Original Article

# Timing of intraoperative crystalloid infusion may decrease total volume of infusate without affecting early graft function in live related renal transplant surgery: A randomized, surgeon-blinded clinical study

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## ABSTRACT

**Introduction:** Early graft function is crucial for successful kidney transplantation. Intravascular volume maintenance is paramount in ensuring reperfusion of transplanted kidney. This study was planned to compare whether the timing of fluid infusion can help to decrease amount of fluid given without altering early graft function during renal transplantation.

**Materials and Methods:** The present study included forty recipients, randomized into standard (Group-S) or targeted fluid therapy (Group-T). Group S received fluid according to conventional fasting deficit while Group T received at 1 ml/kg/h from the start of surgery till start of vascular anastomosis after which fluid infusion rate in both group was increased to maintain a central venous pressure of 13–15 mm of Hg till reperfusion. Primary outcome measured was serum creatinine level on first postoperative day while secondary outcomes were IV fluid given, perioperative hemodynamics, onset of diuresis, graft turgidity, urine output, and renal function during first 6 postoperative days.

**Results:** The study showed Group T postoperatively had early fall in serum creatinine (day 3) than S (day 6) although this difference was not statistically significant. Group T had received significantly less fluid per kg of dry weight (T-42.7 ± 9.7 ml/kg, S-61.1 ± 11.1 ml/kg, $P < 0.001$), had early diuresis, better graft turgidity and urine output than Group S.

**Conclusion:** Targeted hydration significantly decreases the total amount of fluid infused during the intraoperative period without altering early graft function. Targeted hydration during vascular anastomosis produced stable hemodynamics and early diuresis without any side-effects pertaining to hypo or hyper-volemia.

Clinical trial identifier number-CTRI/2016/07/007111.

## INTRODUCTION

Early graft function is crucial for successful kidney transplantation. Many modifiable and nonmodifiable factors are known to affect graft function.[1] One of the important modifiable factors which can potentially improve early graft function is maintenance of adequate perioperative intravascular volume especially at the time of reperfusion of transplanted kidney. With increasing use of organs from extended criteria and post cardiac death donors, it has become even more important to optimize these modifiable factors.

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|---|---|
| Quick Response Code: | Website: www.indianjurol.com |
| | DOI: 10.4103/iju.iju_239_21 |



**Received:** 05.06.2021, **Revised:** 20.11.2021,

**Accepted:** 06.12.2021, **Published:** 01.01.2022

**Financial support and sponsorship:** Nil.

**Conflicts of interest:** There are no conflicts of interest.

Perfusion of the kidneys after vascular anastomosis with the recipient vessels depends on the intravascular volume status and the mean arterial pressure (MAP) of the recipient. Since the transplanted kidney is denervated and not in the autoregulatory loop of the recipient homeostatic function, better hydration, and pressure dependent perfusion immediately after de-clamping of the recipient vessels is purportedly important for immediate urine production. Delay in the onset of diuresis may affect the long-term graft survival as well as increase morbidity in the immediate postoperative period of the recipients.[2] Delayed return of renal function is associated with 20%–40% decrease in graft survival.[3]

Recipients with end stage renal disease (ESRD), however, have a narrow margin of safety with intravenous hydration and may oscillate between hypovolemia and hypervolemia.[4] Maintenance of intravascular volume is a complex process in patients with chronic kidney disease (CKD). Kidney transplant recipients often have incipient or overt myocardial dysfunction and systolic and/or diastolic heart failure. Aggressive and over-zealous volume expansion may lead to cardiac decompensation and pulmonary edema.[5] Intravascular volume and arterial blood pressure need to be carefully adjusted to effectively perfuse the transplanted kidney as well as to avoid over hydrating the recipients. Traditionally fluid replacements for other (non-CKD) patients undergoing surgery are done according to volume deficit due to overnight fasting and maintenance fluid therapy applying the Segar's formula as well as taking into account the intraoperative and third space losses.[6] The aim of fluid infusion in general being to maintain intravascular volume rather than to achieve a slight hypervolemia (as is required in renal transplantation). Isotonic crystalloids are the fluid of choice during surgery; however, crystalloids mostly distribute to the interstitial space. Various studies show that crystalloid intravenous fluid has a distribution phase which results in plasma volume expansion to 50%–60% of the infused volume till infusion lasts which is reduced to 15%–20% within 30 min of stopping the infusion of fluid.[7] Colloids may be considered in renal transplant recipients with severe intravascular volume deficits who require high-volume resuscitation. Crystalloids can easily pass through the luminal glycocalyx layer, but colloids are held tightly in the intravascular compartment by this layer. This is reflected by the higher intravascular presence of iso-oncotic colloids (80%–100%) as compared to crystalloids (around 20%) for as long as the glycocalyx layer is intact.[8] However, colloids should be avoided as they can affect the renal function and cause coagulopathy.[9,10]

