Anesthesia management of renal transplantation: an update

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ABSTRACT

End stage renal disease pool is ever increasing in India due to increased prevalence of type 2 diabetes mellitus which is often detected late when macrovascular and microvascular complications of glycosylated haemoglobin have already set in. Postoperative cardiac surgical patient also land up in ESRD as a sequelae of acute renal failure due to poor perioperative optimization and inadequate control of blood pressure before surgery. Sensitization and awareness created by NOTTO, ROTTO, SOTTO has increased the donor pool especially from deceased brain stem dead donors and more and more donors are available to the ESRD patients in the wait list waiting for organ transplantation. The anesthesiologist plays a pivotal role in coordinating the transplantation programme minimizing transplantation time after organ retrieval to ensure maximal graft survival. The challenges faced by the anesthesiologists in conducting the renal transplant are numerous due to multiorgan affection of the ESRD patient as well as potential drug interaction with the anesthetic agents due to intensive immunosuppressant therapy.

Keywords: Kidney transplant, NOTTO, ROTTO, anesthesia considerations, THOTR,

INTRODUCTION

The incidence of Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD) is an ever increasing phenomenon with a prevalence of CKD being as high as 17.2%.¹ An increased number of patients undergoing off pump coronary artery bypass grafting and other cardiac surgeries in developing countries like India where perioperative optimization of blood pressure is not given adequate importance land up in renal failure, toxic glomerulopathy leading to dialysis requirement.² ESRD is the terminal stage of CKD and the reported incidence in India is about 150 per million.³ Kidney transplant is the treatment of choice for ESRD after all modalities of conservative renal failure treatment fail to arrest the progressive renal failure giving the patient a better quality of life, longer life span and reduced need for frequent dialysis.⁴⁻⁵ First successful kidney transplantation was done in identical twins in December 23, 1954 with minimal monitors used being noninvasive blood pressure monitoring, electrocardiography under subarachnoid block by Dr. Joseph Murray.⁶ The first successful live donor renal transplant in India was conducted by Johny and Mohan Rao in January 1971 in their published case series of five patients.⁷ There have been tremendous developments in surgical techniques, improved immunosuppressive therapy in the field of renal transplant since inception and currently minimally invasive surgery and Robotic Assisted Kidney Transplantation (RAKT) is being utilized by some institutes with an intention to reduce associated postoperative morbidity.⁸ Some centres also attempted total extra-peritoneal robot assisted renal transplant recipient surgery (TERT) instead of standard transperitoneal approach with good postoperative graft function and survival.⁹,¹⁰ There are several contraindications to renal transplant as enlisted in Table 1.

OUTCOME OF RENAL TRANSPLANT

Renal transplantation is the most effective method of treating ESRD, leading to a decrease in death rate,
The best strategy to conduct a renal transplantation incorporates Organization by the practicing institute of a dedicated multidisciplinary transplant program team including doctors, nurses and paramedical stuffs from all respective faculties with proper knowledge and skills necessary to conduct the transplantation procedure with proper communication, management and appropriate care. The heart of the renal transplant programme both cadaveric as well as living donor lies on the skills and acumen of the transplant coordinator. The cadaveric renal transplant donor pool in India is much less with compared to Spain which leads the world in the field of cadaveric organ donation and transplantation. The Transplantation of Human Organs Act (Passed in 1994, amended in 2011 and rules were notified in 2014) of Government of India has mandated the presence of a permanent transplant coordinator in centres conducting renal transplant (both cadaveric and live donor) related and unrelated in the renal transplant unit. The anesthesiologist can supervise better the conduction and coordination of renal transplantation both cadaveric and live donor transplantation if he or she undergoes transplant coordinators training programme which is conducted biannually by National Organ & Tissue Transplant Organization (NOTTO), an autonomous body which regulates free and fair organ allocation and transplantation in India as well as creating awareness and motivation about organ donation after brain stem death as well as cardiovascular death. The role of anesthesiologist is of paramount importance in this aspect to serve as the intermediate coordinator among all the respective departments and maintain effective communication thereby save valuable time after organ harvesting and conducting transplantation which ensures a better graft function postoperatively, duly respecting the warm and the cold ischemic time of the kidney. Therefore the anesthesiologist plays a pivotal role in a transplant team who maintains smooth simultaneous operation of all respective fields in the perioperative period and ensures appropriate care of the recipient as well as the donor.

