TARGETED CONTROL OF PULSE PRESSURE VARIATION VERSUS CENTRAL VENOUS PRESSURE ON REDUCTION OF INTRAOPERATIVE BLOOD LOSS DURING HEPATIC RESECTION

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In liver resection, central venous pressure (CVP) was used conventionally as a method of volume status evaluation, and low CVP technique (≤ 5 mmHg) was used to reduce blood loss since the 1990s. In recent years, CVP was regarded as a static indicator to assess intravascular volume status. Pulse pressure variation (PPV) is a preload index that can be used to predict an individual's fluid responsiveness through an existing arterial line. The purpose of this study was to determine if PPV is as safe and effective as CVP as a guide for fluid management during hepatic resection. Between February 2018 and June 2019 total 50 patients who met inclusion and exclusion criteria were randomized to PPV targeted group (group A) or CVP targeted group (group B). In both groups, central venous catheter and arterial line were inserted. Fluid was restricted at 2ml/kg/hr starting before induction of anaesthesia. Nitroglycerine was started with 0.5 ug/kg/min and titrated to achieve targeted values of PPV (13-18%) in group A and CVP (2-5 mmHg) in group B. Type of hepatic resection, transection time, blood loss, amount of blood transfusion, and additional operative factors were collected prospectively. There was no statistically significant difference in background demographic characteristics and operative factors between two groups. The PPV group included 25 patients with 8 right hepatectomy, 6 left hepatectomy, 6 left lateral segmentectomy and 5 other types of hepatectomy. Mean transection time was 104.4 ± 24.07 (range 60-150) min, and mean intraoperative blood loss was 676.0 ± 243.5 (range 270-1350) ml, with intermittent Pringle maneuver utilized. The CVP group included 25 patients with 6 right hepatectomy, 6 left hepatectomy, 8 left lateral segmentectomy and 5 other types of hepatectomy. Mean transection time was 104.2 ± 28.27 (range 50-150) min, and mean intraoperative blood loss was 818.3 ± 387.7 (range 370-1800) ml, again with use of intermittent Pringle maneuver. This study concluded that pulse pressure variation can be used safely as an alternative to central venous pressure in hepatic resection with equivalent outcomes of intraoperative blood loss and duration of parenchymal transection.

Keywords: central venous pressure, pulse pressure variation, hepatic resection, intraoperative blood loss

INTRODUCTION

Liver resection refers to removal of part of the liver. In Yangon Specialty hospital there were 72 cases of liver resection in 2015, 102 cases in 2016, 115 cases in 2017 and 126 cases in 2018. Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and has risen to become the third most common cause of cancer-related deaths worldwide, accounting for over >800,000 deaths/year. The incidence in Asian countries is up to ten times higher compared to the Western World countries due to the endemic presence of hepatitis B virus. About 80% of HCCs develop on the background of alcohol-toxic or primary biliary cirrhosis.[1]

Blood loss during liver resection is an important factor affecting complications and mortality in people undergoing liver resection. Estimates of blood loss have ranged from 200mL to 2 L per patient. There are various methods to reduce blood loss during liver resection surgery.

A combination of vascular inflow occlusion and low central venous pressure anesthesia was used during all hepatectomies since 1993 in an effort to reduce intraoperative blood loss and lower the risk of severe haemorrhage.[2] Techniques described to lower CVP to less than 5 mmHg include fluid restriction, diuretics, epidural blockade, nitroglycerine (NG) infusion and alterations in patient position. These simple methods help to maintain a state of hypovolaemia and vasodilation reduces hepatic vein backpressure, which in turn reduces venous bleeding during hepatic transection.

Recently numerous studies have documented the usefulness of direct measures of positive-pressure ventilation-induced variations on left ventricular output as a robust marker of preload responsiveness. Less invasive dynamic preload indices such as pulse pressure variation (PPV) and stroke volume variation (SVV) have been introduced and advocated by an increasing number of clinicians to guide fluid management. Pulse pressure variation is a derivative of the arterial pulse waveform integrated in monitors of most anaesthesia workstations and values can be displayed automatically in real time. The principle of predicting fluid responsiveness through PPV is based on the transmission of positive respiratory pressure generated by controlled mechanical ventilation to the intra-thoracic vascular compartment.

