JURNAL KOMPLIKASI ANESTESI
E-ISSN 2354-6514
VOLUME 10 NOMOR 3, AGUSTUS 2023

PENELITIAN

Anesthesia in Renal Transplant

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Article Citation : Juni Kurniawaty, Cornelia Ancilla, Novita Intan Arovah. Anesthesia in Renal Transplant. Jurnal Komplikasi Anestesi 10(3)-2023.

ABSTRACT

Background: Transplantation provides near-normal life and excellent rehabilitation compared to dialysis and is the preferred method of treating end-stage renal disease (ESRD) patients. **Methods:** We conducted a retrospective analysis of anesthesia management from 20 cases of live renal transplants carried out between August 2017 and April 2019 at Dr. Sardjito Central General Hospital, Yogyakarta. The subjects ' preoperative patient status, anesthesia management, and postoperative care were assessed. **Results:** Most patients had preoperative anemia, normal serum potassium, serum creatinine, and average ejection fraction. Anesthesia management began 24 hours before surgery, in which the patients were hospitalized, had peripheral IV access and fluid maintenance, and hemodialysis, followed by premedication 1 hour before surgery. Before surgery, anesthesia induction and intubation were done, followed by maintenance of anesthesia and intraoperative monitoring. Postoperative care consisted of the administration of analgesia and management of complications. **Conclusion:** Optimization of preoperative status, proper anesthesia management, and good postoperative care are keys to a successful renal transplant program.

Kata kunci: Renal transplant, ESRD, anesthesia

Background

Good organ viability in renal transplants results from donor management, allograft, and recipient. The short-term and long-term outcomes are affected by fluid therapy and perioperative medications. Close intraoperative monitoring, optimization of intravascular fluid status to boost renal perfusion, and immediate electrolyte disorder correction (especially potassium) are the key to successful short-term and long-term kidney transplants.

A retrospective analysis of 20 living renal transplant cases was done to identify the trend based on patient age, gender, end-stage renal disease (ESRD) etiology, anesthesia management, and patient outcome in our hospital.

Methods

This study applied a retrospective approach. The inclusion criteria were all adult renal transplant cases from August 2017 – April 2019 in Dr. Sardjito Central General Hospital. Patients with incomplete medical records regarding anesthesia management were excluded. All medication usage and perioperative events were manually documented. Age, gender, chronic kidney disease

etiology, preoperative status, and dialysis history were also recorded. Preoperative preparation, supporting examinations, details of anesthesia management, monitoring, and outcome were also recorded and included in the baseline data.

American Society of Anesthesiology (ASA) status from the renal donor was generally ASA I-II. Renal extraction from the donors was done through open nephrectomy dan laparoscopic nephrectomy with general anesthesia and controlled ventilation or epidural anesthesia. This study focused on the perioperative management of renal transplant patients.

Results

Of 20 patients undergoing renal transplantation from August 2017-April 2019, most were male (65%). Most (50%) of ESRD etiology was not defined. Of 20 patients, 18 patients (90%) underwent routine hemodialysis, whereas two patients (10%) had not done either hemodialysis or CAPD (continuous ambulatory peritoneal dialysis) (Table 1).

Table 1. Subject characteristics

Variables	N(%) / mean ± SD
Age (years)	40.8 ± 12.5
Gender	
• Male	13 (65)
• female	7 (35)
ESRD etiology	
• not defined	10 (50)
• diabetic nephropathy	6 (30)
• nephrotic syndrome	1 (5)
• chronic glomerulonephritis	1 (5)
• analgesic nephropathy	1 (5)
• obesity and gout arthritis	1 (5)
Routine hemodialysis	18 (90)
The interval between dialysis and renal transplantations (months)	16.65 ± 15.7

ESRD: end-stage renal disease; N: number of patients; SD: standard deviation

a. Preoperative status

Preoperative anemia was the most common finding. The mean hemoglobin was 9,2 ± 1,6 g/dL. Hemoglobin concentration < 8 g/dL was found in 3 patients (15%). Iron supplementation was not given to patients before the transplant, and one patient (5%) required a blood transfusion due to low hemoglobin concentration (5.4 g/dL). Serum potassium concentration was within the normal range (3.6-4.7 mEq/L) with a mean of 4 mEq/L. Serum creatinine concentration varied between 2.1-7.8 mg/dL with a mean of 4.4 mg/dL (Table 2).