DONOR

1. Preoperative evaluation:
Donor safety is of paramount importance to the anesthesiologist during graft harvesting. However the Govt. of India, in order to streamline organ allocation transplantation
has mandated certain legal formalities to be fulfilled for living donor transplantation as well as deceased donor transplantation. This in turn will reduce if not eliminate the unethical practices in the process of organ allocation and transplantation in India especially in deceased donor and brain stem dead donor transplantation. Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare, Government of India has provided a legal framework necessary to establish brain death, followed by organ donation. The Transplantation of Human Organs Act (THOA) was passed in 1994 and the subsequently amended in 2011 and rules were established in 2014 in India to form the legislative foundation for brain death and organ donation.22-24

Both in live donor and cadaveric donor, obtaining a detailed informed consent from appropriate person before proceeding to any further step is of utmost importance for ethical as well as medicolegal purpose. Most of the donors belong to ASA I and II. Complete preanesthetic assessment should be performed including complete history, physical examination, laboratories studies with special attention to renal system (complete hemogram, FBS/PPBS, urea/creatinine, serum electrolyte, LFTs, coagulation profile, CXR, 12 lead ECG and echocardiography). It is also advisable to obtain psychiatric evaluation of the donor, mental fitness and his ability to understand to undergo the minimal risk of the operation.25 There are several techniques for living donor kidney harvesting enlisted in Table 3.

2. Perioperative management:

There are several goals for perioperative management for living donor organ harvest27-31 enlisted in Table 4

Most commonly general anesthesia with supplemental regional or local anesthesia is chosen. Standard ASA monitoring is used including Non invasive blood pressure monitoring, 5 lead ECG, ETCO2, SPO2, Temperature and urine output. Invasive monitoring in donor is reserved for complicated donors including patients with comorbidities such as symptomatic coronary artery disease or history of congestive heart failure and obesity.27 Invasive arterial line is placed before or after induction of anesthesia. Patient is placed in lateral decubitus position with varying flexion of the table for adequate access to donor kidney. Special attention should to be taken during positioning to prevent pressure necrosis, airway and venous access compromise. Maintenance of adequate perfusion pressure and sufficient fluid administration (10-20 ml/kg/hour) should be done with aim of maintaining a urine output of >2 ml/kg/hour. Mannitol 12.5-25 gram g/kg, given 15 minutes before clamping of renal artery is associated with improved kidney preservation.29 Loop diuretic such as furosemide 20-40 mg can also be used. Furosemide maintains natriuresis, decreases renal oxygen consumption by inhibition Na-K ATPase in the ascending limb of loop of henle and proximal convoluted tube.27-29 Protective interventions including atrial natriuretic peptide-analogue, dopamine and fenoldopam have also been tried.30,31 Use of systemic heparinization prior to arterial clamping is controversial with some studies showing no benefit.32,33

