Original Article

Effect of discontinuing morning dose of antihypertensive for renal transplant surgery on haemodynamic and early graft functioning: A prospective, double-blind, randomised study

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ABSTRACT

Background and Aims: Antihypertensive drugs are continued until the day of renal transplant surgery. These are associated with increased incidence of hypotension and bradycardia. Hence, this study was designed to evaluate perioperative haemodynamic and early graft functioning in renal recipients with discontinuation of antihypertensive drugs on the morning of surgery. **Methods:** This prospective, randomised, double-blind study recruited 120 patients. Group 1 patients received placebo tablet while Group 2 patients received usual antihypertensive drugs on the day of surgery. Perioperative haemodynamics and time for reinstitution of antihypertensives were the primary outcome measures. The secondary outcome measures were need for inotropic support and graft function. Perioperative haemodynamics were analysed using ANOVA and Student's *t*-tests with Bonferroni correction. Fischer's exact test was used for analysis. **Results:** Systolic blood pressure (SBP) declined, which was more in Group 2. Forty-one patients developed significant hypotension; a correlation was found between the maximum observed hypotension and number of antihypertensive medications ($P = 0.003$). Four cases had slow graft function (one in Group 1 and three in Group 2). Twenty-eight patients in Group 2 required mephentermine boluses to maintain their SBP compared to 13 patients in Group 1 ($P < 0.001$). Two patients in Group 2 required dopamine to maintain SBP above 90 mmHg after the establishment of reperfusion as compared to none in Group 1. **Conclusion:** Single dose of long-acting antihypertensive drugs can be omitted on the morning of surgery without any haemodynamic fluctuations and graft function in controlled hypertensive end-stage renal disease renal transplant patients receiving a combined epidural and general anaesthesia.

Key words: Antihypertensive therapy, graft function, haemodynamic, perioperative, renal transplant

INTRODUCTION

Hypertension is the second most common cause of chronic renal failure after diabetes mellitus.[1] These patients are invariably on a combination of two or more antihypertensive drugs.[2] The standard guidelines for perioperative management of hypertensive patients are to continue antihypertensive medications until the day of surgery.[3] These drugs need to be started as soon as possible after surgery as an interruption of these drugs may cause perioperative rebound hypertension, tachycardia or myocardial infarction.[4] Usually, the same guidelines for drug management of hypertension

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are used for end-stage renal disease (ESRD) patients undergoing renal transplantation. The administration of antihypertensive drugs until morning of surgery in renal disease patients is associated with a high incidence of hypotension and bradycardia requiring inotropes.[4] Intraoperative hypotension due to the combined effect of anaesthetic and antihypertensive drugs in these patients with blunted cardiovascular reflexes might make maintenance of adequate perfusion pressure difficult. Intraoperative hypotension is known to cause delayed graft function and allograft rejection with poor long-term outcomes.[5]

Studies have shown that central venous pressure (CVP) and blood pressure (BP) in the high normal range are of benefit to the transplanted kidney.[6] Whether or not to continue angiotensin-converting-enzyme (ACE) inhibitors on the day of surgery is equivocal.[7] We aimed to evaluate whether omitting the morning dose of antihypertensive medication in controlled hypertensive ESRD patients undergoing renal transplant under combined epidural and general anaesthesia (GA) would preserve haemodynamics than in those continuing antihypertensive medications.

METHODS

After approval of the Institutional Ethics Committee and written informed consent of the patients, this prospective, double-blind, randomised controlled study was conducted on 120 ESRD patients with hypertension undergoing elective renal transplant surgery under combined epidural GA. The patients with uncontrolled hypertension, valvular heart disease, cardiomyopathy, ejection fraction <45%, age <12 years, and contraindication to epidural anaesthesia were excluded from the study. All the patients were randomly divided into two groups using computer-generated random number table: Group 1 - Patients were given placebo tablets instead of antihypertensive drugs on the morning of surgery 2 h before surgery; Group 2 - Patients received anti-hypertensive drugs except ACE inhibitor (if any) on the morning of surgery 2 h before surgery.

All patients received haemodialysis on the day before surgery to their dry weight as per our institutional protocol. Oral diazepam 0.1 mg/kg was administered on the night before surgery. Oral ranitidine 150 mg and metoclopramide 10 mg were given on the night before and 2 h before shifting the patient to the operation room.

