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Low Central Venous Pressure with Milrinone During Living Donor Hepatectomy

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Maintaining a low central venous pressure (CVP) has been frequently used in liver resections to reduce blood loss. However, decreased preload carries potential risks such as hemodynamic instability. We hypothesized that a low CVP with milrinone would provide a better surgical environment and hemodynamic stability during living donor hepatectomy. Thirty-eight healthy adult liver donors were randomized to receive either milrinone (milrinone group, n = 19) or normal saline (control group, n = 19) infusion during liver resection. The surgical field was assessed using a four-point scale. Intraoperative vital signs, blood loss, the use of vasopressors and diuretics and postoperative laboratory data were compared between groups. The milrinone group showed a superior surgical field ($p < 0.001$) and less blood loss (142 ± 129 mL vs. 378 ± 167 mL, $p < 0.001$). Vital signs were well maintained in both groups but the milrinone group required smaller amounts of vasopressors and less-frequent diuretics to maintain a low CVP. The milrinone group also showed a more rapid recovery pattern after surgery. Milrinone-induced low CVP improves the surgical field with less blood loss during living donor hepatectomy and also has favorable effects on intraoperative hemodynamics and postoperative recovery.

Key words: Central venous pressure, living donor hepatectomy, milrinone, surgical field

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Introduction

Recent advances in surgical techniques/equipment and intraoperative management have made living donor hepatectomy a relatively safe operation with minimal blood loss (1,2). In spite of some controversies (3), maintaining a low central venous pressure (CVP) is thought to be an important management aspect of liver resection based on reports that suggested an association between low CVP and less blood loss during liver resection (4,5). Low CVP during liver resection is thought to reduce blood loss by sequentially enhancing venous drainage from the hepatic sinusoids resulting in less venous backflow. The goal of maintaining a low CVP during living donor hepatectomy is to reduce blood loss and as a result, increase the chance of a better surgical field.

However, conventional low CVP technique with the use of fluid restriction has several problems that add to the anesthesiologists' workload. The reduction in effective circulating volume increases the chance of hemodynamic instability and requires frequent use of vasopressors. Maintaining a low CVP often requires additional vasodilators or diuretics, especially in healthy living donors. The risk of inadequate perfusion of end organs is another potential problem.

In this study, we attempted to evaluate the vasodilatory, inotropic and lusitropic (6) effects of milrinone on living donor hepatectomy. To test the hypothesis that maintaining a low CVP with milrinone during living donor hepatectomy would improve the surgical field and provide hemodynamic stability with less effort, we performed a randomized controlled trial.

Materials and Methods

Donor selection and randomization

After obtaining informed consent, 38 living liver donors, scheduled for donor hepatectomy at Seoul National University Hospital from January to December 2008, were enrolled in this prospective, randomized, placebo-controlled, double-blinded study. Donors were evaluated and selected according to the recently published international guidelines (7). According to the study protocol approved by the institutional review board, patients were randomized into two groups using an Excel program-generated randomization table, the milrinone group and the control (normal saline) group.

Study protocol

Under standard monitoring, anesthesia was induced with 1.5 mg/kg of propofol, 100 mcg of fentanyl and 0.6 mg/kg of rocuronium. Under the discretion of the anesthesia provider, 30 mg of esmolol was used in donors anticipated to be tachycardic after intubation. Anesthesia was maintained with sevoflurane and 50% oxygen in air, and intermittent bolus of vecuronium. Mechanical ventilation was initiated using a tidal volume of 8 mL/kg with a frequency 10/min to maintain normocarbia. An arterial line was inserted to the radial artery and was connected to the Vigileo® cardiac output (CO) monitor (Edwards Lifesciences LLC, Irvine, CA), which measured arterial pressure and CO. A double lumen central venous catheter was also inserted into the right internal jugular vein. Either milrinone or normal saline

was administered once the peritoneum was fully open. In the milrinone group, 12.5 mcg/kg of milrinone was administered over 10 min as a loading dose and thereafter, maintenance infusion was continued at a rate of 0.5 mcg/kg/min until the liver graft was resected. In the control group, normal saline was infused in the same fashion as the milrinone group. Both the anesthesia provider and surgeons were blinded from the study groups.

