의 학 석 사 학 위 논 문

원격 허혈 전 조건화가 생체 간이식 기증자의 수술 후 간 기능에 미치는 영향

Effect of remote ischemic preconditioning on postoperative liver function in living liver donors: a randomized clinical trial

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이 논문을 의학석사 학위 논문으로 제출함.

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강지원의 의학석사 학위 논문을 인준함.

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Abstract

Background: Liver ischemia/reperfusion injury (IRI) is associated with poor outcomes after liver resection. In addition, hepatectomy itself can cause inflammation response and oxidative stress related to postoperative liver injury, hepatic regeneration. Remote ischemic preconditioning (RIPC) has been shown to have protective effects on liver IRI. However, the impact of RIPC focused on living donor has not been elucidated. In this study, we investigated the effects of RIPC on postoperative liver function in donors after living donor hepatectomy.

Methods: A total of 148 living liver donors were enrolled in this study. They were randomly assigned into two groups: Group I (Control, n=73) and Group II (RIPC, n=75). In the RIPC group, three cycles of 5-minute RIPC in the upper limb were performed before hepatectomy. Postoperative liver function test was assessed by measuring aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), and prothrombin time INR (PT_{INR}). The incidence of delayed recovery of hepatic function (DRHF), postoperative liver regeneration index (LRI) and postoperative complications were assessed during the first 7 postoperative days.

Results: RIPC group showed higher maximal and 3rd postoperative day PT INR (1.6 [1.5; 1.7] vs. 1.7 [1.6; 1.8], P= 0.045 and 1.5 [1.4; 1.6] vs. 1.6 [1.5; 1.6], P=0.047). However, there were no statistically significant differences in maximum AST, ALT, and total bilirubin values between the control group and the RIPC group (152.0 [129.0, 180.0] vs. 145.0 [118.5, 188.0], 152.0 [126.0, 196.0] vs. 148.0 [120.5, 197.0], and 2.7 [2.0; 3.2] vs. 2.4 [2.0; 3.0], P=0.568, P=0.775, and P=0.344, respectively). There was no statistically significant difference in LRI at postoperative 1 month (94.9 [61.4;131.2] vs. 83.3 [47.7;117.7], P=0.182). The incidence of DRHF was higher in the RIPC group (0% vs. 6.7%, *P*=0.074) without statistical significance.

Conclusion: RIPC has no effects on postoperative liver function in living liver donors.

Keywords: remote ischemic preconditioning, living donor, liver transplantation

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Introduction

Liver transplantation (LT) is the gold standard treatment for patients with end-stage liver disease[1]. Contrary to the western countries, where over 90% of transplantations are from cadaveric donors[2], living donor liver transplantation (LDLT) is the most common form of LT in east asia[3]. The safety of living donor remains important ethical issue because a healthy donor is exposed to low but definite risk of operative morbidity and mortality[4]. Ischemic reperfusion injury (IRI) occurs when the blood supply to organ or tissue is temporarily cut-off and then restored[5]. Inflow occlusion by clamping of the portal triad (Pringle maneuver) combined with a low central venous pressure (CVP) is widely applied to prevent blood loss during resection of the liver. It can cause ischemic-reperfusion injury to the remaining liver with a risk of poor postoperative outcome[6]. Furthermore, hepatectomy itself can cause systemic inflammation and oxidative stress[7] in addition to IRI. Both of them can lead to necrosis, apoptosis, impaired microvascular function, and edema by derivatives from oxygen-derived free radicals[8]. It may influence postoperative hepatobiliary problem or delayed recovery of donors.

Accordingly, many efforts were made to prevent against perioperative complications of LDLT donors. [5, 9-11] Stringent selection of the donor (with liver biopsy in many centers), preparation of the recipient, anti-inflammatory agents, ischemic preconditioning and avoidance of vascular clamping during procurement[12] are the examples. Although there were many attempts to ameliorate hepatic IRI and other injuries, there are no proven therapies for that.