3. Considerations for laparoscopic living donor nephrectomy:

Patients undergoing laparoscopic procedure have

Table 3: Goals of anesthesia management of donor27-31

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Allaying anxiety</td>
<td>• Alprazolam on night before surgery</td>
</tr>
<tr>
<td></td>
<td>• Midazolam on the morning of surgery</td>
</tr>
<tr>
<td>Stable hemodynamics</td>
<td>• Systolic blood pressure 130 to 160 mm of Hg</td>
</tr>
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<td></td>
<td>• Liberal hydration</td>
</tr>
<tr>
<td></td>
<td>• Central venous pressure between 10-15 mm of Hg</td>
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<tr>
<td></td>
<td>• Mean pulmonary artery pressure of 18-20 mm of Hg</td>
</tr>
<tr>
<td>Elimination of surgical stress</td>
<td>• Opioids</td>
</tr>
<tr>
<td>response</td>
<td>• Epidural analgesia</td>
</tr>
<tr>
<td></td>
<td>• Preemptive analgesia</td>
</tr>
<tr>
<td>Maintenance of renal blood flow</td>
<td>• Stable hemodynamics</td>
</tr>
<tr>
<td></td>
<td>• Blood volume greater than 70ml/kg</td>
</tr>
<tr>
<td></td>
<td>• Plasma volume greater than 45ml/kg</td>
</tr>
<tr>
<td>Maintain of urine output &gt; 2 ml</td>
<td>• Liberal hydration</td>
</tr>
<tr>
<td>kg/hr</td>
<td>• Balanced salt solution alternating with normal saline</td>
</tr>
<tr>
<td></td>
<td>• Mannitol</td>
</tr>
<tr>
<td></td>
<td>• Diuretics</td>
</tr>
<tr>
<td>Adequate postoperative analgesia</td>
<td>• Patient controlled analgesia (PCA)</td>
</tr>
<tr>
<td></td>
<td>• Epidural</td>
</tr>
<tr>
<td></td>
<td>• Multimodal analgesia</td>
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shorter hospital stay and faster recovery compared to open surgery. There are higher concerns for deterioration renal function in patients undergoing laparoscopic donor nephrectomy due to creation of pneumoperitoneum and increased Intra Abdominal Pressure (IAP) of 15-20mmHg has been shown to decrease GFR, renal blood flow and leads to transient decrease in urine output. increased IAP over 15 mmHg can also lead to decreased cardiac output which decreased perfusion to the kidneys. The decrease in renal function during pneumoperitoneum depends on IAP, volume status of the patient, degree of hypercarbia and baseline renal function. To offset this effect the aim is to maintain adequate renal perfusion pressure and adequate volume infusion. Borg et al recommended overnight infusion of crystalloid and bolus of colloid infusion before starting pneumoperitoneum which resulted in higher urine output and stroke volume. A well targeted mean arterial pressure >70 mmHg and urine output >100 ml/hour during pneumoperitoneum maintains adequate renal perfusion pressure.

4. Postoperative pain management:

Postoperative pain management is important particularly in open surgery where pain from large incision interferes in breathing. In case of laparoscopic surgery the origin of pain is from the tissue dissection, port site pain, low abdominal incisions to retrieve the kidney, pelvic organ nociception as well as from the diaphragmatic irritation due to residual pneumoperitoneum. Patient Controlled Analgesia (PCA) with fentanyl is commonly used for pain control. Other options include thoracic paravertebral block, Transversus Abdominis Plane (TAP) block, epidural analgesia with or without continuous infusion of local anesthetic, local infiltration of long-Acting local anesthetics agents, intravenous paracetamol etc. A multimodal balanced analgesia regimen is safe and provides the best post operative pain relief and decreases the opioid requirement post operatively. NSAIDs are usually avoided because of concern regarding their potential nephrotoxicity.

THE KIDNEY RECIPIENT

1. Perioperative management:

In India, the patients requiring renal transplantation far exceeds the number of transplantation annually. Therefore, it is important for the practising institute to maintain an updated registry for patients requiring renal transplantation and to communicate via an organ sharing network for selection of the most appropriate patient in terms of serocompatibility whenever a brain stem dead donor is available. This work at the national level in India is regulated by National Organ & Tissue Transplant Organization (NOTTO) with Five Regional Organ and Tissue Transplant Organization (ROTTO) functioning in different geographical zones in India catering to their respective zonal states and State Organ and Tissue Transplant Organization (SOTTO) in the states who have taken up deceased donor organ transplant incipiently. The serocompatibility is assessed by ABO compatibility, HLA matching and testing of donor T cells against stored recipient serum. The recipients of renal transplantation are often posted for surgery on urgent or emergency basis depending on availability of organ in case of brain dead organ transplantation. In such cases rapid assessment of the recipient by the anesthesiologist, transplant surgeon and the nephrologist is essential for earliest planning for surgery, fast and precise preoperative optimization and to reduce the ischemia time.