Echocardiograms revealed left ventricular diastolic dysfunction in 8 patients (40%) with ejection fractions between 32-76%, tricuspid regurgitation, and mitral regurgitation. An ejection fraction of 30-40% was reported in 4 patients. Ejection fraction below 30% was found in 2 patients before hemodialysis, but repeat echocardiograms post-hemodialysis showed an ejection fraction > 30%. There was only one patient (5%) with minimal pericardial effusion. In the chest X-ray examination, two patients (10%) had bilateral pleural effusion (Table 2).

Table 2. Preoperative status

Parameter	N (%) / mean ± SD
Hemoglobin (g/dL)	9.2 ± 1.6
Hemoglobin < 8 g/dL	3 (15)
Serum potassium (g/dL)	4 ± 1.3
Serum creatinine	4.4 ± 1.5
Diastolic dysfunction	8 (40)
Ejection fraction	
• > 40%	14 (70)
• 30-40%	4 (20)
• < 30%	2 (10)
Pericardial effusion	1 (5)
Bilateral pleural effusion	2 (10)
Anti-HLA antibody > 300 MFI	6 (30)

dL: deciliter; g: gram; HLA: Human Leukocyte Antigen; MFI: Mean Fluorence Intensity; N: number of patients; SD: standard deviation

Human Leukocyte Antigen (HLA) matching among donor and recipient tissues was conducted in all patients. HLA matching results exhibited Anti-HLA antibody > 300 MFI in 6 patients (30%), and preoperative plasmapheresis was conducted. Immunosuppressive drugs such as steroids (including methylprednisolone), tacrolimus, anti-lymphocyte globulin, and basiliximab were given to reduce the incidence of graft rejection.

b. Anesthesia management

General anesthesia with continuous epidural anesthesia was conducted in all cases. Hemodialysis was done in all recipients 24 hours before surgery to diminish the risk of volume overload, hyperkalemia, and massive bleeding. One day before surgery, patients were hospitalized in the intensive care unit (ICU) as the regular procedure in Dr. Sardjito Central General Hospital, which involved hemodynamic (blood pressure, electrocardiography, oxygen saturation, and temperature) monitoring and immunosuppressive drugs administration. Antihypertensive drugs were continued until the day of the surgery. Premedication was given 1 hour before surgery, consisting of sedatives and individual regular medication (Figure 1).

Peripheral intravenous access was performed in the contralateral hand of the arteriovenous (AV) shunt the night before surgery. Maintenance fluid was given according to insensible water loss (IWL) calculation. Coinduction was done via midazolam 0.05 mg/kg BW and fentanyl three mcg/kg BW. Anesthesia induction was done using propofol (1-2 mg/kg BW) in 18 patients (90%), dexmedetomidine in 2 patients (10%), and fentanyl (2-4 mcg/kg BW) in all patients. Muscle relaxant choices included atracurium 0.5 mg/kg BW in 14 patients (70%), rocuronium 0,6 mg/kg BW in 5 patients (25%), and vecuronium in 1 patient (5%). All patients were intubated and underwent controlled ventilation. Anesthesia maintenance throughout the surgery was carried out using Oxygen 50% with 1-2% sevoflurane supplementation and fresh gas flow of 2 L/min. Analgesia was retained with fentanyl 1-2 mcg/kg BW/hours or through a continuous epidural of 2-4 cc/hours bupivacaine/ropivacaine 0.25% with prior 10 ml bolus (target the T6-L2 vertebrae). Most patients were given a combination of colloid (gelofusine or BES) and crystalloid (normal saline) infusion. A 40 mg of furosemide injection was administered to all patients, and four patients were given mannitol and an additional dose of furosemide (Table 3).