Surgical procedure and intraoperative management

All donor hepatectomies were performed by the same operator and first assistant and managed by a single anesthesia supervisor.

Donors were scheduled to undergo left lateral segmentectomy, conventional left or right hepatectomy or modified extended right hepatectomy, depending on the appropriate liver mass required for the recipient. Hepatectomy was performed by ligation of arteries and veins with Hem-o-lock clips or hand ties, parenchymal resection using ultrasonic aspirator (CUSA EXcel, Valleylab Corp., Boulder, CO) and hemostasis with bipolar electrocautery.

The operating table was in a horizontal position except side tilt throughout the duration of surgery. The reference point for CVP measurements was at the level of four-fifths of the antero-posterior diameter of the thorax from the back (8). During donor hepatectomy, the anesthesia provider was asked to maintain the CVP at 5 mmHg or less primarily by restricting intravenous fluids. If the CVP exceeded 6 mmHg at the time of hilar dissection, 10 mg of furosemide was administered. The target mean arterial pressure was above 60 mmHg, and 5 mg of ephedrine was administered to restore pressure when the mean arterial pressure fell below 60 mmHg.

Morphine and fentanyl based intravenous patient-controlled analgesia was used for postoperative pain control.

Data acquisition

The primary outcome of interest was the condition of the surgical field during liver resection and secondary outcomes of interest included hemodynamic stability and the ease of maintaining a low CVP by measuring the frequency and dose of vasopressors and diuretics, respectively.

The attending surgeon and the first assistant were blinded from the study groups and gave independent assessments of the condition of the surgical field during liver resection using a four-point grading scale (Table 1) and the grades were averaged. The surgical field grading was performed by comprehensively assessing the degree of bleeding, tension of the inferior vena cava and hepatic veins, and ease of operability. Blood loss was estimated by measuring collected blood in the bottle, weighing the wet gauzes and visual evaluation of the surgical field. The total amount of fluid and drugs administered, duration of anesthesia and surgery and urine output were also recorded.

Table 1: Grading criteria for evaluating the surgical field

Grade	Description
I	Very lax IVC[1] and hepatic veins, minimal bleeding at resection plane, very easy to operate
II	Lax IVC and hepatic veins, a little bleeding at resection plane, easy to operate
III	Tense IVC and hepatic veins, appreciable bleeding at resection plane, somewhat difficult to operate
IV	Very tense IVC and hepatic veins, profuse bleeding at resection plane, very difficult to operate

IVC = inferior vena cava.

Hemodynamic data, including heart rate, systolic, diastolic, and mean arterial pressures and CO, were recorded at the following six time points: before milrinone/normal saline loading (BL), after milrinone/normal saline loading (AL), just before initiation of liver resection (BR), midway through liver resection (MR), just after completion of liver resection (AR) and when the peritoneal closure started (CL).

Blood samples were taken before surgery, immediately after surgery and at postoperative days 1, 3, 7 and 21. Measured items include hemoglobin, prothrombin time as INR, serum albumin, serum total bilirubin, blood urea nitrogen, serum creatinine and serum aminotransferases.

Sample size calculation and statistical analyses

Using a pilot study performed to assess the effect of milrinone on the surgical field condition using four-point scale (Table 1), sample size estimation was performed to detect any significant difference between groups with a type I error of 0.05 and a power of 0.8. It was calculated that a total number of 34 donors (17 donors per group) were required. Expecting a dropout rate of 10%, we aimed for enrolling 19 donors per group.

All statistical analyses were performed using SPSS software (version 12, SPSS Inc., Chicago, IL). Surgical field grades were compared with Wilcoxon rank sum test between groups. Interobserver variability between the attending surgeon and first assistant was assessed using the Kappa statistic. Group characteristics and intraoperative data were compared with unpaired *t*-test or chi-square test between groups. Hemodynamic data and laboratory values were compared with repeated measures ANOVA and unpaired *t*-test if any significant difference was found between groups. Paired *t*-tests with Bonferroni correction for multiple comparison were performed to detect any significant changes from baseline (preoperative) values. Values are expressed as mean $\pm$ SD or absolute numbers. A p-value < 0.05 was considered significant.