Crystalloids given according to Segar's calculation may be redistributed by the time of de-clamping of the anastomotic vessels of the transplanted kidney and thus be unable to provide the volume head required for adequate graft perfusion. We hypothesized that infusing crystalloids aggressively over a short duration of time prior to de-clamping of anastomosed vessels may improve graft perfusion and result in the earlier return of graft function rather than the traditionally calculated method of fluid infusion. The aim of the study was to compare two different fluid hydration regimens-traditional fluid replacement method and targeted fluid replacement on early graft function during live related renal transplantation (LRRT) as well as their effect on various other metabolic parameters in recipients undergoing surgery. We also sought to evaluate any side–effects associated with the focused fluid infusion thus given. The primary outcome of the study was serum creatinine level on the first postoperative day in recipients receiving fluid according to the two different fluid regimens. The secondary outcomes were overall intravenous fluid infused during the surgery, graft turgidity score, graft diuresis time and urine output in the postoperative period. We also evaluated any signs of fluid overload or metabolic acidosis in both the groups.

## MATERIALS AND METHODS

### *Study design and protocol*

The study was a single-blinded, prospective randomized controlled trial conducted from December 1, 2015 to October 30, 2016. A similar study done by Othman *et al*.[11] reported a mean serum creatinine value of 2.4 ± 0.7 mg/dL on postoperative day 1 when a central venous pressure (CVP)-directed fluid infusion was done only at the time of warm ischemia time during anastomosis. The control group in their study, however, received fluid at a constant infusion rate. We decided to derive the sample size in our study according to the serum creatinine values in their CVP target and constant infusion rate group as recipients in their CVP target group was planned in our interventional group. With an alpha error of 5%, power of the study being 90%, we needed 16 cases in each group. Considering the problems with technical failure, drop out from the study and to show increased variability in data, it was decided to enroll minimum of 40 cases in total with 20 cases in each group. The study was approved by the Institutional Ethical Committee (Reference no. IESC/T-451/23.12.2014) and all recipients signed informed consent after detailed information about the study protocol.

Inclusion criteria was recipients aged between 18 and 65 years undergoing LRRT for ESRD. All the donors were kept 8 h of fasting for solid and 2 h for clear water. They underwent laparoscopic nephrectomy with pneumoperitoneum pressure between 11 and 14 mm of Hg. All recipients were screened with preoperative echocardiography along complete blood count, liver function and renal function test. Recipients having severe left ventricular dysfunction with ejection fraction <40%, diabetes, hemoglobin <8 g/dL, severe pulmonary or liver disease, vascular anomaly of donated

organ and requiring intraoperative blood transfusion or inotropic support were excluded from the study.

All recipients recruited for this study underwent routine preanesthetic check-up on the evening prior to surgery. All recipients were dialyzed 16–20 h before surgery with ultrafiltrate volume decided according to recipient's dry weight. All recipients undergoing renal transplantation are dialyzed to dry weight and received same immunosuppressive therapy according to our Institutional protocol. Recipients were fasting overnight. All preoperative post dialysis investigations were noted. It was not possible to implement blinding for the anesthesia team. The recipients and the surgical team were blinded to the group allocation. All recipients were monitored using 3-lead electrocardiogram, pulse oximetry and noninvasive blood pressure. Noninvasive estimated continuous cardiac output and cardiac index were monitored using NIHON KOHDEN monitor. Once intravenous access was obtained recipients were randomized into either of the two groups, standard fluid therapy (Group-S) or targeted fluid therapy (Group-T) using a computer-generated randomization sequence. Induction of anesthesia was done with etomidate, 0.2 mg per kg and fentanyl (2–3 mcg/kg). Atracurium was given for muscle relaxation and endotracheal intubation was done once adequate muscle relaxation was achieved. All the recipients were put on volume-controlled ventilation with tidal volume set at 8 ml/kg of predicted bodyweight, standard positive end expiratory pressure of 5 mm of Hg, and minute ventilation was adjusted to maintain EtCo2 between 35 and 40 mm of Hg. Anesthesia was maintained with isoflurane in oxygen and nitrous-oxide 1:1 mixture.

A triple lumen central venous catheter was placed under aseptic precautions with ultrasound guidance in either the right or left internal jugular vein and CVP was measured and recorded after zeroing the transducer at the level of right atrium (fourth intercostal space in the mid axillary line when the recipient was lying supine). Intraoperatively, Ringer's acetate was used in both the groups according to the following regimen.

In Group-S, recipients received intra venous fluid using the Holliday and Segar's formula. The fasting deficit was calculated as 2 ml per kg[12] body weight per hour of duration of fasting up to a maximum of 10 h. Fifty percent of this deficit was replaced in the 1st h of surgery, 25% each in the next 2 h. Maintenance fluid was calculated as 4 ml, 2 ml and 1 ml of body weight for the first and second 10 kg and subsequent weight in kilograms (4-2-1 rule) and replaced each hour.