Since Przyklenk et al.[13] suggested a concept of Remote ischemic preconditioning (RIPC) in myocardium, further animal studies subsequently reported. RIPC is a simple therapeutic method to lessen harmful effects of IRI[14, 15]. It indicates that brief episodes of ischemia with intermittent reperfusion are introduced at, for example, a limb, leading to systemic protection against subsequent insults as evinced on kidney, heart, liver, and other tissues[16-18].

RIPC has been shown to reduce hepatic IRI[9, 19], and also have beneficial effect for liver resection on several studies[6, 20, 21]. Although several studies have been performed about the effect of IPC of donor livers before retrieval, most of them were confined to deceased donor and graft function for

recipients[14, 15] and have not been always consistent[22]. Therefore, there are limited studies relating to the clinical trials concentrating in donor liver function.

Thus, our aim was to assess whether RIPC provide any beneficial clinical effect in donor liver function following living donor hepatectomy.

Methods

Study design and ethical approval

The single-center, double-blinded, randomized controlled study was approved by the institutional review board of the Asan Medical Center (2015-0851) and was registered with ClinicalTrials.gov (NCT03386435).

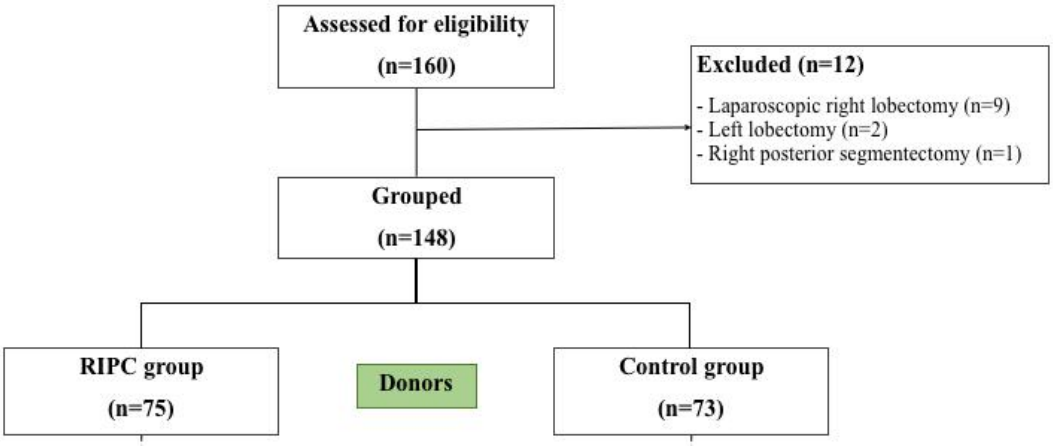
Sample size

The sample size was based on an estimation of the difference in maximal AST level within postoperative 7 days after following RIPC in living donor hepatectomy. After a pilot study we performed, total 160 participants (80 to each arm) are needed for sample size according to a power calculation including 10% dropout rate.

Patient selection

From August 2016 to July 2017, adult (18-60 years) liver donors scheduled for elective donor right hepatectomy were screened for eligibility at Asan Medical Center in Seoul, Korea. The major selection criteria for living liver donors at our institution[23)] is that the sum of macro- and microvesicular hepatic steatosis had to be < 30% and the left liver volume had to be > 35% of the whole liver volume for right lobe donation. One hundred and sixty patients were assessed for eligibility and among them, twelve donors were excluded which were underwent other than open right lobectomy (e.g., laparoscopic right lobectomy [n=9], right posterior segmentectomy [n=1], and left lobectomy [n=2]). Remained 148 donors were randomly assigned to either the RIPC group (n=75) or to the control group (n=73). For randomization, computer-generated random numbers were generated and stored in sealed envelopes which were opened following induction of anesthesia. Concealed envelopes that were opened up by an anesthesia nurse who was unaware of the study. A flow chart of the study patients is provided in Figure 1.

Figure 1. Flowchart of patient inclusion and exclusion.



