Original Article

Pulmonary hypertension and post-operative outcome in renal transplant: A retrospective analysis of 170 patients

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ABSTRACT

Background and Aims: Renal transplant is the best possible treatment for patients suffering with end-stage renal disease (ESRD). Cardiovascular events are the commonest factors contributing to perioperative morbidity and mortality in this population. These patients have a high incidence (up to 60%) of pulmonary hypertension (PH) and that may affect the perioperative outcome. **Methods:** In this study, we aimed to study the impact of PH on perioperative outcome after renal transplant. PH was defined as patients with pulmonary artery systolic pressure ≥35 mmHg on pre-operative echocardiography. Medical records of 170 patients who had undergone renal transplantation in the past 3 years were reviewed. Primary outcome was delayed graft functioning and secondary outcomes were perioperative complications such as hypotension, arrhythmias, need of post-operative mechanical ventilation, atelectasis and pulmonary oedema. **Results:** We observed 46.5% incidence of PH in ESRD patients. Compared to patients without PH, more patients with PH had postoperative hypotension (26.58% vs. 9.89%, $P = 0.004$) and delayed graft functioning (8.8% vs. 1.1%, $P = 0.026$). On multivariate analysis, however, PH was not an independent predictor of delayed graft functioning. **Conclusion:** In ESRD patients, although PH is not an independent predictor of delayed graft functioning, patients having PH are more prone for perioperative hypotension and delayed graft functioning after renal transplant.

Key words: End-stage renal disease, hypertension, pulmonary, transplantation

INTRODUCTION

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg on rest as assessed by right heart catheterisation.[1] It has been documented that pulmonary artery systolic pressure (PASP) may help estimate mPAP in adults with high accuracy and reasonably good precision (mPAP = 0.61 PASP + 2 mmHg). The threshold of 25 mmHg used to define PH accurately corresponds to a PASP of 38 mmHg.[2] Depending on the aetiology, PH is classified into five groups.[3] In patients with chronic kidney disease (CKD), PH is categorised as 'PH with unclear multifactorial mechanisms' (Group 5).[3] In CKD patients, the estimated prevalence of PH is approximately 12%–45%.[4] Most frequently associated pathophysiologic factors are arteriovenous (AV) fistula for haemodialysis (HD), arterial stiffness due to vascular calcification and endothelial dysfunction, volume overload and elevated left heart filling pressure due to left ventricular dysfunction.[5-7] The incidence is significantly higher in patients receiving HD in comparison to peritoneal dialysis.[8-10] Perioperative management is very critical for these patients undergoing non-cardiac surgeries. The primary objective of this retrospective analysis was to evaluate graft functioning, i.e., incidence of

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delayed graft functioning, and the secondary objective was to determine the perioperative complications following renal transplantation in patients who had pre-operative PH.

METHODS

Institutional Ethics Committee approval was obtained for a retrospective analysis of medical records of patients who had undergone renal transplant over a period of 3 years. All renal transplant recipients' medical records were accessed for complete blood count, renal and liver function test, coagulation parameters, serum biochemistry, cardiac and pulmonary evaluation as a set protocol.

Pre-operative demographic characteristics (age, sex, duration of CKD, duration of HD/peritoneal dialysis, presence of AV fistula, live/cadaveric donor, etc.) and co-morbidities (hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, etc.) and relevant investigations with two-dimensional echocardiography were reviewed from pre-anaesthesia check-up sheets. Patients were divided into two groups by the presence or absence of PH on pre-operative echocardiography. PH was defined as patients with PASP ≥35 mmHg (mPAP by invasive method was not measured in any patient) on pre-operative echocardiography. Anaesthetic techniques, drugs given for induction and maintenance of anaesthesia were reviewed. Intraoperative and post-operative complications like hypotension (≥20% decrease from baseline), significant arrhythmias, pulmonary oedema, post-operative mechanical ventilation >24 h, delayed graft functioning (need for haemodialysis within a week postoperatively) were reviewed from operating room notes, post-anaesthesia care room notes, renal transplant unit notes and patient file. Patients, whose files and operative notes were not found, were excluded. The primary outcome was to determine the incidence of delayed graft functioning (need of dialysis within 7 days of transplant), and the secondary outcome was to determine the incidence of perioperative complications such as hypotension, arrhythmias, need of post-operative mechanical ventilation, atelectasis and pulmonary oedema.

Demographical and clinical related variables are presented as frequency (percentage) and mean ± standard deviation or median as appropriate. Group comparisons are 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). SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used for statistical analysis of parameters. $P < 0.05$ was considered statistically significant.