In the operating room, after instituting 12 lead electrocardiogram, non-invasive BP and pulse oximetry (oxygen saturation [SpO_2]), a peripheral venous access with 16-gauge cannula was secured. An infusion of normal saline at the rate of 2 ml/kg/h was started and intravenous (i.v.) fentanyl 1 μg/kg was administered. A 20-gauge arterial cannula was inserted in a radial artery under local anaesthesia. Under aseptic precautions, an 18-gauge epidural catheter was placed through $T_{12} - L_1$ interspace in the left lateral position. Correct placement of the epidural catheter was confirmed by injecting a test dose of 3 ml of 2% lignocaine with adrenaline 1:200,000. The patient was made supine and 10 ml of 0.25% bupivacaine with 40 μg fentanyl were given through the epidural catheter. After 15 min boluses of 2.5 ml 0.25% bupivacaine given until sensory analgesia was achieved between T_6 and L_1 dermatomes. The haemodynamic stabilisation was allowed for 15 min, and GA was induced in standardised manner. Anaesthesia was induced with i.v. propofol 1.5–2 mg/kg followed by atracurium 0.5 mg/kg. Anaesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane 0.2%–2% end-tidal concentration, titrated to bispectral index (BIS) value of 40–60. Intermittent positive pressure ventilation was done to maintain end-tidal carbon dioxide ($EtCO_2$) of 35–40 mmHg. A double-lumen central venous catheter was inserted. All patients received 20 mg of basiliximab (Simulect®, Novartis Pharmaceuticals, New Jersey, USA) at induction of anaesthesia and 500 mg of hydrocortisone before starting of vascular anastomosis. Intraoperative monitoring included arterial BP (systolic BP [SBP], diastolic BP [DBP], mean BP [MBP]), heart rate (HR), SpO_2, $EtCO_2$, CVP and nasopharyngeal temperature and recorded every 5 min interval. Half hourly urine output was monitored after revascularisation of the graft. Any fall in systolic pressure <90 mmHg or 25% of MBP baseline value persisting for more than 5 min was considered as a hypotensive episode. It was managed by bolus of 250 ml of normal saline, repeated twice. If MBP still remained <25% mean basal value or <90 mmHg systolic, i.v. mephentermine 6 mg bolus was given. If hypotension persisted for more than 15 min, inotropic support with dopamine was started. The mean of first three recordings of monitored parameters at 5 min interval taken during the stabilisation period was considered as baseline values for subsequent comparison.

In all the patients, CVP was gradually built with crystalloids (up to 70–80 ml/kg of normal saline) and

colloids (2–4 ml/kg of 20% albumin) up to 15 mmHg until revascularisation. i.v. furosemide 2 mg/kg and 20% mannitol 2 ml/kg was given to all patients just before reperfusion of grafted kidney. Blood transfusion was considered to target haemoglobin of 8 g/dL. Once graft diuresis established, fluid therapy was guided by hourly urine output, and to maintain CVP 8–10 mmHg. In case there was no urine output, fluid administration was restricted. Intraoperative rescue analgesia in the form of i.v. fentanyl 0.25μg/kg was given whenever there was a 20% rise in HR and/or BP. At the end of surgical procedure, residual neuromuscular blockade was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.02 mg/kg). The patient was extubated or shifted to post-transplant intensive care unit for ventilatory support depending on the condition of individual patient. Analgesia was provided with epidural infusion of 0.125% bupivacaine 6–10 ml/h with fentanyl 2 μg/ml.

Haemodynamics along with SpO_2 and hourly urine output were monitored hourly for first 24 h. Post-operatively antihypertensive drugs were administered once patient's BP recordings were more than 160/90 mm Hg for more than 4 h. Time interval between surgery and post-operative reinstitution of antihypertensive drug therapy was recorded. Patients requiring post-operative mechanical ventilation were excluded from analysis.

The sample size was calculated for the decrease in the incidence of intraoperative hypotension which was the primary outcome of the study. The incidence of hypotension in ESRD patients following anaesthesia has not been quantified. Based on the incidence of significant hypotension following administration of anaesthesia noted in studies of subjects without ESRD, a sample size of 58 patients per group would be required to demonstrate a 50% decrease in significant hypotensive episodes following a therapeutic manoeuvre with an alpha of 0.05 and 80% power.[8] Hence, we enrolled sixty patients per group to ensure for possible exclusion.