In Group-T, recipients received intra venous fluid at a rate of 1 ml/kg/h from start of surgery till the start of vascular anastomosis. In both the groups, at the start of vascular anastomosis, fluid infusion rate was increased to maintain a CVP of 13–15 mm of Hg. This value of CVP was maintained till de-clamping of the anastomosed vessels. The MAP in both the groups was targeted to more than 90 mm of Hg. Intra venous ephedrine was used in 3 mg bolus doses if required.

In both the groups, allowable blood loss (ABL) was calculated with the transfusion trigger taken as a hemoglobin value of 8 g per deciliter. It was calculated using the following formula.

ABL = (Initial HB-final HB [transfusion trigger]/Initial HB) × (body weight × average blood volume) Average blood volume for adult male was taken as 75 ml/kg while for female as 65 ml/kg.

Any volume of blood lost during the surgery below the calculated ABL was replaced with crystalloids. The volume of blood lost more than the calculated ABL was replaced with cross matched blood and these patients were excluded from the study.

The same surgical team operated on all the recipients. The right external iliac artery and vein of the recipient were used for anastomosis with the donor organ. Immediately after de-clamping of the anastomosed vessels, the surgical team evaluated the turgidity of the transplanted kidney as 1-soft graft, 2-moderately turgid graft and 3-highly turgid graft as done by Othman *et al.*[11] An arterial blood gas analysis was done after re-perfusion of the anastomosed organ. Post de-clamping of vascular anastomosis the fluid therapy was guided according to the amount of urine produced. Intraoperative use of mannitol and furosemide was done according to standard protocols (Both groups received mannitol at 0.5 g/kg and furosemide @ 2 mg/kg). At the end of the surgery any signs of fluid overload such as conjunctival edema, eyelid edema and/or pulmonary crepitation were looked for and noted. A postoperative chest X-ray was done in all recipients to look for any congestion in the lung fields.

### *Statistical analysis*

Statistical analysis was carried out using software STATA 12.0 (STATA Corp LP College Station, Tx77845, USA). A categorical variable was presented as number (%) and the continuous variable was presented as mean ± standard deviation/median (minimum-maximum). Categorical baseline characteristics were compared between the groups using Chi-square/Fisher's exact test and continuous variables were compared between the groups using *t*-test for independent samples/Wilcoxon rank sum test. Primary outcome which was serum creatinine level on postoperative day one, was compared between the groups using Wilcoxon rank sum test. Other continuous outcomes which were measured for only one time point were compared between the groups using *t*-test for independent samples or Wilcoxon

rank sum test. The $P < 0.05$ was considered statistically significant for all data in this study.

## RESULTS

A total of ninety recipients with ESRD scheduled to undergo LRRT were screened for possible inclusion in the study. Fifty recipients satisfied the inclusion criteria. Intra-operative protocol violation occurred for two recipients in targeted therapy group and one recipient in standard therapy group. Three recipients in Group T and 2 recipients in Group S received blood transfusion and were excluded from the study. Two more recipients in Group S underwent re-exploration and subsequent graft nephrectomy were also excluded. Recruitment in the study was stopped after forty recipients (twenty in each group) successfully completed the study [Figure 1].

### *Baseline demographic, biochemical and intraoperative surgical parameters*

Donor and Recipients' demographic parameters were comparable in both the groups [Table 1]. The preoperative recipient parameters such as native urine output, ultra-filtrate removed during preoperative dialysis and the recipients' pretransplant dialysis regimen, dialysis duration and preoperative pre and post dialysis biochemical parameter were comparable in both the groups [Table 1]. The intraoperative surgical parameters such as duration of surgery, vascular anastomosis, and cold and warm ischemia time of graft were also comparable in both the groups [Table 1].

### *Primary outcome-serum creatinine*

The primary outcome in our study was serum creatinine level on the first postoperative day. The median level was 2 mg/dl in Group T and 1.95 mg/dl in Group S and it was not statistically significant. Maximum fall in median serum creatinine levels in Group T was seen on third postoperative day while in Group S it was seen on sixth postoperative day demonstrating early return of renal function in Group T but results were not statistically significant on follow-up till 6$^{th}$ postoperative day [Table 2].

### *Secondary outcomes – renal function parameters*

Maximum fall of mean blood urea level in the targeted group was seen on a postoperative day 2 while in standard therapy Group was on postoperative day 3. Although the mean blood urea level was comparable in both groups in postoperative period, but the values were lower in targeted therapy group as compared to the standard therapy group [Table 2]. Urine output at the end of the surgery and in postoperative follow up was comparable in both the groups and was not statistically significant [Table 2]. Recipients in Group T had better graft turgidity, earlier onset of urine production and required fewer ephedrine boluses as compared to Group S [Table 2].