Results

The enrollment, randomization and analysis process is summarized in Figure 1. All living donors who were enrolled in our study were classified as American Society of Anesthesiologists (ASA) class I. Of the 38 donors randomized, 1 donor in the milrinone group was excluded from the analysis due to an accidental hepatic vein rupture during hilar dissection. Donor characteristics and types of surgery were comparable between the two groups (Table 2).

Surgical field grading was significantly better with less intraoperative bleeding in the milrinone group compared to the control group ($p < 0.001$) (Tables 3 and 4). A kappa statistic of 0.644 (95% CI 0.423–0.865, $p < 0.001$) revealed substantial agreement between the two surgeons. Hemodynamic changes were similar between the two groups (Figure 2). However, more donors in the control group required the use of furosemide to maintain a low CVP and the dose of ephedrine required for blood pressure support was also higher in the control group (Table 4). None of the donors received blood transfusion during or after surgery.

Both groups showed a similar trend in hemoglobin, serum albumin and serum bilirubin levels. The milrinone group showed lower levels of prothrombin time and serum

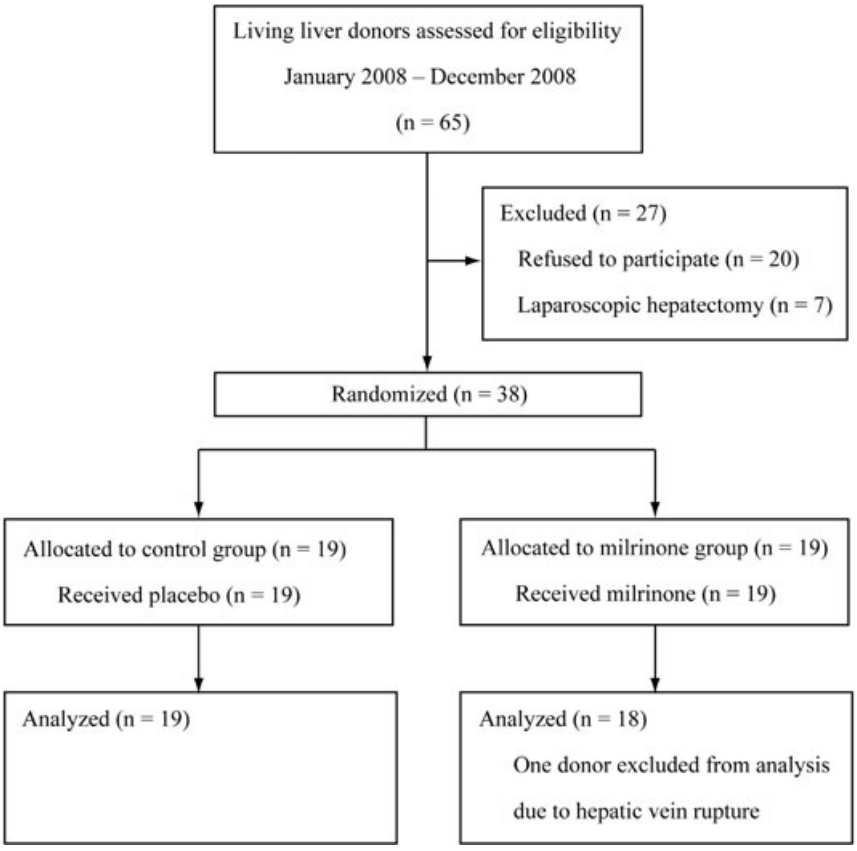

Figure 1. CONSORT flow diagram. CONSORT = Consolidated Standards of Reporting Trials.

aminotransferases on postoperative days 1 or 3 (Figure 3). Postoperative blood urea nitrogen and serum creatinine levels were within normal limits and did not differ from preoperative levels in both groups. All the donors in both groups were discharged without any major complications in 10 ± 2 days.