The patient with ESRD posted for transplantation is a challenge to anesthesiologist because of comorbidities associated with ESRD. The clinical challenges in a patient with ESRD involve almost every major organ system as enlisted in Table 5.

2. Preoperative assessment and optimization:

Patients posted for renal transplant need to have complete routine investigations done including complete blood counts, coagulation profile, liver function tests, urea,
creatinine, electrocardiography, chest radiogram and echocardiography. All patients with ESRD need to be investigated for coronary artery disease particularly patients with diabetes mellitus. Dobutamine stress echocardiogram is especially useful in high risk patients. Anemia is a common problem in patients posted for renal transplant with ESRD. Recombinant erythropoietin (EPO) is widely used for patients of chronic renal failure leading to quick rise of hemoglobin to target level at least 10 g/dl which decreases postoperative transfusion requirement. EPO can lead to worsening of hypertension and increased incidence of cerebrovascular accidents.

Most patients on hemodialysis will require preoperative dialysis within 24 hours prior to surgery on the basis of metabolic and fluid abnormalities to reduce risk of hypervolemia, hyperkalemia and increased bleeding. Hypovolemia post dialysis should be avoided by keeping post dialysis weight near to the dry weight of the patient. These patients have delayed gastric emptying because of stress, uremia, diabetes mellitus etc which requires prophylactic administration of H2 receptor antagonists, proton pump inhibitors and prokinetic drugs like metoclopramide and may require rapid sequence induction. Magnesium and aluminum containing antacids should be avoided in patients with ESRD because of accumulation and toxicity in the presence of low GFR and low renal perfusion pressure. These patients are more susceptible to infection because of uremia, associated comorbidities like diabetes, coupled to donor related acquired infection and therapeutic immunosuppression. Therefore, broad spectrum antibiotic should be administered prior to surgery. First generation cephalosporin or if penicillin allergic, vancomycin may be considered for antibiotic prophylaxis.

Antihypertensive and antianginal medications are to be continued till morning of surgery. Oral hypoglycaemic agents are discontinued on the day of surgery with conversion to regular insulin regime.

3. Surgical approaches for kidney transplantation:

There are several surgical approaches for kidney transplantation in the recipient after organ harvesting from the donor which have undergone up gradation with advances in technology; the most advanced being robotic technique for kidney transplantation. The several approaches include the following:

- Conventional Open kidney transplant - using an abdominal incision 15-25 cm in length.
- Minimal Incision Kidney Transplantation (MIKT) - this uses a smaller 5-9 cm incision resulting in reduced requirement of postoperative analgesia and better cosmetic healing.
- Laparoscopic technique for kidney transplantation - first attempted in 2009 by rosales et al. using 7 cm incision for kidney placement and 3 extra port sites.
- Robotic technique for kidney transplantation - recent advancement.

4. Anesthesia considerations in recipient:

Commonly general anesthesia is used for renal transplantation although cases of renal transplantation under regional anesthesia have been reported. Standard ASA monitoring is recommended. Patients may require invasive monitoring in the form of central venous line (fluid status assessment) and invasive blood pressure monitoring. In patients with coronary artery disease and cardiomyopathies pulmonary artery pressure monitoring and transesophageal echocardiography may also be used.

In case of presence of arteriovenous fistula or hemodialysis shunts, the said limb should be examined for infection, redness, soreness, warmth, patency and presence of distal pulses. The particular limb with such shunts should not be used for fluid administration. The fistula should be carefully padded and patency should be checked intermittently throughout the procedure. During patient transfer and positioning great caution should be practised as there is risk of pathological fracture in renal failure patients.

Rapid sequence induction is commonly practised after proper preoxygenation. These patients have low levels of albumin due to plasma volume expansion, albumin redistribution, exogenous loss (in peritoneal dialysis patients), and decreased albumin synthesis. Low blood albumin level predisposes to increased free fraction of drugs. Uremia leads to disruption of blood brain barrier. Hence there occurs an increase in level of unbound drugs crossing the blood brain barrier leading to exaggerated effect of the anesthetic agents. Dose modification of drugs is essential also in view of volume status, acid base status, and increased sensitivity of central nervous system to drugs.