Anesthetic Techniques

Standard American Society of Anesthesiologists monitoring was applied before anesthesia. The anesthetic management, patient care, and hemodynamic data recruitment for LT and donor right hepatectomy were performed according to the standard institutional protocol of Asan Medical Center, which was previously described in detail[24, 25]. Briefly, anesthesia was induced with propofol and rocuronium and maintained with desflurane and target-controlled infusion of remifentanil in donors. Mechanical ventilation was performed without positive end-expiratory pressure, using a constant tidal volume of 6-8 mL/kg and a respiratory rate of 10-12 breaths/min to maintain a constant end tidal carbon dioxide tension of 30-35 mmHg. After induction, arterial catheterization was performed for continuous blood pressure monitoring and the central venous catheter was inserted into the internal jugular vein to infuse fluid and monitor central venous pressure.

Intervention

RIPC was performed following anesthetic induction but prior to skin incision in donors. The protocol involves 3 cycles of 5-minute inflation of a 9 cm-width blood pressure cuff to 200 mm Hg to one upper arm, followed by 5-minute reperfusion with the cuff deflated. In the control group, the same maneuver was applied, but without cuff inflation. All interventions were performed by the anesthetic nurses, who were not involved in the study.

Data collection & Outcome measurement

In donors, plasma concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured on a daily basis within the first postoperative week to assess the extent of hepatocellular damage. Additionally, total bilirubin and prothrombin time international normalized ratio (PT INR) were collected. The postoperative liver regeneration index (LRI) at postoperative one month and the incidence of delayed recovery of hepatic function (DRHF) were used as surrogate parameters indicating the possible benefits of RIPC. The LRI was defined as $[(V_{LR} - V_{FLR})/V_{FLR})] \times 100$, where V_{LR} is the volume of the liver remnant and V_{FLR} is the volume of the future

liver remnant[24]. Liver volume was calculated by CT volumetry using 3-mm-thick dynamic CT images. The graft weight was subtracted from the total liver volume to define the future liver remnant. A Picture Archiving and Communication System (PACS; Petavision2, Asan Medical Center, Seoul, Korea), which is capable of image processing and various measurements, was used to calculate the liver volume. DRHF was defined based on a proposal by the International Study Group of Liver Surgery.[26] The International Study Group of Liver Surgery designated DRHF as follows: an impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased PT INR and concomitant hyperbilirubinemia (considering the normal limits of the local laboratory) on or after postoperative day 5. The normal upper limits of PT and bilirubin in our institutional laboratory were 1.30 INR and 1.2 mg/dL, respectively. If the INR of PT or serum bilirubin concentration was preoperatively elevated, DRHF was defined by an increasing the concentration of them on or after postoperative day 5 (compared with the values of the previous day).

Lastly, we also collected postoperative donor complication like pleural effusion, biloma, delayed extubation or re-operation in 7 postoperative days.

Statistical analysis

Data are presented as the mean ± standard deviation (SD), median (interquartile range), or frequency (percentages). Between-group differences in preoperative and intraoperative characteristics and postoperative outcomes were compared using the Chi-square test or Fisher exact test for categorical variables and the Student t test or Mann-Whitney U test for continuous variables, as appropriate. And $P<0.05$ was considered statistically significant and SPSS12.0 software was used in all statistical analysis.

Results

Patient Demographics

The demographic data and results of preoperative evaluation of donors are presented in Table 1. Between two donor groups, there was no difference in terms of demographic information such as age (p=0.444), gender (p=0.916), BMI (p=0.327) or ICG R15 (p=0.479). Intraoperative requirement of crystalloid or ephedrine injection was not significantly different in both groups (p=0.23, p=0.33). Preoperative AST and ALT were higher in RIPC group than control group (AST: 18.0 IU/L [16.0, 21.0] vs. 19.0 [18.0, 22.0], p = 0.036, ALT: 18.0 IU/L [16.0, 21.0], 19.0 IU/L [17.0, 23.0], p = 0.033). Other preoperative demographic variables did not significantly different between two groups.