Discussion

Our study shows that infusion of milrinone during living donor hepatectomy was associated with (1) significantly improved surgical field with less blood loss, (2) maintenance of low CVP with less use of diuretics, (3) stable hemodynamic profile with less amount of vasopressors and (4) a more favorable recovery pattern in the immediate postoperative period, compared to the conventional low CVP technique.

CVP or inferior vena caval pressure of 5 mmHg or less has been reported to play a key role in reducing intraoperative blood loss and transfusion requirements during liver resection (4,9). The suggested mechanism was that decreased right atrial pressure sequentially enhances venous drainage from the inferior vena cava (IVC), hepatic vein and hepatic sinusoids, and thereby reduces bleeding from the resection plane caused by venous backflow. However,

Table 2: Donor characteristics and type of surgery

Group	Control (n = 19)	Milrinone (n = 18)
Sex (M/F)	18/1	15/3
Age (years)	26 ± 9	29 ± 11
Height (cm)	171 ± 7	168 ± 7
Weight (kg)	69 ± 8	66 ± 8
Type of surgery	Right lobectomy (18) Extended right lobectomy (1)	Right lobectomy (15) Extended right lobectomy (1) Left lobectomy (1) Left lateral segmentectomy (1)

Values are expressed as numbers or mean ± SD.

Table 3: Grade of surgical field

Grade	I	II	III	IV
Control group (n = 19)	2	18	17	1
Milrinone group* (n = 18)	17	18	1	0

Values are expressed as numbers.
Each donor was graded by the attending physician and first assistant independently.
Interobserver variability: $\kappa = 0.644$ (95% CI 0.423–0.865, $P < 0.001$).
* $p < 0.05$ compared to control group.

Table 4: Intraoperative data

Group	Control (n = 19)	Milrinone (n = 18)
Estimated blood loss (mL)	378 ± 167	142 ± 129*
Duration of anesthesia (min)	309 ± 33	312 ± 30
Duration of surgery (min)	265 ± 25	263 ± 33
Duration of graft resection (min)	67 ± 15	71 ± 20
Infused fluids (mL)	1966 ± 607	2045 ± 497
Urine output (mL)	853 ± 408	228 ± 108*
Donors requiring furosemide	18/19	1/18*
Donors requiring ephedrine	9/19	8/18
Dose of ephedrine (mg)	6.3 ± 8.1	2.2 ± 2.6*

Values are expressed as mean ± SD or numbers.
*$p < 0.05$ compared to control group.

conventional low CVP techniques such as fluid restriction frequently cause hemodynamic instability. Furthermore, volume restriction alone takes time and often fails to lower CVP before liver resection starts especially in healthy living donors and thus, as seen in our control group, frequently requires diuretics and vasopressors. Our study shows that infusion of milrinone, a drug with inotropic and vasodilatory effects, quickly achieved both hemodynamic stability and low CVP.

The basic mechanism of milrinone is inhibition of cellular phosphodiesterase III leading to recruitment of cyclic 3′,5′-adenosine monophosphate (cAMP), which modulates calcium channel activities in vascular smooth muscles and cardiac myocytes. In spite of potent systemic arterial vasodilation, systemic arterial pressure is usually maintained because milrinone improves cardiac performance by inotropic (increased cardiac contractility) and lusitropic (enhanced diastolic relaxation of the heart) actions (6). From the hepatic resection perspective, positive lusitropy is a favorable property because it acts as a driving force that enhances venous drainage from the IVC, the hepatic vein and sinusoids sequentially. This result in less hepatic congestion and increased cardiac preload compared to the conventional low CVP technique, in which pressure gradient is the sole factor of hepatic venous drainage and cardiac filling. These effects of milrinone are helpful during general anesthesia because most volatile anesthetics results in systolic and diastolic dysfunctions at higher analgesic concentrations (10). Finally, increased CO with maintenance of arterial pressure contributes to the increase of renal blood flow (11).