Numerous studies have documented that a SVV >10% or a PPV >13-15% on a tidal volume of 8 ml/kg or greater is highly predictive of volume responsiveness.[3] Rathore *et al* (2017) concluded that SVV assessed by a FloTrac transducer and Vigileo monitor, and PPV assessed by anaesthesia workstation-integrated monitors showed comparable performance in predicting fluid responsiveness in patients undergoing major surgeries.[4] In a systematic review of Marik *et al* (2009), mean discriminatory thresholds for PPV and SVV were found to be 12.5% ± 1.6% and 11.6% ± 1.9%, respectively.[5] In present study higher PPV values >13% (range 13-18%) was targeted to maintain relative hypovolaemic state in one group (high PPV group) in comparison with low CVP guided group to reduce intraoperative blood loss. Monitoring of PPV requires placement of an arterial catheter, still an invasive procedure with associated risks. However, its low complication rate < 1 % appears favorable compared to the 5-19 % risk of central venous catheter (CVC) complication.[6]

The aim of this study was using pulse pressure variation as a predictor of fluid status could prove to be advantageous by avoiding the need for CVC insertion and being more dynamic parameter to assess intravascular volume status for patients undergoing major hepatic resection.

MATERIALS AND METHODS

The study was performed as a prospective randomized trial at the operating rooms of Yangon Specialty Hospital between February 2018 and June 2019 after getting approval by the local ethical committee. All patients scheduled for hepatic resection of 2 or more segments were found eligible for study inclusion. Exclusion criteria were: age less than 18 or more than 65, ASA physical status more than III, irregular heart rhythm, severe cardiovascular disease (chronic heart failure, valvular abnormality, cardiomyopathy etc.), history of cerebrovascular disease, severe liver dysfunction (Child-Pugh score C) and donor hepatectomy for liver transplantation. All participants signed informed consent prior study inclusion.

Eligible patients were randomly allocated into two study groups: PPV targeted group and CVP targeted group. Patients were fasting from midnight before the surgery. Fluid therapy was restricted at 2ml/kg per hour starting before induction of anaesthesia.

General anesthesia was induced using propofol (2.5 mg/kg) and fentanyl (1μg/kg). Vecuronium (0.1 mg/kg) was used for muscle relaxation. Anesthesia was maintained using oxygen and isoflurane with minimum alveolar concentration (MAC) 1 – 1.5 adjusted for age. Patients were ventilated in the volume control mode with tidal volume of 8 ml/kg of predicted body weight without positive end expiratory pressure. Urinary catheterization was done with Foley's catheter. After induction of general anaesthesia, arterial line and CVC were inserted in both groups. The first set of readings of both variables was noted and the values were recorded as baseline after establishing the apparatus. The PPV level of the patients was below 9% and the CVP levels was ranged from 6 to 10 mmHg at the start of the operation. During parenchymal transection, the goal was to maintain PPV over 13% (range 13–18%) in group A. In group B the goal was to maintain CVP under or equal to 5 mmHg (range 2–5 mmHg).

Whenever the simple restriction of fluid administration was not sufficient to guarantee hypovolaemia, intravenous infusion of nitroglycerine (0.5-10 μg/kg/min) was administered. Volume status of patient was guided by PPV and CVP values in respective group. Operation was done by the same group of surgeons. Intermittent pringle maneuver method was used from the surgical aspect to block the hepatic inflow. Cavitron ultrasonic surgical aspirator (CUSA) was used during parenchymal transection to reduce haemorrhage.

In present study, intraoperative blood loss was calculated as the sum of the blood aspirated into the suction canisters, blood loss as calculated by weighing the sponges and that in the operative field. As far as possible mean arterial blood pressure was maintained above 65 mmHg. If the mean arterial blood pressure was lower than 65 mmHg, a bolus of 5-10 mg ephedrine was given and nitroglycerine infusion was reduced or stopped for a while. Intermittent fluid boluses (100 to 200 ml) were given to maintain MAP> 65 mmHg and urine output above 0.5ml/kg/hr. After completion of liver parenchymal transection, intravenous nitroglycerin was stopped. The PPV was kept under 9 % in group A and the CVP was brought up to 5-9 mmHg in group B with crystalloid. Allowable blood loss (ABL) was calculated before resection. When the blood loss was more than ABL, packed red cells and blood product transfusion was done according to local transfusion guidelines of Yangon General Hospital.