RESULTS

In a period of 3 years, a total of 197 patients underwent for renal transplantation. Files and records of 25 patients were not found, and two patients were excluded due to intraoperative cancellation of surgery in view of the presence of atheromatous calcification of vessels. A total of 170 patients were included in the analysis. Patients were in the age group of 15–64 years with a male preponderance over females. Mean age was similar in both groups. Of 170 patients, 79 (46.5%) were diagnosed with PH on pre-operative echocardiography with PASP ≥35 mmHg. Mean PASP was 42.3 ± 9.6 with a range of 35–70 mmHg. Duration of kidney disease and mean time on HD were similar in both the groups (21.97 ± 22.05 vs. 17.23 ± 19.93 months and 15.56 ± 14.43 vs. 13.50 ± 15.81 months, respectively). AV fistula was present in 96% versus 88% patients in the PH group and non-PH group, respectively ($P = 0.092$). Patients in the PH group had higher grade of New York Heart Association score. Other parameters such as pre-operative co-morbidities, left ventricle systolic and diastolic functions and measured ejection fraction on echocardiography, live versus cadaveric donor and duration of surgery were similar in both groups [Table 1].

Pre-operative serum biochemistry, renal and liver function tests and coagulation parameters were similar in both groups. General anaesthesia with endotracheal intubation was used in all patients. Propofol was used as the induction agent in 84.8% in the PH group versus 81.3% in the non-PH group. Thiopentone sodium was used as the induction agent in 15.2% and 18.7%, respectively, in the PH and non-PH groups. Intraoperative and post-operative epidural analgesia was used in 63.29% and 65.93%, respectively, in the PH and non-PH groups. An epidural catheter was placed in all patients (110 (64.7%) patients with international normalised ratio <1.3 and platelet counts of >100,000/mm^3 Intravenous (IV) fluids used were Ringer lactate and normal saline according to central venous pressure (CVP) nearly in equal

amount, and CVP target was 10–12 mmHg. No colloid was used in any patient. IV methylprednisolone 500 mg was given to all patients, started at initiation of anastomosis as infusion. Mannitol (20 g) was used in 92.4% cases and 91.2% cases in the PH and non-PH groups, respectively, for diuresis. Two patients in the PH group and one patient in the non-PH group had received 40 mg furosemide in addition to 20 g mannitol. Basiliximab 20 mg as IV infusion over 30 min was used as an immunosuppressive agent in both the groups. Anti-thymocyte globulin was used in nine patients in the PH group and 13 patients in the non-PH group.

Delayed graft functioning (need for HD in the 1st post-operative week) was significantly more frequent in the PH group (8.86% vs. 1.1%, $P = 0.026$). Perioperative hypotension (≥20% decrease from baseline) was significantly more frequent (26.58% vs. 9.89%, $P = 0.004$) and required perioperative inotrope and vasopressor support in the PH group, irrespective of pre-operative blood pressure. Other postoperative complications, including need for mechanical ventilation, lung atelectasis and pulmonary oedema in the PH and non-PH groups are described in Table 2. One patient in the PH group had post-operative myocardial infarction and needed coronary stent [Table 2].

On univariate analysis, presence of PH (Odds Ratio [OR] 8.75, 95% confidence interval [CI] 1.05 – 72.75; $P = 0.017$), presence of perioperative hypotension (OR 9.13, 95% CI 2.05 – 40.66; $P = 0.001$) and duration of CKD ($P = 0.000$) were significant factors for occurrence of delayed graft functioning. For occurrence of perioperative hypotension, on univariate analysis, presence of PH (OR 3.299, 95% CI 1,41 – 7.72; $P = 0.004$) and duration of CKD ($P = 0.042$) were significant factors.

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. Pulmonary hypertension was an independent predictors for occurrence of perioperative hypotension whereas duration of CKD ($P = 0.999$) was not an independent predictor [Table 3].

In patients having PH, duration of CKD was an independent predictor of delayed graft functioning (OR 1.054, 95% CI 1.000–1.11; $P = 0.049$), but not of perioperative hypotension. Duration of maintenance HD and age were not independent predictors of delayed graft functioning or hypotension in patients having PH [Table 4].

Table 1: Demographic profile and pre-operative co-morbidities

Parameters	Pulmonary hypertension group (*n*=79)	Non-pulmonary hypertension group (*n*=91)	*P*
Male:female	67:12	77:14	NS
Age (years), mean±SD	35.7±9.8	36.2±11.2	NS
Duration of CKD (months), median and IQR	12 (17)	10 (13)	NS
Duration of HD (months), median and IQR	10 (13)	7.5 (12.75)	NS
NYHA class (I/II/III/IV)	17/60/2/0	34/57/0/0	NS
Diabetes mellitus, frequency (%)	3 (3.8)	7 (7.7)	NS
Hypertension, frequency (%)	70 (88.6)	77 (84.6)	NS
Coronary artery disease, frequency (%)	2 (1.3)	0	NS
Ejection fraction (%), mean±SD	53.5±8.02	55.7±8.2	NS
Donor (live:brain dead)	76:3	89:2	NS
Duration of surgery (min), mean±SD	171.2±14.5	172.1±14.1	NS

CKD – Chronic kidney disease; HD – Haemodialysis; NYHA – New York Heart Association; SD – Standard deviation; IQR – Interquartile range; NS – Not significant