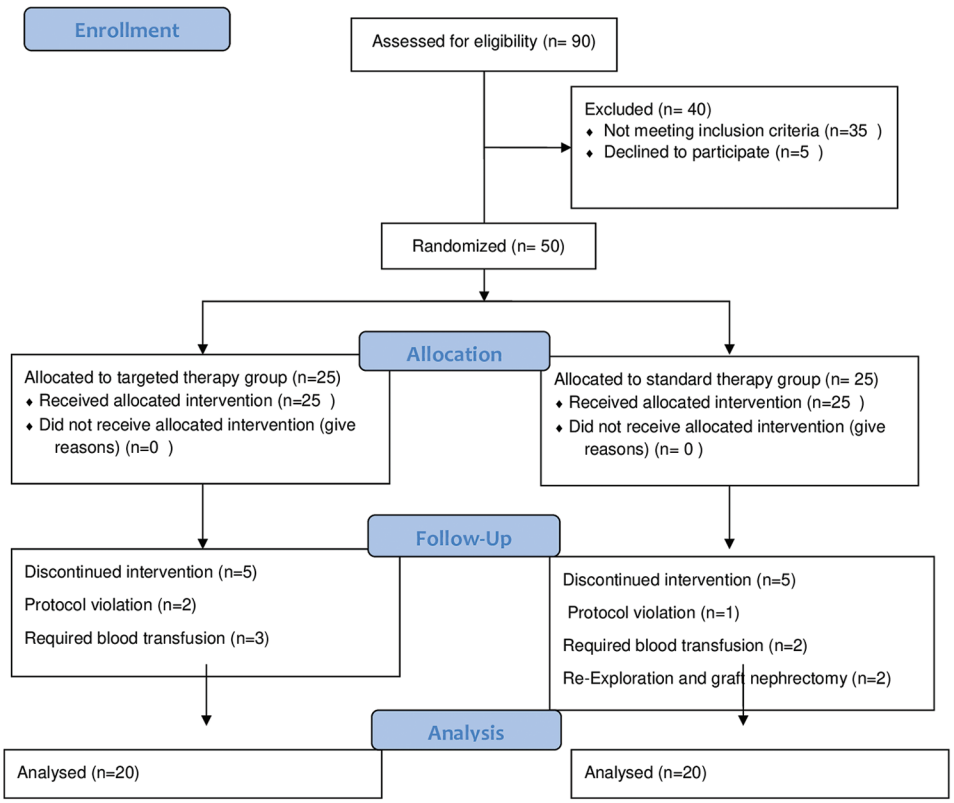


**Figure 1:** Consort diagram

**Table 1: Clinical parameters of donors and recipients**

| Parameters | Mean±SD | | *P* |
|---|---|---|---|
| | Group T (*n*=20), *n* (%) | Group S (*n*=20), *n* (%) | |
| Donor | | | |
| Age (years) | 47.6±11.3 | 44.4±7.8 | 0.31 |
| Sex | | | |
| Female | 19/20 (95) | 16/20 (80) | 0.34 |
| Male | 1/20 (5) | 4/20 (20) | |
| Weight (kg) | 58.3±8.0 | 58.9±8.8 | 0.81 |
| Body surface area | 1.58±0.11 | 1.60±0.10 | 0.57 |
| Relation with recipient | | | |
| Genetic | 12/20 (60) | 12/20 (60) | 1 |
| Nongenetic | 8/20 (40) | 8/20 (40) | |
| Recipient | | | |
| Age (years) | 36.5±13.0 | 36.7±12 | 0.97 |
| Weight (kg) | 56.1±11.6 | 53.9±10.1 | 0.51 |
| Body surface area | 1.60±0.16 | 1.56±0.15 | 0.38 |
| Sex | | | |
| Female | 4/20 (20) | 4/20 (20) | 1 |
| Male | 16/20 (80) | 16/20 (80) | |
| Preoperative dialysis parameters | | | |
| Native urine output (ml/day) | 250 (20-2000) | 200 (0-2000) | 0.31 |
| Dialysis duration (month) | 10 (1-60) | 11.5 (1-36) | 0.83 |
| Dialysis regimen | 3/week | 3/week | - |
| Ultra-filtrate removed (ml) in preoperative dialysis | 500 (0-2000) | 500 (0–3000) | 0.11 |
| Preoperative predialysis biochemical parameters | | | |
| Hemoglobin (g/dl) | 9.27±1.12 | 9.55±1.03 | 0.41 |
| Serum creatinine (mg/dl) | 7.9±2.5 | 7.5±1.9 | 0.56 |
| Blood urea (mg/dl) | 91.6±30.3 | 96.2±24.1 | 0.59 |
| Serum sodium (meq/l) | 136.5±4.7 | 137.3±4.7 | 0.59 |
| Serum potassium (meq/l) | 5.1±0.6 | 4.8±0.6 | 0.23 |
| Preoperative postdialysis biochemical parameters | | | |
| Blood urea (mg/dl) | 30.6±12.9 | 34.8±21.6 | 0.46 |
| Serum creatinine (mg/dl) | 3.3±1.6 | 3.4±1.7 | 0.87 |
| Serum sodium (meq/l) | 137.8±4.6 | 139.1±4.5 | 0.39 |
| Serum potassium (meq/l) | 4.2±0.6 | 4.1±0.5 | 0.31 |
| Surgical parameters | | | |
| Duration of surgery | 136.9±20.4 | 136.3±9.5 | 0.90 |
| Duration of vascular anastomosis | 35.8±9.0 | 35.7±5.3 | 0.96 |
| Graft warm ischemia time* | 4.3±1.2 | 3.63±1.4 | 0.13 |
| Graft cold ischemia time** | 45.2±12.2 | 50.6±10.0 | 0.13 |