Statistical analysis was performed using SPSS 12.0 (SPSS for Windows, IL, Chicago, USA). Data are presented as mean (±2 standard deviation). Normality of distribution was tested by one-way Kolmogorov–Smirnov test. The demographic data were analysed using Chi-square test and independent samples *t*-test. A repeated measure ANOVA was used to analyse perioperative changes in BP, HR and CVP within group and between the groups using Student's *t*-tests with Bonferroni correction. The quantitative data (i.v. fluids, propofol, end-tidal isoflurane, warm and cold ischaemic time, time interval between revascularisation of graft and onset of diuresis and serum creatinine [Cr]) was analysed using Mann–Whitney U-test. Fischer's exact test was used to analyse the difference in resumption of antihypertensive therapy in post-operative period and Kaplan–Meier analysis was performed with a plot of reinstitution of antihypertensive over time as a hazard function. Since the drug intake of our patients was heterogeneous, the possibility of individual drug and the degree of decrease in mean arterial pressure by drug groups were evaluated by Spearman correlation coefficient to the number and types of antihypertensive separately. $P < 0.05$ was considered statistically significant.

RESULTS

The flow of the participants is as per the attached CONSORT flow diagram [Figure 1]. Baseline demographic characteristics such as age, gender, body weight, pre-operative weight loss and pre-operative

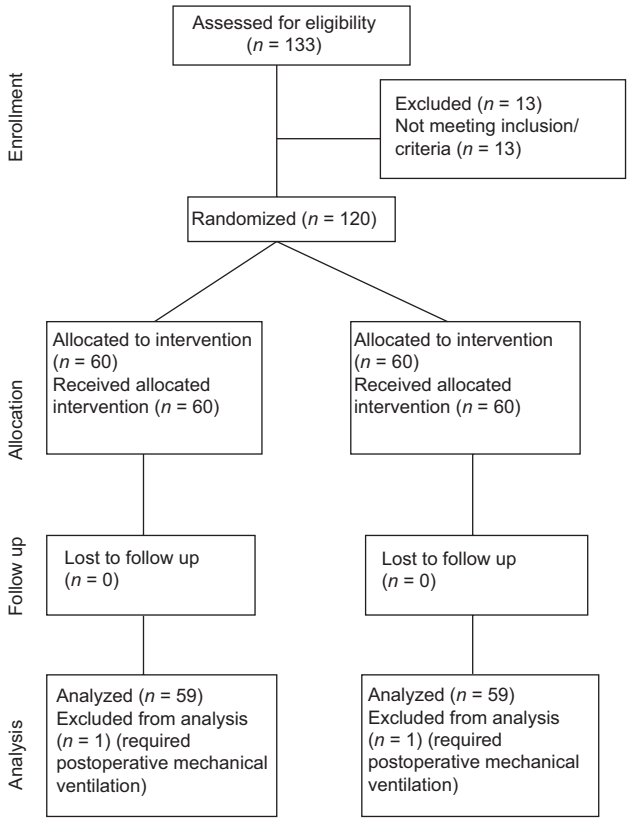

Figure 1: CONSORT diagram showing flow of participants through each stage of randomized trial

antihypertensive therapy were comparable in both groups [Table 1]. Baseline haemodynamic parameters (BP, HR and CVP) and subsequent degree of intubation response were comparable between the two groups. BP showed a decline 10 min after epidural administration in both groups which was more in Group 2 for systolic BP and remained significantly lower than the basal value for rest of the intraoperative period and until 4 h post-extubation ($P < 0.05$). However, in Group 1, SBP approached baseline values 8 min post-intubation and remained comparable to baseline during rest of the intraoperative period. The fall in SBP after reperfusion of grafted kidney was significantly less in Group 1 (124.6 ± 15.26) mmHg as compared to Group 2 (110.15 ± 13.42) mmHg, respectively ($P = 0.042$) [Figure 2]. The DBP showed fewer fluctuations as compared to SBP but was significantly higher in Group 1 at all times ($P < 0.05$) [Figure 3]. Both groups showed decline in MBP at 10, 20 and 30 min after epidural. The MBP although maintained within 25% of baseline values in both the groups was significantly higher in Group 1 than in Group 2 and remained so till 4 h of extubation ($P < 0.05$) [Figure 4].

Twenty-eight patients in Group 2 and 13 patients in Group 1 required mephentermine boluses to maintain their SBP ($P < 0.001$). A correlation was found between the maximum observed hypotension and number of antihypertensive medications (Spearman's correlation coefficient = 0.453, $P < 0.003$). There was no correlation with any individual drug combination and the degree of intraoperative hypotension (coefficient 0.027; $P = 0.72$). Kaplan–Meier analysis showed lesser survival times in Group 2 indicating earlier antihypertensive resumption in the first 24 h of post-operative period [Figure 5]. Four cases had slow graft function (one in Group 1 and 3 in Group 2) defined by drop in serum Cr <50% by post-operative day 3 without need for dialysis post-transplant.