TABLE 1. Patient Demographics and Preoperative and Intraoperative Characteristics

Donor characteristics	**Total (n = 148)**	**RIPC group (n = 75)**	**Control group (n = 73)**	***P***
Sex (male)	105 (70.9%)	54 (72.0%)	51 (69.9%)	0.916
Age (year)	29.0 [24.0, 35.0]	29.0 [24.0, 35.0]	28.0 [25.0, 35.0]	0.584
BMI (kg/m^2)	23.9 ± 2.7	23.7 ± 2.6	24.1 ± 2.7	0.327
Fatty change (%)	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]	0.743
ICG R15 (%)	11.5 [9.6, 14.1]	11.7 [9.6, 14.3]	11.3 [9.1, 13.8]	0.479
RLV (%)	35.2 ± 4.3	34.8 ± 4.3	35.6 ± 4.1	0.233
Preoperative laboratory data				
Hemoglobin (g/dL)	14.6 [13.6, 15.6]	14.5 [13.2, 15.2]	15.2 [13.8, 15.9]	0.030
Platelets (×10^3/μL)	257.5 [232.0, 286.0]	263.0 [233.5, 294.0]	252.0 [229.0, 279.0]	0.209
Prothrombin time INR	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.015
Total bilirubin (mg/dL)	0.6 [0.5, 0.9]	0.6 [0.5, 0.8]	0.6 [0.4, 0.9]	0.952
AST (IU/L)	19.0 [16.5, 21.5]	18.0 [16.0, 21.0]	19.0 [18.0, 22.0]	0.036
ALT (IU/L)	19.0 [16.0, 22.0]	18.0 [16.0, 21.0]	19.0 [17.0, 23.0]	0.033
Intraoperative variables				
Crystalloid (L)	2.8 ± 0.7	2.9 ± 0.7	2.8 ± 0.7	0.857
Use of ephedrine (%)	37 (25.0)	21 (28.0)	16 (21.9)	0.506
Ephedrine (mg)	0.0 [0.0, 2.5]	0.0 [0.0, 5.0]	0.0 [0.0, 0.0]	0.456
Duration of operation (min)	424.5 [384.0, 455.0]	424.0 [386.0, 463.5]	425.0 [381.0, 448.0]	0.494

Patient characteristics were compared using the *t* test, Mann-Whitney rank sum test, or chi-square test, as appropriate. Data are presented as number (%) or means ± standard deviation or median (1st quartile and 3rd quartile). Abbreviations: BMI, body mass index; ICG R15, indocyanine green retention test; RLV, remnant liver volume; INR, international normalized ratio; AST, aspartate transaminase; ALT, alanine transaminase; MELD, model for end-stage liver disease; GRWR, graft recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Donor outcome

There were no statistically significant differences in maximum AST, ALT, and total bilirubin values between the control group and the RIPC group (AST: 152.0 [129.0, 180.0] vs. 145.0 [118.5, 188.0], ALT: 152.0 [126.0, 196.0] vs. 148.0 [120.5, 197.0], total bilirubin: 2.7 [2.0; 3.2] vs. 2.4 [2.0; 3.0] *P*=0.568, *P*=0.775, and P=0.344, respectively) (Figure 2). However, RIPC group showed higher maximal and at 3rd postoperative day PT INR with statistical significance (1.6 [1.5; 1.7] vs. 1.7 [1.6; 1.8], P= 0.045, 1.5 [1.4; 1.6] vs. 1.6 [1.5; 1.6], P=0.047). Postoperative trend of laboratory data is shown in figure 2.

There was no statistically significant difference in LRI at postoperative 1 month (94.9 [61.4;131.2] vs. 83.3 [47.7;117.7], P=0.182) (Figure 3). The incidence of DRHF was higher in the RIPC group (0% vs. 6.7%, P=0.074) without statistical significance.

In postoperative period, pleural effusion occurred in 43 (58.9%) and 41 (54.7 %). At least one postoperative complication except pleural effusion occurred in 6 (8.2%) and 6 (8 %) donors in the control and RIPC group, respectively (P = 1.0). None of these complications were life-threatening and had no significant difference between two groups.

Figure 2. Serial changes in postoperative laboratory data in living donors.

A green colored-area means normal range of each parameters. (blue box, control group; red box, RIPC group). The box represents the interquartile range, and the line within the box is median value. The whiskers extend to the fifth percentile and 95th percentile values. *P < .05. MAX crude indicates maximal value within 7 postoperative days in crude data; POD, postoperative day; PT (INR), international normalized ratio of prothrombin time.