*Represents warm ischemia time of graft in the donor. It starts with clamping of renal artery in the donor and ends with harvesting the graft out of the donor body, **Represents cold ischemia time of the harvested graft. It starts with placing the graft in cold irrigation fluid and ends when the graft is placed in recipient for vascular anastomosis. $P<0.05$ statistically significant. SD=Standard deviation

### *Intravenous fluid*

The intraoperative period was arbitrarily divided into three time phases. The first phase (T-1) started as soon as recipient was shifted to the operation theater and intravenous access was obtained. The second phase (T-2) started after the placement of renal graft in the recipient, and start of anastomosis of graft vessels to recipient to recipient vessels. Third phase (T-3) started when reperfusion was started and lasted till the end of surgery. The intravenous fluid infusion was different during the first phases according to the group allocation. The volume of intravenous fluids (crystalloids) infused in the two groups during different time phases and the total fluid infused during the surgery is shown in Table 2. The mean total amount of fluid given during surgery to recipients in Group T was significantly less than that infused to recipients in Group S ($P < 0.001$). Total amount of fluid given with respect to dry weight was also significantly less in Group T.

### *Hemodynamics*

The trends of perioperative hemodynamic parameters like MAP, CVP, cardiac output, and cardiac index in both groups are shown in Figures 2 and 3. Base line hemodynamic parameters were comparable in both groups. With start of vascular anastomosis, CVP was significantly higher in Group S but at the time of de-clamping CVP and all other parameters were comparable. At the end of the surgery MAP was significantly higher in Group T while CVP was higher in Group S.

### *Intraoperative acid base, electrolyte status, and postoperative fluid overload*

In both the groups there were no signs of intraoperative metabolic acidosis, electrolyte imbalance or fluid overload as shown by the intraoperative arterial blood gas analysis and postoperative chest X-ray in all the recipients.