Two patients in Group 2 required inotropic support (dopamine) to maintain SBP above 90 mmHg after establishment of reperfusion as compared to none in Group 1. Baseline and perioperative HR was comparable between the groups at all times including the intubation response. The target BIS was

Table 1: Demographic profile and antihypertensive therapy of both groups

Variable	Group 1	Group 2	*P*
Age (years) Mean±SD	36.2±10.2	35.4±11.2	0.80
Gender (Male: Female) %	85:15	75:15	0.63
Weight (kg) Mean±SD	55.7±34	50.3±9.1	0.06
Weight loss (kg) after preoperative hemodialysis Mean±SD	1.8±0.8	1.5±0.7	0.13
Hemoglobin (gm%) Mean±SD	7.8±1.8	8.5±1.9	0.24
Antihypertensive drugs			
Amlodepine	15	10	0.65
Amlodepine + Atenolol	33	36	0.74
Amlodepine + Atenolol + Prazosin	3	6	0.52
Amlodepine + Atenolol + Clonidine	2	3	0.62
Amlodepine + Atenolol + Prazosin + Tarsomide	6	4	0.62

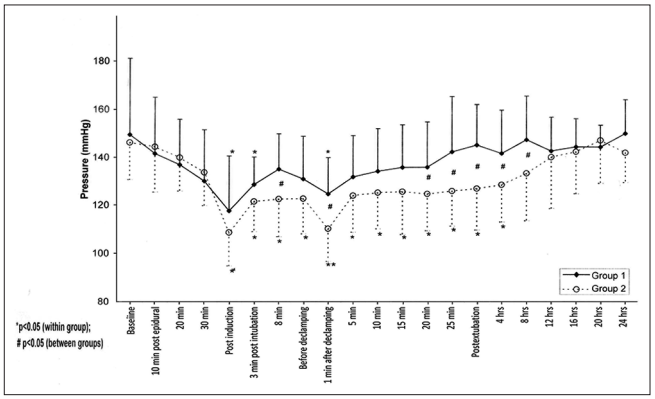

Figure 2: Intraoperative haemodynamic parameters in the two groups; SBP: Systolic blood pressure

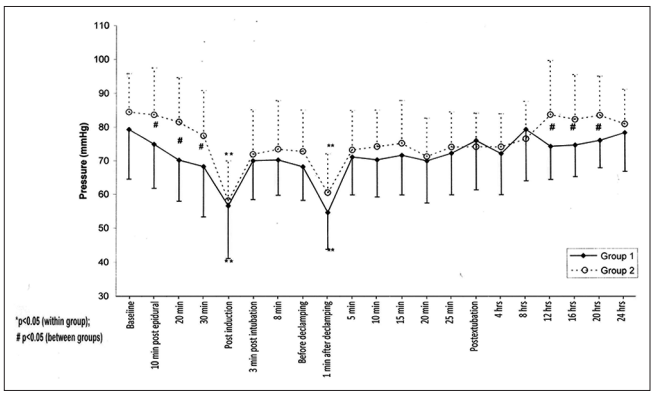

Figure 3: Intraoperative haemodynamic parameters in the two groups. DBP: Diastolic blood pressure

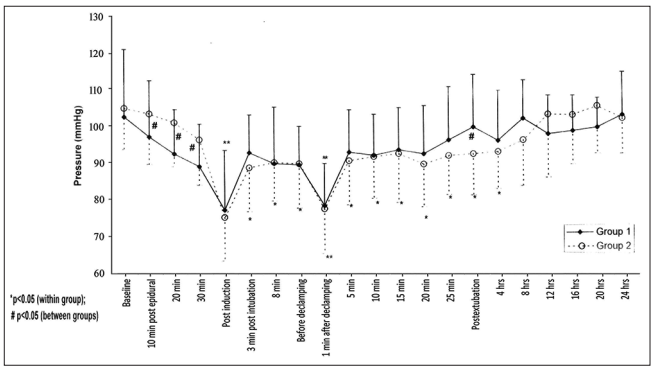

Figure 4: Intraoperative haemodynamic parameters in the two groups; MBP: Mean blood pressure

