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TO EVALUATE PERIOPERATIVE CARDIOPULMONARY OUTCOMES IN PATIENTS WITH AND WITHOUT PULMONARY HYPERTENSION UNDERGOING RENAL TRANSPLANTATION.

Anaesthesiology

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ABSTRACT

Background: High prevalence of pulmonary hypertension (PH) has been reported in patients with ESRD, distinctly among hemodialysis patients accompanying adverse outcomes. This study was conducted to evaluate perioperative cardiopulmonary outcomes in patients with and without pulmonary hypertension underwent renal transplant. **Methods:** The prospective, observational study was conducted in our institute in department of anaesthesiology, over a period of 1 year. All the vital parameters were recorded in intra-op and post-op period. Hypotension (SBP ≤20% of baseline), significant arrhythmias (require any medical management), Myocardial ischemia/Infarction (ECG change), Pulmonary edema (Pink frothy secretion from ETT), mechanical ventilation (>24HRS) was recorded as primary outcome. Delayed graft functioning (need of dialysis within a week of transplant) was recorded as secondary outcome. All patients were shifted to kidney transplant unit (KTU) after reversal of anaesthesia. Hence based on the PH, subjects were divided into two groups i.e. Group A (N=34) having PH and Group B (N=119) without PH. **Results:** The median duration on dialysis was more in the PH group and the difference between the two groups were statistically significant. In the perioperative period, hypotension was found significantly more in PH group 17 patients (50%) in group A. **Conclusion:** Hypotension was more frequent in patients with pulmonary hypertension, but it didn't show any significant adverse impact on the post-operative cardiopulmonary and renal outcome.

KEYWORDS

Delayed Graft Functioning, Hypotension, Pulmonary Hypertension, Renal Transplant,

INTRODUCTION:

ESRD is defined as irreversible decline in a patient's kidney function, 10-15% of their normal capacity, which is severe enough to be fatal necessitate for dialysis or transplantation. Estimated Glomerular Filtration Rate (GFR) less than 15ml per minute per 1.73m^2 body surface area for more than 3 months, or those requiring dialysis irrespective of GFR.[1-5] The occurrence of Chronic kidney disease (CKD) and its progression to the end stage results in a reduced quality of life and premature mortality.[3]

Diabetes mellitus and Hypertension are seen as the dominant cause of kidney disease, triggering left ventricle dysfunction, which bound to increase pulmonary venous and arterial pressure.[4] In recent observational studies, high prevalence of pulmonary hypertension (PH) has been reported in patients with ESRD, distinctly among hemodialysis patients accompanying adverse outcomes.

Pulmonary Hypertension is designated as resting mean pulmonary artery pressure ≥35 mmHg estimated by pre-operative echocardiography and ≥25mmHg when measured by right heart catherization. In PAH, pulmonary wedge pressure should be ≤15mmHg and pulmonary vascular resistance ≥3 woods units. A new pressure level to define an abnormal elevation in mPAP >20mmHg and need for PVR ≥3 WU to define the presence of pre-capillary PH.[6]

Prevalence of PH estimated in CKD patients is as high as 40% and is a strong predictor of increased mortality and adverse outcomes following renal transplant. It may be secondary to an underlying cardiac or pulmonary pathology or can occur afresh when an intrinsic pulmonary arteriopathy occurs[7]. Mechanisms that have been filed for the development of PH in CKD/ESRD patients are cardiac dysfunction and fluid overload, arteriovenous fistula, uremia, bone mineral disorders and hemodialysis.

Patients typically presents with symptoms such as dyspnea, fatigue, reduced exercise tolerance. Definitive diagnosis is made by right heart catheterization by measuring pulmonary artery pressures and pulmonary vascular resistance. Non-invasive technique to diagnose PH is by echocardiography. Systolic and diastolic dysfunction is very commonly seen in patients with chronic kidney disease and it usually results due to salt and fluid overload, hypertension, uremia, and myocardial ischemia (MI). Diastolic dysfunction in advanced renal disease is likely due to fluid overload. Also, low ejection fraction was found in patients with PH on echocardiogram and low diastolic blood pressure, suggesting a crucial role of arterial stiffness in the pathogenesis of this condition. PH is more prevalent in hemodialysis patients. Beigi et al conducted a study on 34 patients and data showed a statistically significant correlation between fistula flow and PAP[8]. A study conducted by Domenici A et al 58.9% of prevalent hemodialysis patients and 22.2% of peritoneal dialysis patients suffered from PH[9]. Also duration of CKD and duration on dialysis are significant factors.

