients - no. (%)	5 (17)	15 (48)	0.006

RPC - Units
   Mean
   Range
	0.47±1.31
	0 - 6
		0.90 ± 1.24
		0 - 5
			0.014

Serum alanine amino-transferase - U/l
on day 1
   Mean
   Range
	247 ± 210
	45 - 852
		450 ± 650
		54 - 2888
			0.25

Serum bilirubin - mg/dl
on day 1
   Mean
   Range
	1.40 ± 1.26
	0.23 – 5.59
		1.44 ± 1.73
		0.4 – 9.83
			0.69

Postoperative complications - no. (%)
   Total
     Fatal liver failure
     Severe liver dysfunction
     Biliary leakage (Total)
     Major biliary leakage*
     Minor biliary leakage
     Other complications
	6 (20)
	0 (0)
	1 (3)
	3 (10)
	1
	2
	2‡ (7)
		14 (45)
		2 (6)
		2 (6)
		6 (19)
		2*
		4
		4 (13)
			0.04

Intensive care stay - days
   Mean
   Range
	2.43 ± 3.70
	0 - 16
		2.68 ± 5.57
		0 - 25
			0.43

* requiring re- operations; ‡ including one death

Table 3. Factors predicting intraoperative blood loss.

	Univariate Analysis p- value	Multivariate Analysis p- value
Patients age	0.35	—
Treatment with ischemic preconditioning	0.001	0.005
Duration of Pringle maneuver	0.015	0.02
Volume of resected liver	0.0003	0.001
Steatosis of the liver	0.31	—
Fibrosis of the liver	0.57	—

Table 4. Factors predicting occurrence of postoperative complications.

	Univariate Analysis p- value	Multivariate Analysis p- value
Patients age	0.41	—
Treatment with ischemic preconditioning	0.038	0.047
Duration of Pringle maneuver	0.043	0.022
Volume of resected liver	0.067	—
Steatosis of the liver	0.81	—
Fibrosis of the liver	0.94	—

much as possible [19-21]. Some experimental [22, 23] and clinical studies [1] suggested that intermittent clamping of the portal triad avoids the adverse effects of prolonged continuous warm ischemia on hepatic reperfusion injury. However, the most important problems associated with this more complicated procedure are increased blood loss during the episodes of reperfusion [1, 24, 25] and prolongation of operation
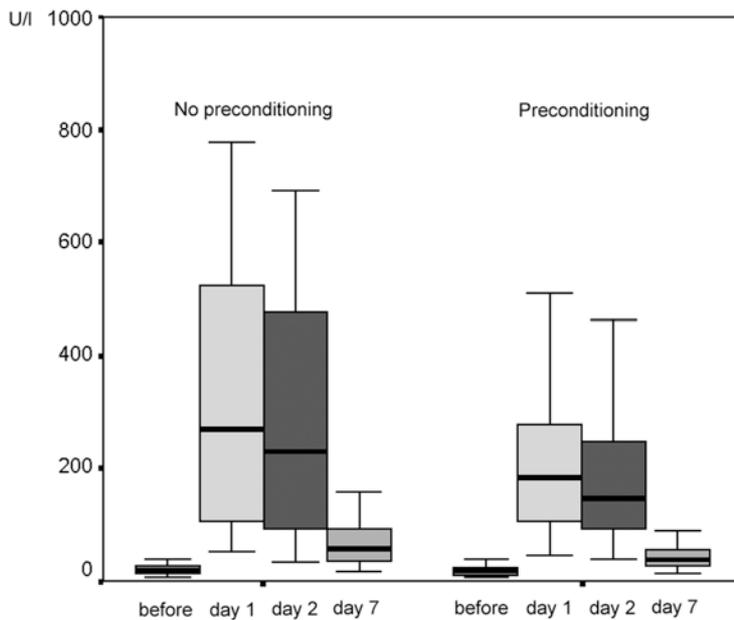
Fig. 2. Comparison of alanin- aminotransferase (ALT) levels in the serum of patients without (n = 31) and with ischemic preconditioning (n = 30) during hepatic resection. Pre- and postoperative values (days 1, 2 and 7) are presented by means of box- and- whisker plots, showing the 2.5,- 25,- 50,- 75- and 97.5% centiles of ALT. Reduction of ALT concentrations in the group with ischemic preconditioning did not reach significance.

time [24-26]. This may reduce the overall protective effect of repetitive clamping. Ischemic preconditioning seems to combine the beneficial effects on reperfusion injury with the avoidance of additional blood loss during surgery. Experimental data suggests that ischemic preconditioning is a biological adaptation of various cell types to sustained ischemic stress [14, 15]. Moreover, ischemic preconditioning of the animal liver is associated with better survival [13, 15, 27].

