Original Article

A randomized comparison between pulse pressure variation and central venous pressure in patients undergoing renal transplantation

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Abstract

Background and Aims: Intraoperative fluid management is important in renal transplant recipients with end-stage renal disease. Conventionally, central venous pressure (CVP) has been used to guide perioperative fluid administration but with high incidence of poor graft outcome. There is a requirement of reliable parameter to guide the fluid therapy in these patients so as to minimize the perioperative complications and improve the outcome. Hence, this study was conducted.

Material and Methods: This prospective study included 75 patients of chronic kidney disease undergoing renal transplantation. Patients were divided into two groups. Group A (control group): Intraoperative fluids were guided by CVP; Group B: Intraoperative fluids were guided by pulse pressure variation (PPV). Primary outcome measure of this study was incidence of delayed graft functioning, i.e., need of hemodialysis within 7 days of renal transplant. Secondary outcome measures were incidence of perioperative hypotension, post-transplant pulmonary edema, tissue edema, and lactic acidosis.

Results: Total amount of fluid before reperfusion was significantly greater in the control group ($P = 0.005$). However, the total amount of fluid required at the end of surgery was comparable. Delayed graft functioning was seen only in CVP group, although it was not statistically significant. The postoperative tissue edema was more in CVP group ($P = 0.03$). The postoperative nausea and vomiting, pulmonary edema, and mechanical ventilation were more in CVP group but not statistically significant. Increase in lactate value was more in CVP group.

Conclusion: Perioperative fluid guidance by PPV is better than central venous pressure in renal transplant patients.

Keywords: Central venous pressure, end-stage renal disease, pulmonary edema, renal transplantation

Introduction

Renal transplant is the ideal treatment modality in patients with end-stage renal disease.[1] Intraoperative fluid management in this patient population is very challenging in view of cardiopulmonary compromise due to uncontrolled hypertension, dilated cardiomyopathy, concentric left ventricular hypertrophy, ischemic heart disease, pulmonary hypertension, pericardial or pleural effusion, and restrictive lung disease. Intraoperative fluid therapy is usually guided by monitoring of mean arterial pressure (MAP), urine output, and central venous pressure at most transplant centers but none is proved ideal for this purpose.[2-5] Inappropriate fluid administration can lead to either hypovolemia or hypervolemia intraoperatively and resulting complications like postoperative acute tubular necrosis, delayed graft functioning, volume overload, pulmonary edema, and need of mechanical ventilation,

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leading to increased morbidity, length of in hospital stay, and mortality.[6-8]

Pulse Pressure Variation (PPV), a dynamic hemodynamic parameter, is very accurate in the assessment of intraoperative fluid requirement in comparison to static values.[9,10] The hypothesis behind conducting this study was that it will reduce complications related to both hypo- and hypervolemia, thereby improving graft outcome in patients undergoing renal transplant.

Material and Methods

This prospective randomized interventional study was conducted in the Department of Anaesthesiology over a period of 6 months from April 2018 to September 2018. Approval from institutional ethical committee (MGHCH/IEC/JPR/2018/11) and written informed patient consent was obtained prior to surgery. Inclusion criteria were all patients undergoing live donor renal transplantation during the study period at our institution. Patients who underwent re-exploration in first 24 h, patients with cardiac disease, medically complex donor, and those for second transplant were excluded from study. Patients were randomized in either of the two groups based on computer-generated random numbers.

In Group A, intraoperative fluids were administered guided by central venous pressure (control group) and in Group B, intraoperative fluids were administered based on PPV. Target CVP was kept between 12 and 15 mm Hg in group A, whereas in Group B patients target PPV was maintained between 10 and 13%. Intravenous (IV) fluid bolus of 200 ml of crystalloid was given at CVP less than 12 mm Hg and PPV more than 13% intraoperatively and further infusion of fluid was stopped at CVP more than 15 mm Hg and PPV less than 10%. IV fluid (normal saline and plasmalyte in 1:1 ratio) was administered at baseline rate of 5 ml/kg/h when CVP and PPV were in target range [Figure 1]. A total of 20% albumin (100 ml) was administered during intraoperative period in patients with preoperative albumin less than 3 g/dL. No other colloids were used as per our transplant protocol. Packed red blood cells were transfused at hemoglobin values less than 7 gm/dl. Target MAP was kept ≥90 mm Hg after graft reperfusion as per hospital protocol and any drop in MAP was managed with infusion of norepinephrine in titrated dosing.[7,11] Perioperative hypertension was managed with infusion of nitroglycerine or beta blockers (metoprolol, labetalol).