As the incidence of PH is very high in ESRD patients, it might affect the perioperative cardiopulmonary outcome in patients undergoing renal transplantation. So, our hypothesis behind to conduct this study is to evaluate perioperative cardiopulmonary outcomes in patients with and without pulmonary hypertension underwent renal transplant.

MATERIAL AND METHOD:

The prospective, observational study was conducted in our institute in department of anaesthesiology, over a period of 1 year (1st January 2019 – 31st December 2019). Before starting the study, Institutional ethics committee approval was obtained. Written and informed consent of all the patients was obtained before commencing study. Patients undergoing live related renal transplantation and having age 18-60 years were included in the study. Patients undergone re exploration in first 24 hours, medically complex donor and undergoing re-transplant were excluded from the study (Figure 1).

METHOD:

All patients undergone routine preoperative check-up including history, physical examination and detailed cardiopulmonary workup (2-D Echo, ECG, X-ray chest, pulmonary function tests, coronary angiography if required) day before scheduled date of surgery. On day of surgery patients were given tablet alprazolam and tablet pantoprazole 40 mg along with his regular medications with sip of water. On arrival into operating room standard anaesthesia monitors including noninvasive blood pressure, pulse oximeter and electrocardiogram were attached and baseline vital values were noted. An intravenous line was secured with 18G cannula in non-fistula arm and normal saline was started @ 10ml/kg/hr. Pre-oxygenation with 100% oxygen was done to achieve end-tidal oxygen concentrations above 90% to lessen the increased risk of hypoxemia due to a reduction in functional residual capacity that frequently occurs after induction.

General anaesthesia induced with intravenous propofol 2mg/kg preceded by midazolam 1 mg and fentanyl 2 micro/kg. All patients were intubated by an experienced anaesthesiologist in a rapid and smooth manner with appropriate size of endotracheal tube 3 minutes after intubating dose of cisatracurium (0.2mg/kg). Endotracheal tube was attached to ventilator and patients kept on volume-controlled ventilation mode using tidal volume of 8ml/kg without positive end

expiratory pressure to avoid hyperinflation of lungs and to minimize pulmonary vascular resistance by keeping lung volume near functional residual capacity. Anaesthesia was maintained on isoflurane in oxygen and air mixture in 50:50 ratio along with continuous infusion of cisatracurium at rate of 0.01mg/kg/h. Temperature probe inserted orally. Arterial line was placed in nonfistula arm in all patients. An arterial blood gas sample was sent after arterial cannulation and before the end of the surgery.

Central venous catherization established in all patients (except those with hemodialysis catheter in situ) on appropriate side (preferably right) under ultrasound guidance. Baseline values of central venous pressure, mean arterial pressure and pulse pressure variation (PPV) recorded and continued intra-operatively. During Intraoperative period, fluid management was guided by PPV. When PPV reached <10%, fluid was stopped and if value of PPV was>15% fluid bolus of 150 ml normal saline was given. Kabilyte and normal saline in the ratio of 1:1were used throughout surgery. Target mean arterial pressure was kept > 90 mmHg after graft reperfusion as per hospital protocol and any drop in MAP was managed with IV boluses of ephedrine and/or infusion of norepinephrine (2-20 µg/min) in titrated dosing. For pain management, systemic opiates (small boluses of fentanyl) and IV paracetamol 1gm were used. All the vital parameters were recorded in intra-op and post-op period. All patients were shifted to kidney transplant unit (KTU) after reversal of anaesthesia. Hypotension (SBP ≤20% of baseline), significant arrhythmias (require any medical management), Myocardial ischemia/Infarction (ECG change), Pulmonary edema (Pink frothy secretion from ETT), mechanical ventilation (>24HRS) were recorded as primary outcome. Delayed graft functioning (need of dialysis within a week of transplant) was recorded as secondary outcome.