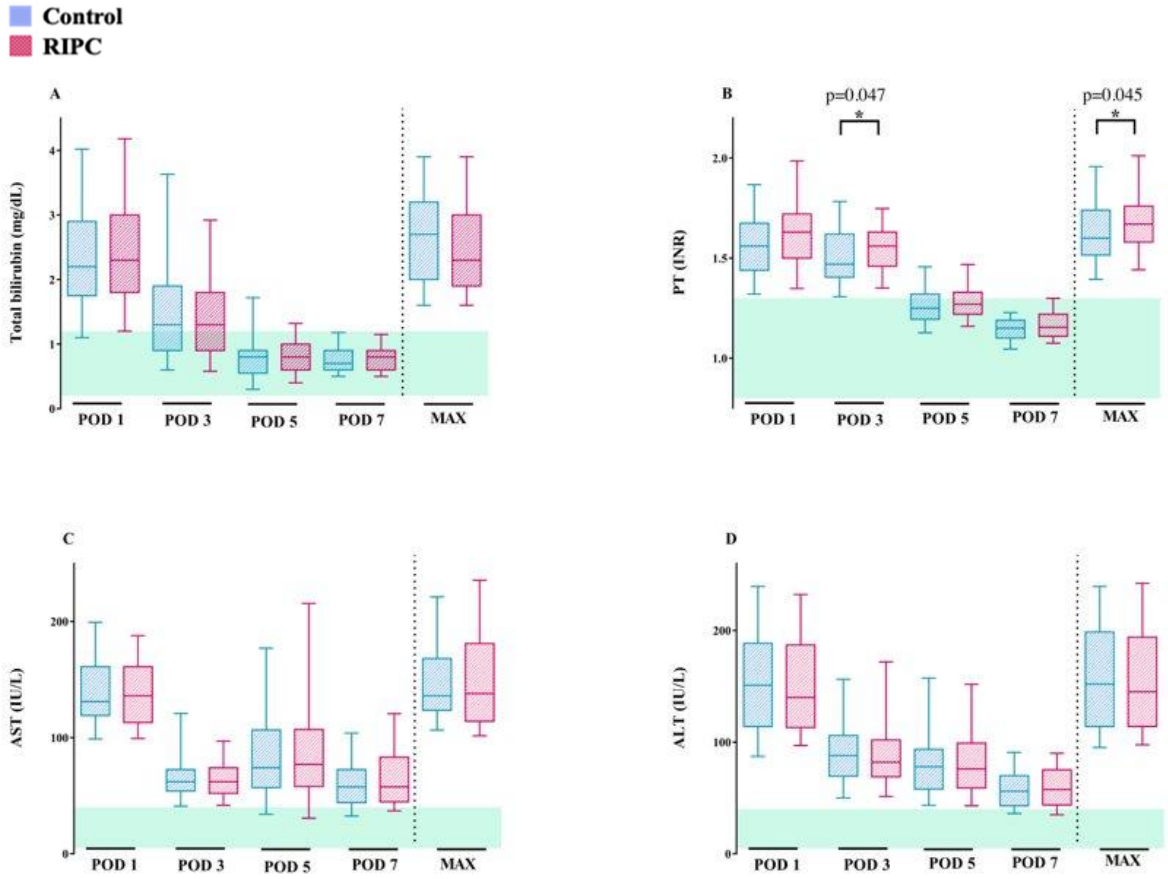


Figure 3. Distribution of liver regeneration index (LRI) between the control and RIPC groups.
The red thick solid horizontal lines represent median LRI values. The red thin horizontal lines indicate interquartile range. There was no significant difference between the two groups (P=0.182, Mann-Whitney rank sum test).