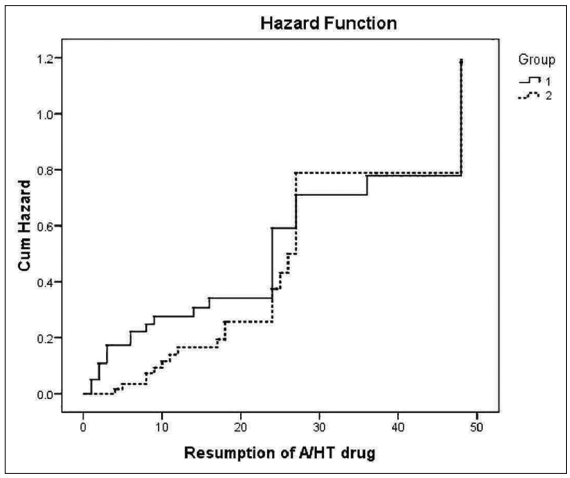

Figure 5: Kaplan–Meier survival analysis with a hazard plot showing earlier restitution of antihypertensive in Group 2 than Group 1 till 24 post-operative hours

maintained at a mean BIS value of 51 ± 8.7 in Group 1 compared to 44 ± 14.2 in Group 2 which was found to be comparable between the two groups (P = 0.36). Other variables such as warm and cold ischaemic times, induction doses of propofol and epidural drug requirements were comparable between the two groups but patients in Group 1 required a higher end-tidal concentration of isoflurane (ET_{iso}) (0.70 [±0.3]) in comparison to Group 2 (0.45 [±0.2]) for maintenance of anaesthesia (P = 0.02). Fluid requirements and CVP were not statistically significant between the two groups [Table 2]. Baseline CVP was comparable between the groups (Group 1: 4.95 ± 1.19 mmHg vs. Group 2: 5.1 ± 1.27 mmHg vs., P > 0.05). The CVP in both the groups was significantly increased (Group 1: 15.5 ± 0.9mmHg) vs. Group 2: 15.5 ± 0.83 mmHg) from basal value before establishing reperfusion of grafted kidney and maintained at a higher value for rest of observation period in both groups (P < 0.05). No significant changes in CVP between the groups throughout observation period were seen (P > 0.05).

Duration of surgery ranged between 125 and 350 min. Time interval between revascularisation of graft and onset of diuresis was significantly lower in Group 1 (2.08 [±2.52]) min in comparison to Group 2 (4.65 [±3.6]) min (P = 0.08). Post-operative recovery profile was similar in both groups, and none of the patients in either group complained of pain in the immediate post-operative period. Post-operative serum Cr was 2.51 ± 1.2 mg/dL in Group 1 and 2.2 ± 0.87 mg/dL in Group 2 (P = 0.76) [Table 2]. Abbreviated modification of diet in renal disease formula was used to estimate glomerular filtration rate

Table 2: CVP, intraoperative fluid requirement and grafted kidney variables

Variable	Group 1	Group 2	*P*
CVP (mm Hg)			
Baseline	4.9±1.2	5.1±1.3	0.42
At anastomosis	15.5±0.9	15.5±0.8	0.17
Crystalloid (ml/kg)	61.4±24.5	74.5±24	0.09
Albumin (ml/kg)	3.7±0.8	4.2±0.9	0.08
Mannitol (ml/kg)	1.8±0.4	2.1±0.5	0.07
Blood (ml/kg)	3.3±5.5	1.3±3.4	0.38
Warm ischaemia time (min)	8.2±6.7	8.1±8.5	0.82
Cold ischaemia time (min)	87.6±23.6	82.2±30.1	0.32
Time interval between declamping and onset of diuresis (min)	2.1±2.5	2.7±3.6	0.08
24 hour serum creatinine (mg%)	2.5±1.2	2.2±0.9	0.76
Postoperative predicted GFR (ml/min)	41.7±33.6	40.1±20.9	0.08

CVP – Central Venous Pressure, GFR – Glomerular Filtration Rate

based on serum Cr which was 41.71 ± 33.64 ml/min in Group 1 and 40.13 ± 20.98 ml/min in Group 2 (P = 0.08).

Twelve patients in Group 1 (19.83%) as compared to none in Group 2 required antihypertensive therapy within 8 h of surgery (P < 0.0001). Between 8 and 16 h, 25 (41.66%) patients in Group 1 and none in Group 2 resumed antihypertensive drugs. By 24 h post-transplant, cumulative number of patients in both the groups restarting antihypertensive drugs was comparable, forty (65.57%) in Group 2 versus 42 (70%) in group 1, respectively (P = 0.41). Eighteen patients (30%) in Group 1 and 21 (35%) patients in Group 2 did not resume antihypertensive drugs by the end of 24 h (P > 0.05).