STATISTICALANALYSIS:

Demographical and clinical variables were presented as frequency (percentage) and mean ± standard deviation or median as appropriate. Group comparisons were made using independent t-test as per the distribution of the data for continuous variables. A multivariate analysis was done for factors which were significant on univariate analysis. Complications were expressed as frequency (percentage). P< 0.05 was considered statistically significant.

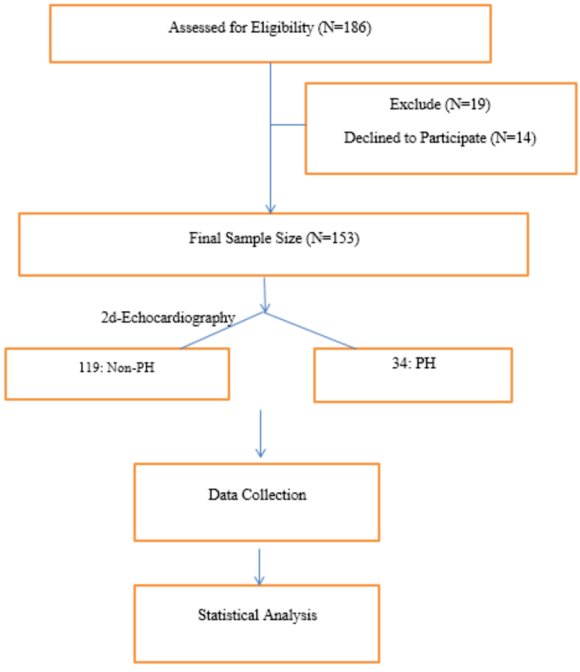

Figure 1: Patient's selection criteria

Results: A total of 153 patients were included in the analysis. Patients within the age group range of 18-60 years were included in this study. In our study, we found male predominance in both the groups (29 in group A and 104 in group B) and difference was not statistically significant (p=0.974). The mean age in Group A was 37.06 ± 10.27 years and in Group B, it is 35.01 ± 12.82 years with a p value of 0.263. [Table 1] Out of 153 patients, 34 (22.2%) were diagnosed with pulmonary hypertension (PH) on pre-op echocardiography with PASP ≥35mmHg. Based on the PH, patients were divided into two groups i.e. Group A (N=34) with PH and Group B (N=119) without PH. Mean PASP was 46.14±8.07mmHg with a range of 35-72 mmHg. Other parameters like ejection fraction, pre-op comorbidities, pre-op serum creatinine, random blood sugar, weight, hemoglobin levels and duration of surgery were almost similar in both the groups.

Table 1: Gender and age distribution among the study subjects

Gender	Group A (N=34)		Group B (N=119)		P value
	No.	%	No.	%	0.974 (NS)
Male	29	85.29	104	87.39	
Female	5	14.70	15	12.60	
Age (Mean ± SD)	37.06±10.27		35.01±12.82		0.263 (NS)

The median duration of CKD in the PH group was more than the non-PH group and the difference between the two groups was statistically significant with the p value < 0.001. The median duration on dialysis was more in the PH group and the difference between the two groups were statistically significant with the p value of 0.0008. [table 2]

Table 2: Comparison of CKD, duration of dialysis and PAH among the study subjects

Parameters	PH	NON-PH	p value
Duration of CKD (months), median and IQR	12.5(11)	9(8)	p <0.001 (S)
Duration on dialysis (months), median and IQR	6(6)	3(2)	p <0.0008 (S)
PAH (mmHg)	46.14 ± 8.07		

S = Significant; IQR- Interquartile range

Mean blood pressure (MAP) showed statistically insignificant values. This result might be due to intraoperative boluses of injection ephedrine and/or noradrenaline infusion to maintain the blood pressure in targeted range in different phases of surgery. [table 3] The pulse rate was compared between both the groups and was found to be statistically insignificant. [Figure 2]