Haemodynamic changes (mean arterial pressure, heart rate), CVP and PPV were monitored continuously and recorded 10 min intervals throughout the operation. When the patient experienced haemodynamic instability at any time, appropriate treatment was given immediately. Duration of parenchymal resection was noted in both groups. After completion of surgical procedure, anaesthetic gas was stopped and neuromuscular block was reversed with iv neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. After confirming the complete recovery of muscle power, effective respiration, reflexes and conscious level regain, extubation was done after thorough suction. The patient was transferred to a high dependency unit.

DATA ANALYSIS

Categorical variables such as ASA physical status and Child-Pugh score were expressed as actual numbers and percentages and were compared using the chi-square analysis. Continuous variables such as estimated blood loss, packed cell requirement and parenchymal transection time were presented as mean ± SD for normally distributed data set and median (IQR) for non-normally distributed data set (skew data). Comparison between means of continuous variables was carried out with a student t test. Mean comparison of MAP changes over time was carried out by repeated measures ANOVA test. P-value < 0.05 was considered statistically significant.

RESULTS

The study was carried out at Operation Theatre of Yangon Specialty Hospital from February 2018 to June 2019. Total 50 patients who met inclusion and exclusion criteria scheduled for elective hepatic resection were randomly allocated into two groups, group A (PPV targeted group, n = 25) and group B (CVP targeted group, n = 25) by using block randomization process.

There was no statistically significant difference in background demographic characteristics (p > 0.05). (Table 1)

Table (1) Patient demographics

	Group A (n = 25)	Group B (n = 25)	p value
Age(years) Mean ± SD	52.56 ± 12.77	49.83 ± 13.01	0.453
Body weight (kg) Mean ± SD	56.56 ± 8.67	58.08 ± 8.99	0.54
Male (n%) Female (n%)	15 (60.0) 10 (40.0)	14 (56.0) 11 (44.0)	0.774
ASA I (n%) ASA II (n%) ASA III (n%)	6(24.0) 12(48.0) 7(28.0)	3 (12.0) 15 (60.0) 7 (28.0)	0.513
Child Pugh classification A (n%) B (n%)	15(60.0) 10(40.0)	16(64.0) 9(36.0)	0.771

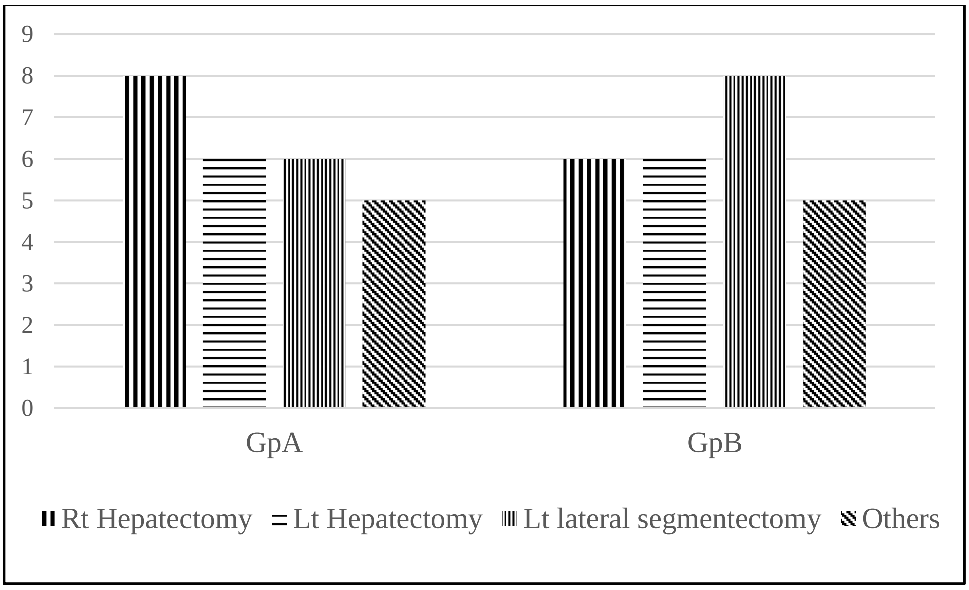

Figure (1) Types of hepatic resection

In this study, there were 8 right hepatectomy patients, 6 left hepatectomy patients, 6 left lateral segmentectomy patients and 5 other types of hepatic resection cases in group A. In group B, 6 right hepatectomy patients, 6 left hepatectomy patients, 8 left lateral segmentectomy patients and 5 other types of hepatic resection cases were included. Types of hepatic resection were comparable between two study groups. (Figure 1)