Table 2: Perioperative complications

Complications	Pulmonary hypertension group (*n*=79), frequency (%)	Non-pulmonary hypertension group (*n*=91), frequency (%)	*P*
Hypotension	21 (26.6)	9 (9.9)	0.004
Arrhythmias	0	2 (2.2)	0.249
Myocardial infarction	1 (1.3)	0	0.465
Post-operative ventilation	2 (2.5)	0	0.214
Atelectasis	1 (1.3)	0	0.465
Pulmonary edema	2 (2.5)	0	0.214
Delayed graft functioning	7 (8.9)	1 (1.1)	0.026

Table 3: Multivariate regression analysis of all patients for occurrence of delayed graft functioning and occurrence of perioperative hypotension

Variables	Statistical hypothesis tests	Occurrence of delayed graft functioning	Occurrence of perioperative hypotension
Presence of pulmonary hypertension	P	0.120	0.021*
	OR	0.178	0.358
	CI	0.020-1.571	0.149-0.859
Duration of CKD	P	0.373	0.999
	OR	1.012	1.000
	CI	0.986-1.039	0.982-1.018
Presence of perioperative hypotension	P	0.019*	NA
	OR	0.157	
	CI	0.034-0.737	

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

Table 4: Multivariate regression analysis of pulmonary hypertension group for hypotension and delayed graft functioning

Variables	Occurrence of perioperative hypotension	Delayed graft functioning
Age		
P	0.072	0.687
OR	1.051	0.982
CI	0.996-1.109	0.899-1.073
Duration of CKD		
P	0.774	0.049*
OR	1.007	1.054
CI	0.961-1.056	1.000-1.111
Duration of maintenance HD		
P	0.951	0.149
OR	0.998	0.925
CI	0.992-1.079	0.832-1.028

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

DISCUSSION

This study showed that renal transplant recipients having PH are at significantly increased risk of perioperative hypotension, but not of delayed graft functioning. Perioperative hypotension however is associated with delayed graft functioning. In the present study, the incidence of PH was 46.5% and that is similar to that mentioned in the previous literature.[9-12]

In renal transplant surgery, perioperative morbidity and mortality depend on large number of factors. Renal transplant recipients with a history of multiple pregnancies, multiple blood transfusions, greater co-morbidity index, higher body weight, age and African-American race, prior history of transplantation, higher panel reactive antibodies levels, lower level of human leucocyte antigen matching and HD in the pre-transplant period have poor outcome with greater perioperative morbidity and mortality.[13] Among these, cardiac events are the most common culprit. The results of our study are in accordance with one study which concluded that PH has a significant negative impact on post-operative outcome in the form of congestive heart failure, haemodynamic instability, sepsis, respiratory failure, need for ventilator support and longer Intensive Care Unit stay.[14] Moreover, two more studies. also concluded similar complications in in patients of portal hypertension.[15,16]

The mechanisms behind the increased prevalence of PH in the CKD patients are poorly understood. CKD patients have elevated levels of the potent vasoconstrictor endothelin-1 and decreased circulating levels of the vasodilator nitric oxide and its metabolites, because of endothelial dysfunction, resulting in pulmonary vasoconstriction. Further, high cardiac output state because of an AV fistula for dialysis leads to further increase in pulmonary pressures because non-compliant pulmonary vasculature is unable to compensate for high cardiac output. Moreover, poorly controlled hypertension in CKD patients and left ventricular diastolic dysfunction increase pulmonary venous pressures and contribute to the development of PH.[17]

High incidence of delayed graft functioning in PH patients may be explained by more frequent haemodynamic instability and alterations in vasoactive substances, leading to poor perfusion of transplanted kidney and acute tubular necrosis. There is usually an inverse relationship between PASP and cardiac output, and it can explain low perfusion to kidneys. Patients with DGF have high circulating serum levels of endothelin-1, and this has been implicated in the development of ischaemia–reperfusion injury after renal transplant.[17]

Pre-operative PH is closely associated with early graft dysfunction either delayed graft functioning or slow

graft function.[18] Commonly encountered risk factors for the development of PH in patients on HD are volume overload due to inadequate dialysis, left ventricular dysfunction and high-flow AV fistula.[7] HD via AV fistula is an independent risk factor of PH among end-stage renal disease patients. Although patients with AV fistula as a dialysis access were more in PH group and causal relation between AV fistula and PH in CKD patients is documented in the literature,[19,20] this difference was not statistically significant in our retrospective analysis.

Our study has several limitations. First, our data do not demonstrate an independent association between PH and delayed graft functioning; however, as this is a retrospective study, this was not designed to definitively demonstrate causality. Second, our study was limited to retrospective data analysis of pre-operative echocardiography, and in the absence of standardisation, fluid status at the time of echocardiography may have impacted the measurement of PASP.

CONCLUSIONS

This review depicts that PH is highly prevalent among CKD patients. While PH was not independently associated with delayed graft functioning, post-operative adverse outcomes in terms of delayed graft functioning and hypotension were more common in PH patients compared to non-PH patients. Hence, extra attention with better pre-operative optimisation may help these patients.

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Conflicts of interest

There are no conflicts of interest.

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