Figure 2: Intraoperative heart rate in study patients

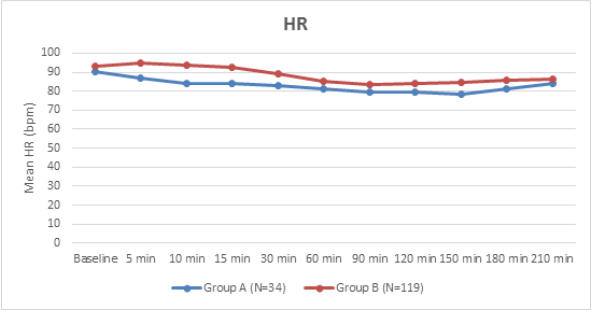

Table 3: Comparison of mean MAP (mmHg) between study groups

Time Interval	Group A (N=34)		Group B (N=119)		p value
	Mean	SD	Mean	SD	
Baseline	126.26	17.15	126.28	17.71	0.997 (NS)
5 min	117.47	19.86	117.30	21.44	0.967 (NS)
10 min	111.68	19.98	110.86	21.00	0.839 (NS)
15 min	105.91	16.91	105.97	20.74	0.987 (NS)
30 min	107.97	21.59	104.70	19.02	0.393 (NS)
60 min	112.21	20.27	109.14	16.25	0.362 (NS)
90 min	106.71	14.15	104.86	13.79	0.496 (NS)
120 min	100.94	15.20	106.22	13.29	0.051 (NS)
150 min	108.09	16.51	108.18	11.33	0.973 (NS)
180 min	109.29	12.44	109.63	16.07	0.925 (NS)

S = Significant; NS = Non Significant

In the perioperative period, hypotension was observed in 17 patients (50%) in group A and 13 patients (10%) in group B and the difference was found to be statistically significant (p<0.001). Hypotension was managed with intraoperative inotropes and vasopressor in both groups. Complications like delayed graft rejection was found to be statistically

insignificant in this study. One of the patients in the non-PH group had postoperative myocardial infarction requiring coronary stenting. Although the percentage of patients requiring mechanical ventilation was high in PH group but the value was insignificant. [table 4]

Table 4: Comparison of complications among the study subjects

Complications	Group A (N=34)		Group B (N=119)		p value
	No.	%	No.	%	
Hypotension	17	50.00	13	10.92	P<0.001 (S)
Arrhythmias	0	0.00	1	0.84	0.503 (NS)
Myocardial infarction	0	0.00	1	0.84	0.503 (NS)
Pulmonary Edema	0	0.00	0	0.00	-
Mechanical Ventilation	3	8.82	4	3.36	0.379 (NS)
Delayed Graft Functioning	1	2.94	1	0.84	0.924 (NS)

On multivariate regression analysis, presence of pulmonary hypertension and duration of CKD were not independent predictors of DGF whereas perioperative hypotension was an independent predictor of DGF. [table 5]

Table 5: Multivariate regression analysis of all patients for occurrence of delayed graft functioning and occurrence of perioperative hypotension

Variables	Value	Occurrence of Delayed Graft Functioning	Occurrence of Perioperative Hypotension
Presence of PH	p value	0.17	0.04
	OR	0.29	0.41
	95% CI	0.023-1.83	0.17-0.89
Duration of CKD	p value	0.41	0.92
	OR	1.19	0.98
	95% CI	0.92-1.21	0.87-1.07
Presence of Perioperative Hypotension	p value	0.023	NA
	OR	0.18	
	95% CI	0.037-0.79	
Age	p value	0.61	0.09
	OR	0.93	1.16
	95% CI	0.80-1.22	0.92-1.12
Duration of maintenance HD	p value	0.21	0.87
	OR	0.90	0.96
	95% CI	0.87-1.10	1.02-1.13

CKD – Chronic kidney disease; HD – Hemodialysis; OR – Odds ratio; CI – Confidence interval; *-Statistical significance

DISCUSSION:

Pulmonary hypertension is well known sequelae of long standing renal failure with high incidence in patients with arteriovenous fistula for hemodialysis. Clinically, it is difficult to diagnose the presence of pulmonary hypertension in ESRD due to similar sign and symptoms due to cardiopulmonary involvement. To ascertain the diagnosis of PH preoperative 2D echocardiogram and/or right heart catheterization (RHC) is mandatory. In our study, we estimated PH using 2-D echocardiogram as RHC is invasive and time consuming procedure.