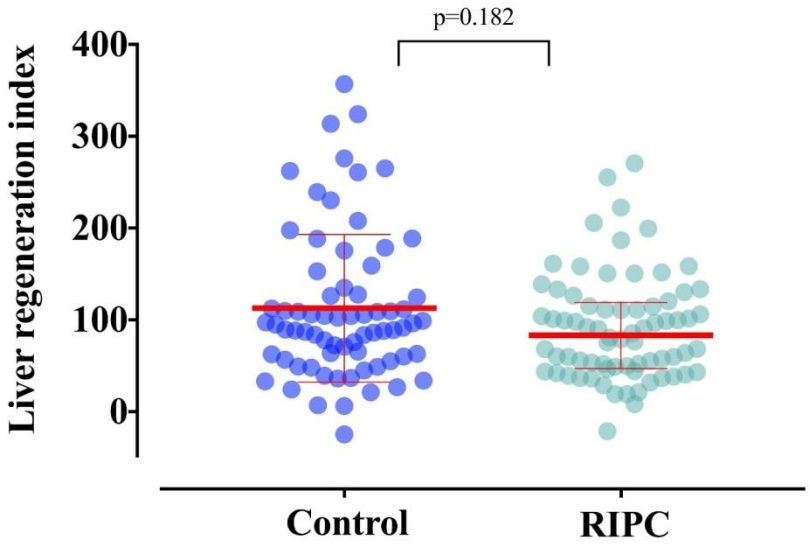


TABLE 2. LRI and DRHF of donors after living donor hepatectomy.

Donor	Total (n = 148)	RIPC (n = 75)	Control (n = 73)	***P***
LRI	90.2 [52.1, 126.3]	83.3 [47.7, 117.7]	94.9 [61.4, 131.2]	0.182
DRHF	5 (3.4)	5 (6.7)	0 (0)	0.074

Clinical outcomes were compared using the *t* test, Mann-Whitney rank sum test, or chi-square test, as appropriate. Data are presented as number (%) or median (1st quartile and 3rd quartile). LRI and GF were assessed at postoperative one month and one year, respectively. Abbreviations: LRI, liver regeneration index; DRHF, delayed recovery of liver function; EAD, early allograft dysfunction; GF, graft failure; AKI, acute kidney injury.

Discussion

Our results demonstrated that RIPC did not influence liver function test in living donor hepatectomy. And there was no difference in LRI and most of postoperative laboratory findings between two groups.

In recent study that investigated the effect of RIPC for hepatectomy indicated a significant protection with 50% reduction of the postoperative serum transaminases compared to control group[6]. Authors insisted it might be associated with the preservation of post-reperfusion ATP levels as suggested in many animal studies[27, 28]. In human, the results of cadaveric liver donor studies were controversial[29]. Some of them demonstrated a decreased hepatic injury represented as AST, ALT level[30], but recent meta-analysis study found no significant difference in mortality and primary graft function. Another randomized controlled trial on 44 LDLT [12] that was similar to our study design, haven't been shown any significant difference in severity of ischemic injury, morbidity and mortality between RIPC and control group. In addition, effect of ischemic preconditioning on liver regeneration is also reported in several studies. One study found that direct ischemic preconditioning impair liver regeneration[31]. In other study reported that RIPC can enhance liver regeneration in animal model and it may be mediated by interlekin-6[32, 33]. However, similar study in human was rarely investigated until now, then we found there is no relation between RIPC and liver regeneration index in living liver donor.

The negative findings in our results may be caused by several reasons. First, the negative effect of RIPC in this trial can be explained by surgical technique for living donor hepatectomy. To prevent ischemic liver injury and poor outcome, the procedure including vascular clamping like pringle maneuver has been diminished.[1]. Additionally, living donors are healthy people without systemic disease. As postoperative deleterious outcome of donors is rarely occurred, it is hard to compare the difference in postoperative hepatic function. Some studies have been shown that RIPC effect is more prominent in diseased liver like steatosis[6]. Third, anesthetic method can affect RIPC effect related with ischemia reperfusion injury. Contrary to propofol, known to attenuate the effect of RIPC[34, 35], inhalation anesthetic agent like desflurane, sevoflurane may have protective effect against IRI[36] by

activation of signal pathway related to various protein kinase, ATP sensitive potassium channel. However, if RIPC and inhalation agent are used at the same time, it is unclear whether RIPC and inhalation agent could act as additive[37]. In one meta-analysis, they found significant relation between inhalant and attenuated RIPC response[38]. As desflurane was used in this study, there is a possibility that inhalant weakened protective effect of RIPC. Lastly, the effectiveness of RIPC strategies in animal model has a limitation to extrapolate to human because the ability of tissues to respond to the beneficial effects of ischemic conditioning may be different from distinction of species and heterogeneity of age, environment or diet in human group other than animal model [39]