**Table 2: Outcome parameters of renal transplant recipients**

| Parameters | Median (minimum–maximum) | | *P* |
|---|---|---|---|
| | Group T (*n*=20) | Group S (*n*=20) | |
| Creatinine (mg/dl) | | | |
| POD-1 | 2 (1–3.8) | 1.95 (0.7–5.8) | 0.63 |
| POD-2 | 1.35 (0.8–3.8) | 1.6 (0.7–7.5) | 0.54 |
| POD-3 | 1.3 (0.7–4) | 1.55 (0.6–8) | 0.73 |
| POD-4 | 1.3 (0.7–4.1) | 1.5 (0.6–4.9) | 0.87 |
| POD-5 | 1.4 (0.7–2.9) | 1.4 (0.5–6.5) | 0.73 |
| POD-6 | 1.3 (0.7–3.2) | 1.3 (0.5–5) | 0.85 |
| Urea level (mg/dl) | | | |
| POD-1 | 35.4±10.6 | 40.6±17.9 | 0.26 |
| POD-2 | 30.4±13.0 | 37.5±25.3 | 0.25 |
| POD-3 | 32.9±18.8 | 34.4±24.1 | 0.83 |
| POD-4 | 33.9±16.1 | 46.5±35.8 | 0.14 |
| POD-5 | 34.8±10.9 | 44.1±21.6 | 0.08 |
| POD-6 | 38±13.2 | 48.0±27.4 | 0.13 |
| Average postoperative | 34.2±11.8 | 41.8±23.5 | 0.20 |
| Delta postoperative (routine-avgerage postoperative) | 57.3±27.7 | 54.4±28.1 | 0.74 |
| Routine –postoperative day 3 | 58.55±30.0 | 61.75±28.56 | 0.73 |
| Urine output on the day of surgery (ml) | | | |
| Urine output at the end of surgery | 807.8±156.9 | 732.7±154.6 | 0.13 |
| 4-h postoperative | 3764.5±1444.9 | 3322.7±1120.4 | 0.28 |
| 24-h postoperative | 15,817.7±5848.9 | 12,685.5±4284.6 | 0.06 |
| Urine output postoperatively (ml) | | | |
| POD-1 | 14,021.2±4662.4 | 11,702.75±4252.2 | 0.10 |
| POD-2 | 9751±4217.3 | 8792.2±3381 | 0.46 |
| POD-3 | 6511±2852.5 | 6629.8±2977 | 0.89 |
| POD-4 | 5383.6±1947.1 | 5540.1±2592.3 | 0.82 |
| POD-5 | 4944.2±1950.9 | 4539.3±2005.6 | 0.51 |
| POD-6 | 4714.3±1743.1 | 4411.5±2126.5 | 0.61 |
| Average urine output | 7554.2±2532.9 | 6819.3±2634.4 | 0.37 |
| Onset of diuresis in seconds | 34.45±3.46 | 36.70±6.79 | 0.19 |
| Ephedrine use (mg) | 1.65±2.28 | 5.10±6.16 | 0.02* |
| Graft score, *n* (%) | | | |
| Score 1 | 0/20 | 0/20 | 0.03* |
| Score 2 | 2/20 (10) | 9/20 (45) | |
| Score 3 | 18/20 (90) | 11/20 (55) | |
| Amount of intravenous fluid given during surgery | | | |
| IVF-1 (ml) | 57.7±13.9 | 765.5±253.4 | <0.001* |
| IVF-2 (ml) | 1402±432.0 | 1397.5±358.2 | 0.97 |
| IVF-1+2 (ml) | 1459.7±311.7 | 2158±499.2 | <0.001* |
| IVF-3 (ml) | 875.5±292.3 | 1085±272.9 | 0.02* |
| IVF-T (ml) | 2332.2±473.4 | 3243±646.7 | <0.001* |
| IVF (ml/kg) | 42.7±9.7 | 61.1±11.1 | <0.001* |

*Denotes statistical significance ($P<0.05$). Score 1 – soft graft, Score 2-moderately turgid graft and Score 3-highly turgid graft. IVF-1: Amount of fluid given (ml) from start of surgery to start of vascular anastomosis (T1). IVF-2: Amount of fluid given (ml) during vascular anastomosis (T2). IVF-1+2: Amount of fluid given (ml) till declamping of renal graft vessels. IVF-3: Amount of fluid (ml) given from declamping of graft vessels to end of surgery (T3). IVF-T: Total amount of fluid (ml) given during surgery. POD=Post operative day, IVF=Intravenous fluid

## DISCUSSION

The study evaluated serum creatinine levels in recipients with ESRD who received kidney from live donors when intraoperative fluid infusion was done according to two different protocols. The total volume of intravenous fluid infused in the group which received targeted fluid infusion only during vascular anastomosis, however, was significantly less than the standard therapy group. The parameters of graft perfusion after anastomosis which included graft diuresis time, graft turgidity score and the urine output in the immediate postoperative period were better in the targeted fluid infusion group. The possible mechanism may be the significant redistribution of crystalloids within first 30 min of administration.[11] Bolus fluid administration during vascular anastomosis in Group T resulted in greater plasma volume expansion and hydration. As average duration of vascular anastomosis was 35 min, redistribution of infused fluid in Group T was much less as compared to Group S receiving significantly more fluid from the start of the surgery. As far as hemodynamics is concerned, both groups had approximately similar cardiac output at reperfusion, but Group S received significantly higher fluid than Group T. Targeting CVP of 13–15 mmHg in both the groups helped in creating adequate hydration and pressure head at time of reperfusion which was evident as absence of delayed graft function in early postoperative period in both the groups.

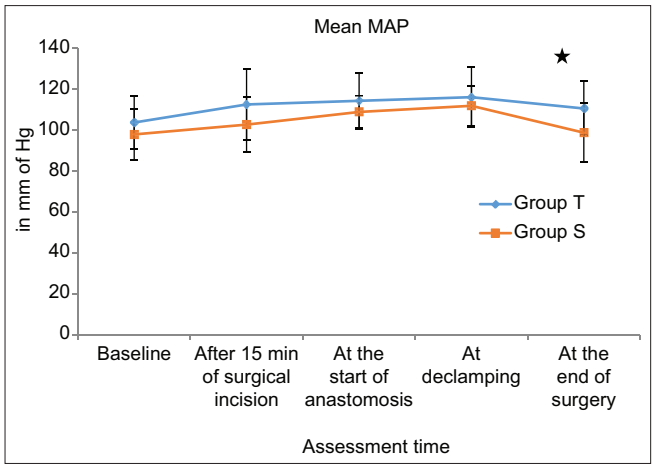


**Figure 2:** Comparative mean arterial pressure at various critical time points. ★ Denotes statistical significance ($P < 0.05$)