All patients underwent routine preoperative checkup including detailed medical and surgical history, physical examination, and relevant investigations day before the scheduled date

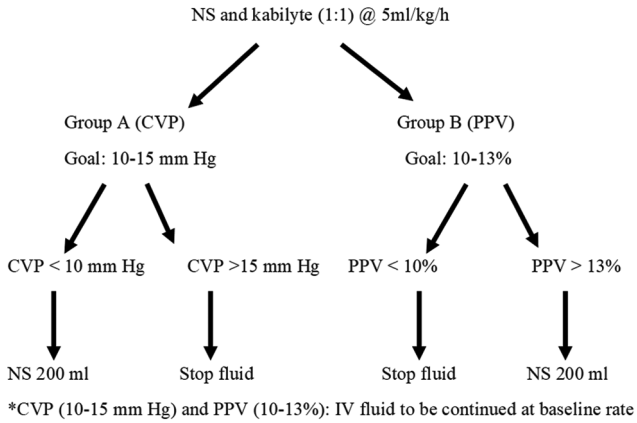

Figure 1: Intraoperative fluid guidance. *CVP (10–15 mm Hg) and PPV (10–13%): IV fluid to be continued at baseline rate

of surgery. On the day of surgery, patients were given tablet alprazolam and tablet pantoprazole 40 mg along with his regular medications with sips of water. On arrival into operating room, standard anesthesia monitors (NIBP, SpO2, and electrocardiogram (ECG) were attached and baseline vital values were noted. An IV line was secured with 18G cannula in nonfistula arm and IV fluid was started @ 5 ml/kg/h as a baseline rate and rate of infusion was changed as per study protocol throughout the surgery. General anesthesia was induced with IV propofol 2 mg/kg after IV boluses of midazolam 1 mg and fentanyl 2 μg/kg. Trachea was intubated with appropriate size endotracheal tube 3 min after intubating dose of cisatracurium (0.2 mg/kg). Patients were attached to mechanical ventilator and kept on volume control mode with tidal volume of 8 ml/kg with positive end expiratory pressure of 5 mm Hg. Anesthesia was maintained on isoflurane in oxygen and nitrous oxide mixture in 40:60 ratios along with continuous infusion of cisatracurium at rate of 0.01 mg/kg/h. Arterial line was placed in nonfistula arm in all patients and connected to monitor (Philips intellivue MX550, USA). Central venous catheter (7F triple lumen) was inserted in either side of internal jugular vein under ultrasound guidance in all the patients. Central venous pressure, MAP, and PPV were recorded at baseline and then continuously throughout intraoperative period at fixed intervals. An arterial blood gas was sent just after arterial cannulation and at the end of surgery. Patients were shifted to postoperative renal transplant unit after complete reversal of anesthesia. Amount of total fluid infused during surgery, first 24 h urine output and serum creatinine values were noted at the end of surgery and postoperatively on days 1, 3, and 7. Any postoperative incidences of hypo or hypervolemia were recorded. Primary outcome measure of this study was incidence of delayed graft functioning, i.e., need of hemodialysis within 7 days of renal transplant. Secondary outcome measures were incidence of intraoperative hypotension (MAP <65 mm Hg and <90

mm Hg before and after graft reperfusion, respectively), tissue edema (swelling on eyelid, face, and feet), pulmonary edema, and lactic acidosis at the end of surgery.

Statistics

Sample size was calculated as 35 patients in each group. This was based on pilot study on ten patients where it was seen that one patient had delayed graft functioning in CVP group. The power of study was 80% with an alpha error of 0.5.

Continuous data were represented as mean ± standard deviation and analyzed using Student's t test. Categorical data were represented as numbers and percentages and analyzed using Chi-square test and two-tailed Fisher's exact test as applicable. Data were analyzed using online graph pad *P* value calculator. Statistical significance was provided when *P* value <0.05.

Results

A total of 88 patients had undergone renal transplant during the study period. And 13 patients were excluded from the study as per exclusion criteria: Re-exploration after transplant (2), re-transplant (2), medically complex donor (6), and refusal to consent (3). Thus, total –75 patients could be included in study.

Demographic variables (age, gender, weight, duration of CKD and hemodialysis, preoperative comorbidities, preoperative Hb and albumin, duration of surgery) were comparable in both the groups [Table 1].