The prerequisite for the implementation of ischemic preconditioning to clinical routine are an easy and safe management during surgery as well as the effectiveness of liver protection following various extents of hepatectomies. Recently, a clinical study suggested that IP of the human liver may reduce I/R injury of livers which were subjected to hemihepatectomy under continuous inflow occlusion (Pringle maneuver) [28]. The main results of this study were a smaller increase of liver enzymes (ALT and AST) 24 h after surgery and a lesser number of apoptotic sinusoidal lining cells 30 minutes upon reperfusion. The authors concluded from these results that the pivotal mechanism of IP- mediated liver protection after I/R might be the preservation of sinusoidal endothelium. However, these interesting results cannot be applied to realistic clinical conditions of liver resection in humans. In this non- randomized, non- stratified study a single surgeon performed only hemihepatectomies under inflow occlusion fixed at 30 minutes independent of the transection times required in the individual patients. Therefore, the differences in morbidity found between the two groups do not allow conclusions to the routine clinical setting with clamping times ranging from some minutes to more than 1 hour and volumes of resected liver tissue from subsegments to extended hepatectomies. In our series the large variations of these parameters may have caused the wide range of postoperative ALT- concentrations, and thus preclude significance of differences in serum liver enzymes.

A main disadvantage of the aforementioned study [28] is the restriction of the study groups to only hemihepatectomies because these operations are usually performed without ischemia to the liver. In such procedures the transection line is predefined by the demarcation of the liver tissue following ligation of the corresponding branches of the hepatic artery and portal vein, respectively. Due to the segmental anatomy of the liver [17] major blood vessels and bile ducts are less frequently encountered along the transection line which additionally might reduce the complication rates. Therefore, we analyzed whether IP confers protection after liver resection other than hemihepatectomies, in particular because these operations are managed under inflow occlusion by the Pringle maneuver to a great extent.

In the present study ischemic preconditioning in patients undergoing various types of liver resection with the interval of inflow occlusion ranging between 8 and 82 minutes significantly reduced intraoperative blood loss by 33% and the number of patients requiring autologous blood transfusion from 48% to 17%. During liver resection blood loss is mainly related to intrahepatic venous bleeding [29, 30]. Therefore, a low central venous pressure (1-3 mm Hg) was maintained in all patients in this study during transection of the liver. Furthermore, parenchymal transection was identically performed with the water jet cutter in the control- and IP group. The observed reduction of blood loss following ischemic preconditioning might be attributed to an undisturbed local haemostasis at the cut surface of the liver, based on a protection of endothelial cells by IP, as reported [28, 31-33]. Consequently, in multivariate analysis, ischemic preconditioning was demonstrated as an independent predictive parameter for the amount of blood loss.

One of the most serious complications following liver resection is the development of liver failure [2, 3, 9]. In our series 2 patients of the Group-B died due to hepatic failure and 2 patients suffered from severe liver dysfunction whereas only 1 patient of the Group-A developed transient liver failure. Interestingly, all patients with liver failure in the Group-B underwent non-

hemihepatectomies, suggesting that segmental resections are more susceptible for complications. These results are in accordance with recent findings, demonstrating increased survival in animals subjected to ischemic preconditioning and subsequent warm ischemia of the liver when compared to a control group [15].

There were 6 biliary leakages in the Group-B but only 3 in the Group-A with 2 and 1, respectively of these classified as major biliary complications. Our meticulous record of biliary complications following surgery revealed a relatively large number of patients with transient bile secretion which contributed to postoperative morbidity. Based on retrospective studies, biliary complications after hepatic resection have been described in 2 – 8% [34, 35]. However, it was recently demonstrated that bile leaks occur in up to 18% following donor hepatectomy in living- related liver transplantation [36], a procedure which is only performed by experienced surgeons in specialized institutions. The relatively high incidence in the present series may be related to a thorough prospective documentation of even small amounts of bile in drainages, irrespective from the duration of its evidence (1 day – 12 days).

Since blood loss during surgery is an independent predictor for the development of postoperative complications [3] and ischemic preconditioning was shown to significantly influence the amount of intraoperative blood loss, this parameter was excluded from univariate and multivariate analysis when the postoperative morbidity was considered (Table 4). We found that pretreatment of patients with ischemic preconditioning significantly correlates with fewer complications after hepatic resection. Therefore, it can be concluded that the protective potential of ischemic preconditioning in liver surgery is not exclusively dependent on its beneficial effects on intraoperative blood loss. In some studies the operation time has been demonstrated to be a major factor influencing the occurrence of postoperative complications [33]. In contrast, the present study does not find significant differences between the two groups (Table 1). Ischemic preconditioning consisted of 10 minutes of ischemia followed by 10 minutes of reperfusion, adding an additional 20 minutes of operation time. During this period no manipulation was made in order to minimize additional insults to the liver. Taking this into consideration the net time for surgery in the Group-A was 240 ± 63 minutes compared to 271 ± 58 minutes in the Group-B (p <0.05). This shorter net time of surgery may be due to a shorter time necessary for haemostasis after liver transection. Independent from the overall- operation time it could be demonstrated that, besides the Pringle time only pretreatment with ischemic preconditioning is an independent protective parameter with regard to postoperative morbidity (Table 4).

In conclusion, this prospective randomized clinical study clearly demonstrates the beneficial effects of ischemic preconditioning in routine liver surgery under continuous inflow occlusion. Despite the relatively small number of patients, our novel findings suggest liver protection by ischemic preconditioning that helps to prevent ischemia- reperfusion- related morbidity in selected patients.

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