Patients affected were mostly young with a mean age of 37.06 ± 10.27 years. Goyal VK *et al*. reported mean age in PH group was 35.7±9.8 years with the majority of the patients in the age group of 15-64 years.[5] Bozbas SS *et al*. in their study, also observed similar results and they have reported the mean age of 33.9±10.8 years.[10] In the present study, we found a male predominance in both the groups. This could be because of male predominance in society and getting higher chance of renal transplant over females. However, this male preponderance had no clinical relevance on the results of the study.

PH is highly prevalent in ESRD patients. Previous studies have shown that PH occurs in about 25-45% of patients with ESRD. In this study we found the similar incidence (22%) on echocardiograph during preoperative evaluation. Multiple pathophysiologic alterations are responsible for the development of PH in ESRD patients. Among them increase volume overload, left ventricular hypertrophy, inability of the pulmonary circulation to accommodate increased cardiac output as a result of increased pulmonary vascular calcification and stiffness, arteriovenous fistula (both duration and flow), duration of dialysis (hemodialysis>peritoneal dialysis) are more frequent. [11,12] other possible mechanisms are elevated levels of vasoconstrictors like endothelin 1 and low levels of endogenous vasodilators, resulting in pulmonary vasoconstriction, vascular remodeling, metabolic changes, renin angiotensin aldosterone system hyperactivity, uremia and secondary hyperparathyroidism. In our study, almost all patients were on hemodialysis before transplant and incidence of PH was more in patients with higher median duration of CKD and hemodialysis. Also, incidence increased in patients with AV fistula than central venous catheter for dialysis. This was well supported by Mahdavi-Mazdeh M et al in their study with higher incidence of PH in patients on haemodialysis.[13]

Hypotension was main adverse event seen during perioperative period. Possible etiologies may be hypovolemia, vasodilatation due to release of inflammatory mediator by antithymocyte globulin or ischemia reperfusion injury, blood loss etc. Other complications like arrythmias, myocardial ischemia, pulmonary edema, post-op need for mechanical ventilation didn't show any significant difference in these two groups. The result is in contrast to the study conducted by Goyal VK et al[5] in which hypotension was significantly more frequent in the PH group (26.58% vs. 9.89%,P = 0.004). Delayed graft functioning was significantly more frequent in the PH group in the same study. Ramakrishna et al[14] in 2005, in their study demonstrated a 7% mortality rate indicating serious impact of PH and found that respiratory failure and right ventricular failure were the most frequent contributing factors. Minai et al[15] reported 19% morbidity and 18% mortality in patients with PH in their study. In one study, Krowka et al[16] reported a 35% mortality rate in patients having PH undergone orthotopic liver transplant. Yigla et al[11] used a higher cut off value of 45mmHg in their study that established PH as an independent predictor of mortality in ESRD. Ramasubbu et al[17] confirmed that the risk of increased mortality rate in PH was seen in patients with higher PAP.

This suggests that the presence of PH should be incorporated in the decision making for renal transplantation, since PH is associated with worse survival and adverse outcomes and appears to improve after renal transplantation.[18]

The present study has few limitations i.e. the study group was small. Use of PPV requires fixed tidal volume and respiratory rate. Also the study was conducted in intraoperative period only because Use of pulse pressure variation to manage volume status may be erroneous due to spontaneous ventilation in patients during postoperative period.

There are very few studies available in literature on patients with PH undergoing renal transplant and there is no prospective study.

CONCLUSION:

Pulmonary Hypertension is commonly seen in patients with advanced chronic kidney disease and end stage renal disease and is associated with significant increase in morbidity and mortality. Long standing renal disease and hemodialysis through A-V fistula are major contributing factors in the pathogenesis of pulmonary hypertension in ESRD patients. In our study, hypotension was found frequent in the patients having PH, but it didn't show any significant adverse impact on the post-operative outcome and it may be due to meticulous use of dynamic indices and hemodynamically stabilizing agents like vasopressors and inotropes.

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