Although clinical significance is undetermined, another potential benefit of milrinone was shown by the more rapid recovery of prothrombin time and liver enzymes. There are three possible explanations. First, several animal studies demonstrated a hepatoprotective effect of milrinone on ischemia/reperfusion injury. The proposed mechanisms were an increase in intracellular cAMP and subsequent activation of protein kinase A (12–14). The results of these reports and our study suggest a possible role of milrinone as a pharmacologic preconditioning agent for living donors. Second, the difference in recovery speed may be due to more meticulous surgery facilitated by the clean and dry surgical field. Third, simultaneous maintenance of CO and systemic arterial pressure contributes to the increase of total hepatic flow (15), and this increase in hepatic perfusion might have improved hepatic metabolism in the residual liver after donor hepatectomy.

Although well tolerated, milrinone has a few reported adverse effects. A high intravenous loading dose frequently result in transient hypotension, which is avoidable by omitting the loading dose, although hemodynamic effects are

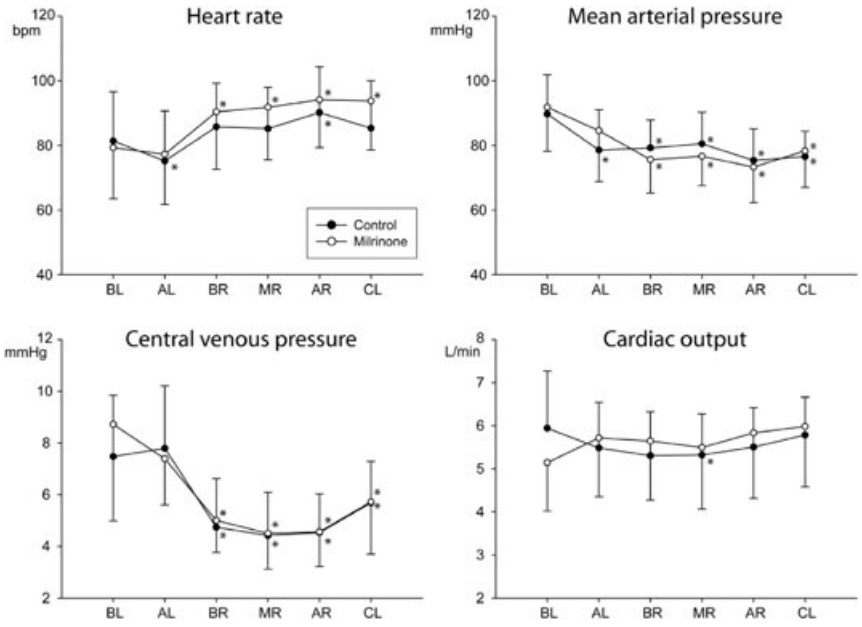

Figure 2. Hemodynamic changes during living donor hepatectomy. *$p < 0.05$ compared to baseline (BL) value. Abbreviations: BL = before loading milrinone; AL = after loading; BR = before resection; MR = mid-resection; AR = after resection; CL = closure