Induction with thiopentone, propofol or etomidate using slow titrated doses can be done. Succinylcholine should be used with caution as it can lead to hyperkalemia, especially in patients with high initial potassium levels (>5 meq/l). For this reason
non depolarizing muscle blockers are commonly used. Atracurium, Cisatracurium, vecuronium, rocuronium and mivacurium can be safely used. RSI may need to be modified accordingly. Short acting beta blockers like esmolol or short acting opioids like fentanyl or remifentanil should be used to prevent surge during laryngoscopy.

Maintenance of anesthesia can be achieved using either inhalation agents like isoflurane, sevoflurane, desflurane or intravenous propofol. Isoflurane is commonly considered agent of choice as minimal amount of it is metabolised and there is reduced production of fluoride ions, though studies have failed to show advantage of one agent over the other.54,55 Analgesia can be maintained using fentanyl or remifentanil. Morphine should be carefully used as morphine-6-glucuronide, its active metabolite can accumulate and can lead to respiratory depression.

4A. Perioperative fluid management:

The goal of perioperative fluid management is maintenance of adequate intravascular volume and sufficient perfusion to the transplanted kidney as hypotension due to depleted intravascular volume can lead to acute tubular necrosis (ATN) which is a major factor in graft dysfunction.56,57 After removal of vascular clamp, large blood volume is directed to the transplanted kidney, resulting in hypotension. There also occurs release of mediators from the ischemic kidney which causes vasodilation. These patients are prone due hypovolemia as a result of excess fluid removal during dialysis and due to perioperative fasting. This is masked in awake patients because of compensatory autonomic responses. Its traditionally recommended to maximize graft function by aggressive fluid management (upto 30 ml/kg/h and central venous pressure >15 mm hg) with caution in cardiac patients [58]. A restrictive hydration regimen was shown by Gasperi et al with target CVP of 7-9mm hg of being equally effective in maintaining graft patency (crystalloids 2400 ± 1000 mL, 15 mL/kg/h). Some institutions recommend that change in CVP is more reliable for fluid administration, with a rise of > 7mm after fluid bolus indicating maximal intravascular volume.59 CVP and PAP are static markers of fluid responsiveness and are generally not considered reliable.60 Transesophageal Echocardiography (TEE) can also be used to monitor the intravascular volume. A study compared the utility of TEE versus CVP in guiding fluid therapy in renal transplant patients and found that TEE was equally effective as CVP in achieving equivalent graft function while requiring lower amount of fluid administration.61 However TEE does not provide continuous monitoring of fluid status and its utility is limited by higher learning curve. Dynamic measures of patients fluid responsiveness (systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV)) are better predictors than static methods.62 SVV was found to be a better predictor of volume responsiveness in patients undergoing renal transplant as compared to CVP and PAO63,64. The disadvantage of SVV is that it can only be used in mechanically ventilated patients.

Timing of fluid administration may also be important. Othman et al compared a biphasic regimen maintaining a CVP of 5 mmhg in pre ischemic phase and 15 mmhg in ischemic phase with a constant infusion of 10-15 ml/kg/hour. They found better early graft function with biphasic regimen.65 Isotonic crystalloids are generally preferred for volume replacement like ringer lactate, plasmalytes, normal saline although normal saline can lead to hypochloremic acidosis but its effect on graft outcome is not known.64,65 Potura et al compared 0.9% saline with acetate buffered balanced crystalloid solution in patients undergoing renal transplant. They did not find any significant difference in incidence of hyperkalemia in the two groups and found lower percentage of patients required inotropes in balanced crystalloid group.66 Hadimoglu et al concluded that among the different crystalloids, plasmalyte cultivated the best metabolic profile of the patients.67

Colloids can also be used to maintain the hemodynamic goals, these include natural colloids like albumin and synthetic like dextrans, gelatins etc. When compared to crystalloids, albumin does not offer any advantage, while being considerably expensive.68,69 Role of gelatins and dextran is not clearly established and should be used with caution.