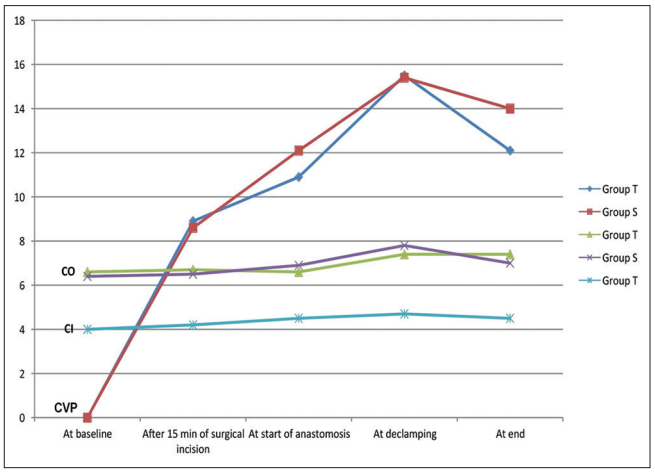


**Figure 3:** Comparative central venous pressure, cardiac output, and cardiac index at various critical time points

Type of intravenous fluid used during renal transplantation also plays a major role in maintaining normal acid base status in renal transplant recipients. Several studies have compared normal saline (NS) and balanced salt solution (BSS) in renal transplant recipients and reported that administration of BSS is safe and may even be superior to NS because it avoids the risk of metabolic acidosis and clinically significant hyperkalemia.[13-15] Therefore, based on above studies we also decided to use BSS (Ringer acetate) as intraoperative fluid of choice in our study.

Recipients with ESRD undergoing regular dialysis to avoid complications of fluid overload and uremia have a complex intra-vascular status. The maintenance hemodialysis usually aims to achieve dry weight of the recipients, which is the minimal weight of the recipient at which there are no signs or symptoms of hypo- or hyper-volemia. It is thus, important to use goal directed fluid therapy in these recipients to achieve adequate perfusion of the transplanted organ. The goal thus selected was CVP in our study. We monitored the cardiac output and cardiac index also in these recipients, but the aim of fluid therapy was to maintain a CVP between 13 and 15 mmHg at the time of reperfusion. Regarding intravascular volume, the most important phase during the transplant surgery is the time at which the vascular clamps are removed. A good perfusion of the transplanted kidney at this time is important not just for initiation of renal function but also to wash off the accumulated oxidative by-products of ischemia-re-perfusion period. The transplanted kidney is denervated and its blood supply is not under control of the autoregulatory mechanisms of the recipient's body.[16-19] A good perfusion of the kidney by the volume and pressure head provided by adequate intravascular volume and MAP in the recipient respectively is thus important for the early onset of graft diuresis. Serum creatinine levels and urine output after the transplant are the earliest, though not very specific, markers for adequate graft function. Both are also markers of volume status of the recipient immediately after graft perfusion in the early postoperative period. Delayed graft function, defined as above, can be due to multiple other immune and nonimmune mediated etiological factors and may not only be indicative of volume depletion.[20-22]

Intraoperative hemodynamics also plays a major role in prevention of delayed graft function in kidney transplant recipients. Many studies suggest that during renal transplantation, one should maintain the recipient's systolic blood pressure >120 mmHg, diastolic blood pressure >85 mmHg, MAP >95 mmHg, CVP >10 mmHg and pulmonary artery pressure >20 mmHg.[23] These values are intended to ensure maximal filling pressure of the graft and rapid recovery of graft function. In our study, we also tried to maintain CVP of 13–15 mmHg, cardiac output and MAP in the range of 5–9 l/min and 111–116 mmHg, respectively, in both the groups.

Intraoperative volume status plays an important part in the immediate graft functioning. Many previous studies have shown that hypervolemia in the transplant recipient may aid in the early diuresis from the transplanted organ. Recipients who have delayed graft function have significantly decreased 3-year and 5-year graft survival rate. Early diuresis, however, may not be a marker of delayed graft function which has been defined variously in literature as need for dialysis in first postoperative week,[24-27] failure of a fall in serum creatinine of more than 10% on 3 consecutive days in the first postoperative week[28] and creatinine reduction ratio of <30% on postoperative day 2.[24] We decided to measure serum creatinine as our primary outcome as we hypothesized that intraoperative volume status of the recipient may affect the graft diuresis and will reflect maximally on the immediate postoperative serum creatinine values. Inadequate intravascular volume is a predisposing factor to complications like acute kidney injury and vascular thrombosis of the graft vessels, both of which are important causes of development of delayed graft function.