The fluid administered was normal saline and plasmalyte in 1:1 ratio as per our practice started @ 5 ml/kg/h. Administration of IV fluid was guided by CVP and PPV as per the group [Figure 1]. Total amount of fluid required before reperfusion was significantly greater in the CVP group ($P = 0.005$) [Table 2]. However, the total amount of fluid required during surgery was comparable in both the groups. The requirement of albumin and packed red blood cells transfusion was also comparable. The parameters of renal perfusion, such as urine output, serum creatinine, and serum lactate, were comparable in both the groups at various

Table 1: Demographic profile of patients

Variable	CVP group (*n*=40)	PPV group (*n*=35)	*P*
Age (years)	33.63±10.20	37.83±11.41	0.094
Gender (M/F)	33/7	31/4	0.528
Weight (Kg)	56.82±10.22	57.74±13.51	0.738
Height (cm)	168.48±9.23	167.74±8.28	0.718
Duration of CKD (months)	15.2±23.15	21.69±34.12	0.331
Duration of HD (months)	4.62±4.72	5.01±5.76	0.747
Hb (g/dL)	9.35±2.23	9.52±2.09	0.733
Albumin (g/dL)	3.69±0.59	3.64±0.59	0.674
Arteriovenous fistula	22 (55%)	16 (45.7%)	0.491
Hypertension	37 (92.5%)	32 (91.4%)	1.00
Diabetes mellitus	2 (5%)	1 (2.5%)	1.00
Pleural effusion	2 (5%)	1 (2.85%)	1.00
Duration of surgery (min)	194.25±36.01	193±22.83	0.859

CKD: Chronic kidney disease, HD: Hemodialysis, Hb: Hemoglobin

Table 2: Intravenous infusions and predictors of renal perfusion

Variable	CVP group (*n*=40)	PPV group (*n*=35)	*P*
Total IV fluid before reperfusion (ml)	1185.71±275.62	992.50±306.67	0.005
Total IV fluid at the end of surgery (ml)	1834.29±319.87	1688.75±430.49	0.102
Packed RBCs	4	1	0.364
Albumin	3	0	0.243
Patients required nitroglycerine	31	19	0.049
Patients required norepinephrine	7	5	0.762
Lactate baseline	1.19±1.051	1.09±0.64	0.621
Lactate at end of surgery	2.13±1.28	1.82±0.97	0.232
Creatinine baseline	5.47±2.21	5.07±1.76	0.384
Creatinine at the end of surgery	4.67±1.82	4.47±1.57	0.467
Creatinine at postoperative day 1	2.33±0.95	2.26±0.90	0.732
Creatinine at postoperative day 3	1.28±0.47	1.30±0.61	0.839
Creatinine at postoperative day 7	1.24±0.50	1.26±0.71	0.886

points of time in the perioperative period. Requirement of norepinephrine infusion was also comparable in both the groups. However, the requirement of nitroglycerine was greater in the CVP group ($P = 0.049$). This may be due to greater MAP values in this group [Table 3]. The MAP was lower in PPV group. However, the values were within acceptable range. Heart rate did not show any significant deviation at any point of time in either group [Table 4]. One patient in CVP group required hemodialysis in postoperative period (DGF) that may be result of acute tubular necrosis developed in same patient. The postoperative tissue edema was more in CVP group ($P = 0.03$). Postoperative nausea and vomiting, pulmonary edema, and mechanical ventilation were apparently more in control group but no statistical significance could be attained [Table 5]. Increase in serum lactate in postoperative blood analysis was more in CVP group as compared to PPV group.

Table 3: Mean arterial pressure at various points of time (mm Hg)

Time interval	CVP group (n=40)	PPV group (n=35)	P
Baseline	122.30±17.98	123.45±19.36	0.789
Arterial ligation	109.27±20.52	108.28±19.29	0.942
Venous clamp	117.29±15.49	107.77±13.60	0.005
Just before reperfusion	106.35±14.34	104.77±11.16	0.596
Just after reperfusion	84.48±13.26	82.84±12.44	0.579
At end of surgery	111.93±11.64	107.43±11.14	0.088

Table 4: Heart rate at various points of time (beat/min)

Time interval	CVP group (n=40)	PPV group (n=35)	P
Baseline	89.5±16.36	94.89±14.19	0.131
Arterial ligation	91.09±14.76	90.476±12.30	0.8453
Venous clamp	82.6±13.82	85.64±11.47	0.303
Just before reperfusion	77.74±13.09	80.5±11.35	0.331
Just after reperfusion	84.09±15.17	87.07±12.26	0.352
At end of surgery	84.81±15.02	82.29±12.91	0.437