Some limitations exist in this study. First, there are several compounding factors that interfere with protective effect on ischemic reperfusion injury in contrary to well-defined animal study model[29]. In addition, there is no standard protocol of remote ischemic preconditioning, such as number of cycles, duration, location, maximum pressure, cuff width, type of cuff device[40]. Lastly, the number of donors might be not sufficient to compare the effect of RIPC.

So it is expected to perform the large study controlled with compounding variables in future study. It is also necessary to establish standard RIPC protocol among various methods.

In conclusion, RIPC does not have demonstrate protective effect on postoperative liver function or regeneration after living donor hepatectomy.

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Abstract (Korean)

서론: 허혈-재관류 손상은 간 절제 이후 악화된 예후와 연관되어 있다고 알려져 있으며 간 절제 자체도 염증반응과 산화 스트레스를 유발해 수술 후 간 손상 및 재생에 영향을 줄 수 있다. 원격 허혈 전 조건화는 간의 허혈-재관류 손상에 대한 보호 효과를 갖는다고 밝혀졌으나, 현재까지 생체 간 기증자에 초점을 맞춘 원격 허혈 전 조건화 연구는 잘 알려져 있지 않았다. 따라서 본 연구에서는 원격 허혈 전 조건화가 생체 간이식 기증자에게 미치는 영향을 알아보고자 한다.

연구 대상 및 방법: 총 148 명의 생체 간이식 기증자를 대상으로 이중 맹검, 무작위 대조 연구를 시행하였다. 이들은 무작위로 2 가지 그룹에 배치되었고 대조군 73 명, 원격 허혈 전 조건화군(치료군) 75 명으로 나뉘었다. 치료군 에서는 상완에서 압력계를 이용해 각 5 분 간 3 회의 원격 허혈 전 조건화를 마취유도 후, 간 절제 전에 시행하였고, 대조군 에서는 상완에 압력계만 감아둔 상태로 이를 시행하지 않았다. 수술 후 첫 7 일 동안 AST, ALT, 총빌리루빈, PT_{INR} 등을 통해 간 기능을 평가하였으며, 간 기능 회복 지연 (delayed recovery of hepatic function)의 발생률과 술 후 1 개월의 간 재생 지수 및 술 후 합병증 등을 살펴보았다.

결과: 수술후 AST, ALT, 총 빌리루빈 의 최대값은 두군 간에 통계적으로 유의한 차이가 없었다. (152.0 [129.0, 180.0] vs. 145.0 [118.5, 188.0], and 152.0 [126.0, 196.0] vs. 148.0 [120.5, 197.0], 2.7 [2.0; 3.2] vs. 2.4 [2.0; 3.0] P=0.568, P=0.775, and P=0.344 respectively). 그러나 수술 후 3 일째의 PT_{INR} 값 및 7 일중 최대값은 RIPC 군에서 통계적으로 유의하게 높은 값을 보였다 (1.6 [1.5; 1.7] vs. 1.7 [1.6; 1.8], P= 0.045, 1.5 [1.4; 1.6] vs. 1.6 [1.5; 1.6], P=0.047). 간 기능 회복 지연 발생률은 경계 수준의 유의성을 갖고 RIPC 군에서 높은 결과를 나타내었으며 술 후 1 개월에 측정한 간 재생 지수는 유의한 차이가 없었다 (94.9 [61.4;131.2] vs. 83.3 [47.7;117.7], P=0.182).

결론: 원격 허혈 전 조건화는 생체 간 기증자의 수술 후 간 기능, 간 재생 지수에 영향을 미치지 않는다.

핵심어: 원격 허혈 전 조건화, 생체 간 이식, 생체 장기 기증자