Hypervolemia, however, may be detrimental in recipients with CKD due to the associated cardiovascular complications that are either overtly or covertly present in these recipients. Cardiovascular diseases may be present in these recipients making them extremely prone to cardiac de-compensation with excessive fluid infusion. Apart from this, recipients on hemodialysis may also have either hyper or hypovolemia depending on the ultrafiltrate extracted during dialysis. The subjective estimation of dry weight can result in both under-and over-hydration of the recipients on chronic hemodialysis with latter (over-hydration) more common than former (under-hydration). Recipients with CKD are unable to secrete $Na^+$. This along with hypoproteinemia leads to increased fluid extravasation into the interstitium. It is thus evident that more amount of crystalloid infusion will redistribute into extravascular space as compared to recipients with normal renal function. The intraoperative fluid management, thus, is evidently complicated. Any technique which can help decrease total amount of fluid infused to the recipient without compromising the perfusion of the transplanted organ is thus, not just desirable but also, critical to the successful outcome from the surgery. Recipients in our Targeted group received significantly less intravenous fluid as compared to recipients who received standard therapy. The practice of with-holding fluid infusion till start of vascular anastomosis is followed in most of the centers world-wide. The study gives an objective proof that by doing so total amount of intravenous fluid given intraoperatively can be significantly decreased without hampering the organ perfusion and/or compromising the hemodynamic or metabolic milieu of the recipient. In the similar study previously published, Othman *et al.*[11] compared the serum creatinine levels in recipients receiving fluid in a targeted manner (as in our study) or by a constant infusion rate. There was however no difference in the total amount of intravenous fluid infused in both of their groups. This could be explained by the fact that the control group received a constant infusion of fluid at the rate of 10–12 ml/kg and a specific CV *P* value was not targeted in the constant infusion group. The CVP was significantly low in the constant infusion group at the time of re-perfusion although the exact values of CVP in each group has not been mentioned by the authors. The total volume fluid infused in the CVP targeted group in their study was more than the volume used in our study group despite following the same methodology which may be because of different recipient demographic profile and longer duration of surgery in their study. Use of the Holliday-Segar method of fluid replacement in our control group was a more objective approach towards fluid management as compared to a constant rate infusion.

Use of CVP to guide fluid infusion has recently been criticized. Central venous access is, however, routinely secured in many centers (including ours) in renal transplant recipients prior to the surgery. Other monitoring modalities including transesophageal Doppler (Doppler vs. CVP),[29] Plethysmography Variability Index,[30] have been used to guide fluid therapy for renal transplant recipients but none of them have shown any difference in posttransplant short and long-term organ function when compared with CVP guided volume management. The presence of a central venous catheter provides a ready access to start inotropic and vasopressor therapy in these, often hemodynamically unstable and cardiomyopathic recipients. CVP monitoring can be easily carried out in the postoperative period as well, unlike the other mentioned modalities, thus, maintaining a monitoring continuum.

This study has several limitations. We only evaluated short-term benefits (e.g., 6 days) and have not considered whether there are long-term benefits. This was a single blinded study with the surgical and nephrology team unaware of the randomization schedule, but the anesthesiologist knew the recipient assignment. The study only evaluated graft anastomosis of single vessels with no surgical difficulties and the results may not be superimposable for recipients undergoing complex vascular anastomosis or surgical procedures taking longer than usual times. Postoperative serum creatinine may not be an accurate parameter for renal function after renal transplant, however, this was the only routinely performed biochemical evaluation available to us. We included only those recipients who were nondiabetic having relatively lower cardiovascular risk; therefore, the benefit of targeted therapy may not be extrapolated to recipients with high cardiovascular risk factors. The use of various intravenous fluids might have to be altered depending on the blood sugar levels of the recipients. The acid-base status and the electrolyte status which were being monitored intraoperatively as secondary outcomes may be altered because of the altered plasma sugar values.

## CONCLUSION

This study shows that administering crystalloids during vascular anastomosis of transplanted kidney, targeting a CVP of 13–15 mm of Hg, while withholding continuous fluid infusion throughout the surgical period prior to this, provides adequate hydration for better graft function after reperfusion in recipients undergoing LRRT. An average of 35–40 ml fluid per kilogram body weight of recipient is usually adequate for achieving this target. The postoperative renal parameters were comparable to the control group and no short-term complications of fluid depletion and/or overload were seen in the study group. However, large multicenter studies with larger sample size and long follow-up are needed to prove clinical benefit from targeted fluid therapy.

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**How to cite this article:** Singh A, Ramachandran R, Chandralekha C, Trikha A, Ray BR, Bansal VK, *et al*. Timing of intraoperative crystalloid infusion may decrease total volume of infusate without affecting early graft function in live related renal transplant surgery: A randomized, surgeon-blinded clinical study. Indian J Urol 2022;38:53-61.