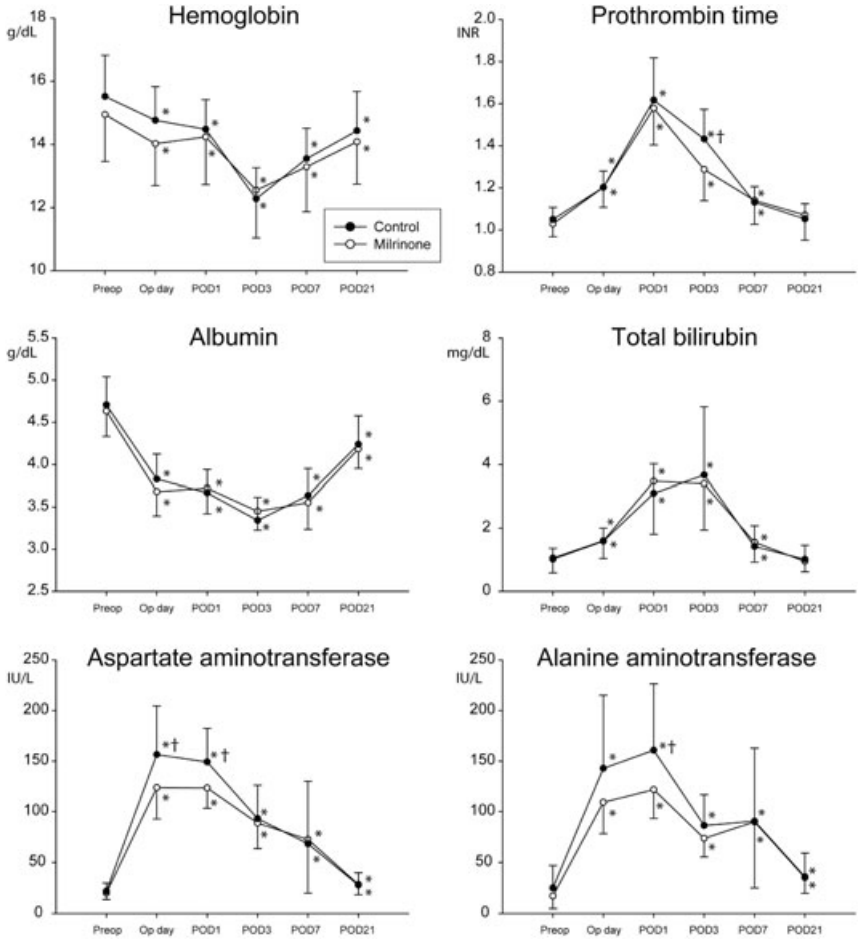

Figure 3. Perioperative changes of hemoglobin, prothrombin time, albumin, total bilirubin, and liver enzymes. *$p < 0.05$ compared to baseline (Preop) value; † $p < 0.05$ compared to milrinone group. Abbreviations: Preop, preoperative day; POD, postoperative days.

delayed (16). Low to intermediate loading doses (12.5 or 25 mcg/kg), as was used in this study, seem sufficient to produce prompt therapeutic effect without undesirable hypotension. Considering the short plasma half-life of milrinone (0.8 h in healthy volunteers) and the duration of living donor hepatectomy, low-dose loading followed by conventional infusion rate (0.5 mcg/kg/min) until the end of liver resection seems to be appropriate for preventing initial hypotension and maintaining hemodynamic stability (17). Unsustained ventricular tachyarrhythmia was reported in early clinical studies in congestive heart failure patients (18). However, in the operating room environment where vital signs are under close observation, clinically significant arrhythmia induced by low-dose milrinone seems unlikely, especially in healthy liver donors. In addition, as in conventional low CVP techniques, milrinone-induced low CVP also carries the risk of air embolism (19). Although the probability of these complications occurring at a clinically significant level is low in healthy living liver donors, close observation of the donor during milrinone infusion and liver resection is essential for evading disastrous events.

Two limitations of this study should be considered. First, we used an arbitrary criterion that is yet to be validated. The recent advance in living donor hepatectomy has outdated previous assessment tools that measure blood loss or units transfused and we reached a consensus among ourselves that a dry and clean surgical field has become increasingly important for skilled surgical teams, and thus came up with our four-point scale based upon our surgical experience in hundreds of living donor hepatectomies. In addition, we used independent scoring by two surgeons blinded to the treatment group to improve the objectivity of the scoring. Second, although we demonstrated a safe and effective use of milrinone in ASA class I living liver donors, extrapolation to a broader spectrum of patients undergoing liver resections should be done with caution. Further study is required before considering the use of milrinone to debilitated patients.

In conclusion, intraoperative infusion of milrinone was a simple and effective technique for providing a better surgical field while maintaining a low CVP and hemodynamic stability during living donor hepatectomy, compared to conventional low CVP technique. Minimal injury and early functional recovery of the remaining liver of the donors seem to be potential additional benefits.

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Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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