DISCUSSION

Our study shows the safety of discontinuing antihypertensive medications on the day of surgery on perioperative haemodynamic and graft survival. Discontinuation of antihypertensive medications resulted in less episodes of intraoperative hypotension, lesser consumption of drugs to maintain adequate perfusion pressures and earlier resumption of antihypertensive in the post-operative period.

Combined epidural and GA technique is associated with decreased requirement of inhalational anaesthetic as well as muscle relaxant and provides adequate perioperative analgesia. It also blunts haemodynamic stress response to intubation and extubation by sympatholysis.

ESRD patients have multitude of factors affecting the outcome of renal transplant surgery.[9] Haemodynamic fluctuations have a direct effect on the transplanted

kidney due to the lack of autoregulation in the denervated graft kidneys. The importance in maintaining adequate perfusion pressure is to prevent the adverse effects of hypertension and hypotension on the grafted kidney. Hypertension may hamper graft function by causing increased leukocyte adhesion and alloantigen expression following exposure of endothelium to shear forces, but on the other hand, hypotension hampers graft perfusion resulting in ischaemic injury and delayed graft function.[2] Continuation of antihypertensives perioperatively is aimed at preventing end-organ damage from intraoperative hypertension such as adverse cardiovascular events.[10] Although these are important in ESRD patients undergoing surgery, focus on graft viability is primary.

Usually, long-acting antihypertensive drugs with once-a-day administration are recommended to improve patient compliance.[11] Continuation of these long-acting medications before combined regional-GA may cause haemodynamic instability. Postponing the morning dose to the post-operative period may be a better strategy to maintain stable perioperative haemodynamics as seen in our study and could be explained by the augmentation of after-load lowering effect of long-acting antihypertensive by epidural and GA in Group 1. We did not find a significant rise in BP as compared to baseline after tracheal intubation in Group 1 patients, a finding that was contrary to previous studies where an exaggerated hypertensive response was reported[12]; hypertension was probably attenuated by the epidural block used in our study.

Forty-seven per cent patients in Group 2 experienced hypotension, while the incidence of the same was comparable in Group 1. This is in contrast to a previous study and could be due to the higher number of antihypertensives received by our patient.[13] Our study found a positive correlation between the number of antihypertensives and the lowest intraoperative BP irrespective of the group. This might be explained by the sustained levels of drugs acting at various sites resulting in profound hypotension.

In titration to anaesthetic depth, Group 1 patients had a higher anaesthetic requirement (ET_{iso}) for maintenance of GA than Group 2 patients. A lower anaesthetic consumption in Group 2 could be due to the effects of circulating antihypertensives like atenolol on BIS, which was used for titration of anaesthetic depth.[14,15] Intraoperative BP variables although higher than those recommended by European Collaborative Transplant Study was higher in Group 1 at all times compared to Group 2 despite use of dopamine in Group 2.[6] Post-extubation BP variables were still significantly lower than baseline in Group 2 till 8 h of extubation. By this time, many patients in Group 1 received their antihypertensive drugs and subsequently, both groups had comparative BP for rest the of observation period. Group 1 patients resumed antihypertensive drugs earlier in post-operative period than Group 2 signifying that antihypertensive drugs dose was just postponed to post-operative period in Group 1 patients. By 24 h, both the groups were receiving antihypertensive drugs similarly.

Post-operative graft function was similar in both the groups suggesting safety of omitting morning dose. Hypertension in early post-operative period has been shown as a predictor of allograft rejection and delayed graft function.[6] These hypertensive episodes reiterate the importance of early resumption of antihypertensive therapy.

A major limitation of the study was exclusion of uncontrolled hypertensive patients and those who are on ACE inhibitors which is common among ESRD patients and needs further studies. Whether or not to continue renin-angiotensin blockade is another dilemma since their continuation might result in significant hypotension, need for inotropic support and mortality[16] Epidural analgesia is commonly employed in renal transplant recipients in our institute which also has renin-angiotensin system (RAS) blocking effects and may partly compensate for RAS hyperactivity even if discontinued preoperatively. The effect of discontinuing antihypertensive with alternative modes of analgesia needs further evaluation.

CONCLUSION

A single dose of long-acting antihypertensive drugs can be safely omitted on the morning of surgery without any adverse consequences on the graft in controlled Hypertensive end-stage renal transplant patients receiving combined epidural and general anaesthesia.

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Conflicts of interest
There are no conflicts of interest.

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