Table (2) Intraoperative demographics

	Group A (n = 25) Mean ± SD	Group B (n = 25) Mean ± SD	p value
Duration of surgery (min)	239.84 ± 71.51	251.68 ± 55.26	0.65
Amount of intraoperative blood loss (ml)	676.0 ± 243.5	818.3 ± 387.7	0.126
Amount of packed cell transfusion (ml)	164.0 ± 131.1	188.4 ± 155.7	0.551
Duration of parenchymal transection (min)	104.4 ± 24.07	104.2 ± 28.27	0.978

Mean duration of surgery was 239.84 ± 71.51 minutes in group A and 251.68 ± 55.26 minutes in group B. There was no statistically significant difference in mean duration of surgery between two study groups ($p > 0.05$). (Table 2)

In comparison of amount of intraoperative blood loss between two study groups, the amount of blood loss was 676.0 ± 243.5 ml in group A (range 270-1350ml), and 818.3 ± 387.7 ml in group B (range 370-1800 ml). In this study, not every patient needed blood transfusion. In group A, the amount of packed cell transfusion was (164.0 ±131.1) ml in group A and (188.4 ± 155.7) ml in group B. There was no statistically significant difference in amount of intraoperative blood loss and packed cell transfusion between the two groups ($p > 0.05$). (Table 2)

Duration of parenchymal transection was noted as the time taken from the start of liver transection to removal of liver segments. In this study, mean duration of parenchymal transection was 104.4 ± 24.07 minute (range 60-150 min) in group A and 104.2 ± 28.27 minute (range 50-150 min) in group B. P value was > 0.05 and it was not statistically significant (Table 2). There was no significant difference between MAP values in group A and group B from the start of parenchymal transection until removal of liver segment.

DISCUSSION

Liver, a unique organ with double afferent blood supply, is a very vascular rich organ, receives almost 25% of the cardiac output, in spite its mass constitutes only 2.5% of the total body weight. Therefore, liver surgery is associated with potential risk of massive blood loss and subsequent massive blood transfusion, which is correlated significantly with postoperative morbidity and mortality.

Emerging research explores the role of dynamic metrics of volume responsiveness as simple and sensitive indicators for evaluating fluid responsiveness and predicting intra-operative blood loss. Recently, use of dynamic preload parameters (like stroke volume variation, pulse pressure variation) has been recommended as a substitute for CVP.

Numerous studies have documented that a SVV >10% or a PPV >13-15% on a tidal volume of 8 ml/kg or greater is highly predictive of volume responsiveness.[3]

In the study of Dunki Jacobs (2014), 80 patients undergoing liver resections were enrolled in CVP guided and SVV guided groups. In the group using a SVV goal of 18 to 21, median transection time was 55 (25–78) min, median blood loss of 255 (range 100–1,150) ml. In CVP guided group median transection time was 43 (range 20–65) min, median blood loss 250 (range 20–950) ml. It was concluded that SVV can be used safely as an alternative to CVP monitoring during hepatic resection with equivalent outcomes in terms of blood loss and parenchymal transection time.[7]

Ratti et al (2016) conducted a randomized trial comparing fluid management guided by SVV or CVP in patients undergoing laparoscopic left lateral resection. They observed that the blood loss was significantly lower in the SVV group. The CVP group had a higher conversion rate because of hemorrhage and consequently increased blood loss.[8] Kitaguchi et al (2018) used SVV >13%–20% and fluid restriction <5 ml/kg/h during hepatic resection compared to a historical cohort and found a significant decrease in blood loss and transfusion rates.[9]

Intraoperative blood loss was calculated as the sum of the blood aspirated into the suction canisters, blood loss as calculated by weighing the sponges and that in the operative field. In PPV targeted group mean intraoperative blood loss was 676.0 ± 243.5 ml during operation and it was 818.3 ± 387.7 ml of blood loss in CVP targeted group intraoperatively. Mean blood loss was not significantly different between two groups ($p > 0.05$) in present study.