To boost kidney function after completion of anastomosis, mannitol is used commonly. Mannitol induced osmotic diuresis and also has protective effect on tubular cells of transplanted kidney against ischemic injury. It enhances the release of vasodilatory prostaglandins in the kidney and may also act as a free radical scavenger.70,71 In most centres mannitol is generally administered at the time of release of anastomosis, however effect of of mannitol in graft function is not clear.72 Furosemide exerts its effects on thin ascending limb of Henle. It also causes a decrease in renal O2 consumption by inhibiting Na-K ATPase. It is given during the vascular anastomosis to stimulate diuresis although it is unknown whether it is actually beneficial in improving early function.72 Dopamine infusion is controversial as
it has not shown any benefit in studies.73,74

4B. Anesthesia considerations in laparoscopic renal transplant:

Patients are placed in trendelenburg position and pneumoperitoneum is created which has adverse effect on cardiovascular, renal and respiratory function. The IAP should be kept below 12 mmHg to maintain adequate cardiac output. CVP in these patients becomes even more unreliable marker for left ventricular filling pressure. It has been suggested that rise in CVP occurs because of increased intrathoracic pressure, which should be kept in mind while using CVP for fluid for guiding fluid management.75

The effect on respiratory system can be minimized by increasing the respiratory rate to increase minute ventilation to washout excessive CO2.

5. Perioperative immunosuppressive therapy in the recipient:

In India several centres use varied regimen of immunosuppressive therapy to decrease the incidence of graft rejection. The use of immunosuppressant is conventionally divided into three phases based on time:

The induction therapy is the first phase which is initiated in the recipient before and during the first week of completion of transplant with a goal in mind to provide maximal possible immunosupression to the recipient to with potent drugs such as thymoglobulin, OKT3, daclizumab, or basiliximab, to minimize the incidence of acute and hyperacute graft rejection. The maintenance therapy is the pivotal second phase which involves continuous administration of immunosuppressive drugs such as steroids, calcineurin inhibitors (e.g., cyclosporin, tacrolimus), target of rapamycin (TOR) inhibitors (e.g., sirolimus, everolimus), polyclonal antibodies (e.g., antilymphocyte globulin), monoclonal antibodies (e.g., interleukin 2, daclizumab, basiliximab) and purine synthesis inhibitors like azathioprine; for a variable period of three to six months with a goal to prevent acute graft rejection and to induce tolerance of the recipient to the transplanted kidney. The third and the final phase involves long term controlled immunosupression with suitable immunosupressants along with infection prevention with appropriate minimally nephrotoxic antibiotics if required for the rest of the recipient's lifespan.75 If such a recipient undergoes any major surgery involving use of general anesthesia along with muscle relaxants due consideration has to be given to potential interaction of the anesthetic agents with the drugs used for immunosupression.

6. Postoperative pain management:

Choice of intraoperative anesthesia influences the post operative pain control. Patients who received propofol had lower pain scores after surgery. PCA with fentanyl is commonly used for post operative pain control. Epidurals may be used carefully avoiding excessive vasodilation and hypotension. TAP and paravertebral blocks can also be used. NSAIDS are to be avoided.

CONCLUSION

End stage renal disease pool is ever increasing in India due to increased prevalence of type 2 diabetes mellitus which is often detected late when macrovascular and microvascular complications of glycosylated haemoglobin have already set in. Postoperative cardiac surgical patient also land up in ESRD as a sequelae of acute renal failure due to poor periooperative optimization and inadequate control of blood pressure before surgery. Sensitization and awareness created by NOTTO, ROTTO, SOTTO has increased the donor pool especially from deceased brain stem dead donors and more and more donors are available to the ESRD patients in the wait list waiting for organ transplantation. The anesthesiologist plays a pivotal role in coordinating the transplantation programme minimizing transplantation time after organ retrieval to ensure maximal graft survival. The challenges faced by the anesthesiologists in conducting the renal transplant are numerous due to multiorgan affection of the ESRD patient as well as potential drug interaction with the anesthetic agents due to intensive immunosuppressant therapy.

Conflict of interest: Nil
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