Table 5: Postoperative complications

Variable	CVP group	PPV group	P
Mechanical ventilation	2	0	0.495
Tissue edema	8	1	0.031
PONV	7	1	0.060
Delayed graft functioning	1	0	1.000
Acute tubular necrosis	1	0	1.000
Pulmonary edema	2	0	0.495

PONV: Postoperative nausea and vomiting

Discussion

Perioperative fluid administration is the essential for maintaining perfusion and functioning of transplanted kidney. This is because of the absence of nerve supply and hence autoregulation in it. This makes it mandatory to exercise strict control over fluid infusion so as to maintain perfusion in the transplanted kidney and improve the outcome.[3-6] Moreover, factors, such as different targets of vital parameters at different phases of surgery, intraoperative vasodilatation by inflammatory mediators released during reperfusion, and cytokine response of polyclonal antibodies and effect of anesthetic drugs further enhance the challenges to appropriate fluid therapy.[12] Under transfusion may result in inappropriate blood flow and tissue hypoxia thereby increasing the chances of graft necrosis and other metabolic complications. On the contrary, over transfusion may result in tissue edema, pulmonary edema, and graft rejection.[13,14] Hence, it is essential to find out the most reliable parameter to guide intraoperative fluid therapy in these patients. Previously, CVP was used for the purpose but results were misleading.[3-6] Good renal perfusion after opening of vascular clamp is mandatory for proper graft functioning. So, it is essential to maintain adequate MAP within autoregulation range of kidney, nearly around 90 mm Hg or more so as to improve the graft outcome.[8] Hence, judicious use of vasopressors or inotropes may be warranted. We used noradrenaline and achieved the target MAP. Srivastava *et al.* observed that transesophageal Doppler is a better guide for safe administration of fluid in renal transplant recipients.[7]

Although colloids are best avoided due to risk of interstitial nephritis but albumin can be safely used in patients with hypoalbuminemia. Primary fluids are crystalloids in these patients. Various crystalloids were compared and it was found that normal saline alone causes hyperchloremic acidosis, whereas ringer lactate can lead to hyperkalemia and lactic acidosis.[14,15] Plasmalyte contains low chloride and acetate as buffer; hence, it is more suitable in this patient population. Thus, the commonly used fluids during renal transplant are normal saline and plasmalyte (balanced salt solution). At our center, we use both plasmalyte and normal saline in a ratio of 1:1.

Srivastava *et al.*, in their study, have shown very high incidence of delayed graft functioning (11 out of 104 patients) in CVP group. Monitoring CVP for fluid guidance is misleading and result in increased postoperative renal complication.[7] Fluid administration under guidance of PPV can definitely improve the graft outcome. Postoperative complication like pulmonary edema is a consequence of excessive intraoperative fluid administration causing perioperative oxygen desaturation. Postoperative oxygen or mechanical ventilation may be needed.[16,17] This increases postoperative morbidity, mortality, and treatment cost by increasing incidence of intensive care admission and hospital length of stay. Pre-existing cardiac

dysfunction (dilated cardiomyopathy, portal hypertension) makes these patients vulnerable to even small change in fluid status.[17] Also, low albumin and hemoglobin further adds to tissue and pulmonary edema by their effect on colloid oncotic pressure. In our study, results favor the use of newer dynamic indices like PPV to reduce the incidence of complications related to fluid overload. Limitation of PPV is controlled ventilation with fix ventilator setting, regular cardiac rate, and rhythm, whereas confounding factors include cardiac autonomic neuropathy in diabetic patients, positioning, intrathoracic pressure, and intraabdominal pressure.[18-20]

Graft survival depends on multiple factors. It is less with increasing donor age, human leukocyte antigen (HLA) mismatching, and poor graft perfusion. Proper graft functioning is more affected by adequate amount and timing of fluid in different phases of transplant rather than the total amount of fluid administered during surgery provided that the hemodynamics are maintained. Fluid transfused before reperfusion was more in CVP group. Hence, delayed graft functioning and acute tubular necrosis (ATN) were seen in CVP group only but it was not statistically significant.

Conclusion

In this study, we can conclude that PPV could be a better guide to intraoperative fluid therapy as compared to central venous pressure in terms of reduced risk of postoperative delayed graft functioning and other perioperative complications related to fluid management in renal transplant recipients. Further studies, with large number of participants, are warranted.

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Conflicts of interest
There are no conflicts of interest.

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