During intraoperative management, infusion volume was generally maintained with crystalloid solution at 2 ml/kg/hr from start of anesthetic induction until completion of liver transection in addition with nitroglycerine infusion (the fluid restriction period). As a result, the target values of PPV and CVP were achieved in both groups. However additional crystalloid (range 100 to 200 ml) had to be administered in episodes of MAP less than 65 mmHg to achieve haemodynamic stability in some patients. The period from completion of liver transection until completion of surgery was defined as the fluid resuscitation period. Mean arterial pressure was targeted at 65 mmHg or above, and urine output ≥ 0.5 mL/kg/hr throughout the surgery. There was no case in which the hemodynamic status became remarkably unstable in this study.

Increased blood loss during liver surgery has a direct effect on postoperative course and negatively affects oncological outcomes. Furthermore, it has been shown that perioperative blood transfusions are associated with a higher rate of recurrence and lower survival after resection of colorectal liver metastases and hepatocellular carcinoma.

In the present study, the mean duration of surgery was not different statistically between two groups. Mean duration of surgery was 239.84 ± 71.51 minutes in PPV targeted group and 251.68 ± 55.26 minutes in CVP targeted group. It was comparable between two groups. Intermittent Pringle maneuver technique and cavitron ultrasonic surgical aspirator (CUSA) were used during liver transection in all cases from the surgical side. Allowable blood loss was calculated for each patient and the packed cell was transfused when intraoperative blood loss was over the amount of allowable blood volume for individualized patients. Not every patient needed transfusion of a packed red cell in both groups.

Mean packed cell transfusion was 164.0 ± 131.1 ml in PPV targeted group and 188.4 ± 155.7 ml in CVP targeted group. No statistically significant difference was found in volume of packed cell transfusion between two groups ($p>0.05$). Fresh frozen plasma was transfused in a ratio of 1:2 with packed cells according to hospital guidelines although it was not noted in study. In this study median parenchymal transection time was 104.4 ± 24.07 minutes (range 60-150 min) in PPV targeted group and 104.2 ± 28.27 minutes (range 50-150 min) in CVP targeted group. The parenchymal transection time was not different significantly between two groups ($p > 0.05$).

In a study conducted by Suu-Nwe-Khin, it was concluded amount of blood loss and total blood product transfusion were significantly reduced in low CVP group. There were no significant changes in mean arterial pressure and heart rate between the two groups. As for renal function creatinine clearance in postoperative day 1 and day 2 were more than 50 ml per minute in all patients and there were no renal function impairments between hypotensive anaesthesia group and conventional group.[10] In the present study, urine output throughout surgery was more than 0.5 ml/kg/hr in both groups. However, in 3 out of 50 cases, urine output reduced to nearly the targeted value 0.5 ml/kg/hr. In these cases, patients had high haematocrit value preoperatively and calculated allowable blood loss was much higher for them. Although blood loss was approached to the determined amount of allowable blood loss, it did not exceed ABL, therefore blood transfusion was not needed in these patients. However, urine output was reduced near 0.5 ml/kg/hr in these patients and when fluid resuscitation was done, the output was over 0.5 ml/kg/hr after parenchymal transection. Use of diuretics was not needed in these cases.

In present study, it was revealed that the values of the CVP were quite static. It was found getting a CVP value of less than 5 mmHg was not easily available although patient's low volume status. Infusion of nitroglycerine was started with the lowest dose in every patient and average dose of nitroglycerine was not higher to achieve targeted values of CVP or PPV. As for PPV, it was reliable to patient's intravascular volume, became dynamic and displayed real time value on the screen of the monitor.

CONCLUSION

This study concluded that pulse pressure variation is a simple and useful index for fluid responsiveness and preload status, and the intraoperative fluid management with PPV can achieve safe intravenous fluid restriction and contributes to decreasing intraoperative blood loss in liver surgery.

ETHICAL APPROVAL

This study was ethically approved by the Research and Ethics Committee, University of Medicine 1, Yangon.

CONFLICT OF INTEREST

There is no conflict of interest.

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