Intraoperative monitoring such as heart rate, invasive blood pressure monitoring (artery line), oxygen saturation, central venous pressure (CVP), end-tidal carbon dioxide ($ETCO_2$), electrocardiogram, stroke volume variation, cardiac output (with Most Care® and ICON™) was conducted in most patients. CVP was installed in the left or right subclavian vein or right internal jugular vein (as opposed to the location of the AV shunt and relied on the presence/absence of a hemodialysis catheter). The hemodynamic parameters were recorded in the 15-minute interval. Dobutamine and/or norepinephrine 0.05 mcg/kg/minutes was administered to 3 patients (15%) (Table 3).

Table 3. Anesthesia management and drugs

Management	Drugs	N (%)
Induction of anesthesia	Propofol (IV)	18 (90)
	Dexmedetomidine (IV)	2 (10)
Co-induction	Midazolam and fentanyl (IV)	All patients
Muscle relaxant	Atracurium	14 (70)
	Rocuronium	5 (25)
	Vecuronium	1 (5)
Maintenance of anesthesia	Oxygen 50% and sevoflurane 1-2%, fresh gas flow 2 L/min (inh)	All patients
Maintenance of analgesia	Fentanyl (IV) or Bupivacaine/ropivacaine 0.25% (IV and epidural)	All patients
Fluid management	Crystalloids only	5 (25)
	Combination of crystalloids and colloids	15 (75)
Diuretics	Furosemide only	16 (80)
	Combination of furosemide and mannitol	4 (20)
Vasopressors	Dobutamine and/or norepinephrine	3 (15)

Inh: inhalation; IV: intravenous; N: number of patients

a. Postoperative care

The mean surgery duration was 6 hours (± 2.3 SD). At the end of the surgery, reverse muscle relaxants using intravenous neostigmine 0.05 mcg/kg and atropine sulfate eight mcg/kg were given to patients with remaining muscle relaxant effects according to the train of four (TOF) monitor. All patients were extubated postoperatively in the operating theater and transported to the ICU with supplemental oxygen using a non-rebreathing mask and a minimally invasive monitor (Most Care®).

All patients were hospitalized postoperatively in the ICU. Intravenous analgesia (i.e., fentanyl 1-2 mcg/kg BW) and epidural analgesia (i.e., bupivacaine/ropivacaine) were administered in 19 of 20 patients (1 patient was not given epidural analgesia postoperatively due to the clot formation in the epidural catheter). Dialysis support was indicated in 1 patient during the postoperative period. Acute graft rejection was witnessed in 2 patients.

Both showed good clinical responses to tacrolimus and plasmapheresis. Reexploration was performed in 1 patient due to the thrombus in the blood vessel proximal to the graft. Sixteen out of twenty patients were given heparin before anastomosis, instigating massive bleeding during and after surgery which dictated leukodepleted PRC transfusion in 10 patients (50%) and fresh frozen plasma (FFP) transfusion in 2 patients (10%). The remaining four patients were not given heparin before anastomosis, abolishing the need for either PRC or FFP transfusion. One patient died more than three months after surgery (Table 4).

Table 4. Postoperative care

Indication	Management	N (%)
Postoperative pain management; routine procedure	Intravenous and epidural analgesia	19 (95)
Acute graft rejection	Tacrolimus and plasmapheresis	2 (10)
Graft thrombosis	Reexploration	1 (5)
Massive bleeding	• Leukodepleted PRC	10 (50)
	• FFP	2 (10)
	• None	8 (40)

FFP: fresh frozen plasma; PRC: packed red cell

Discussion

Renal transplantation is the treatment of choice for patients with ESRD.[1,2] Despite significant evolutions in renal transplant surgery, the risk of perioperative complications remained high. About 25% of all renal recipients suffer from the delayed function of the graft postoperatively, and some still require renal replacement therapy, contributing to 40% of increased mortality. Most renal transplant recipients suffer from cardiovascular, hematology, respiratory, and metabolic problems secondary to kidney failure. These factors complicated anesthesia management.[1,3]

Cardiovascular disease remains an essential factor in postoperative morbidity and mortality, particularly in patients over 50.[2] The incidence of coronary artery disease in ESRD patients is 25%. If patients are added to the waitlist for organ transplantation for several years before the donor organ is available, repeated cardiac evaluations are recommended, especially in patients with active cardiac disease such as unstable

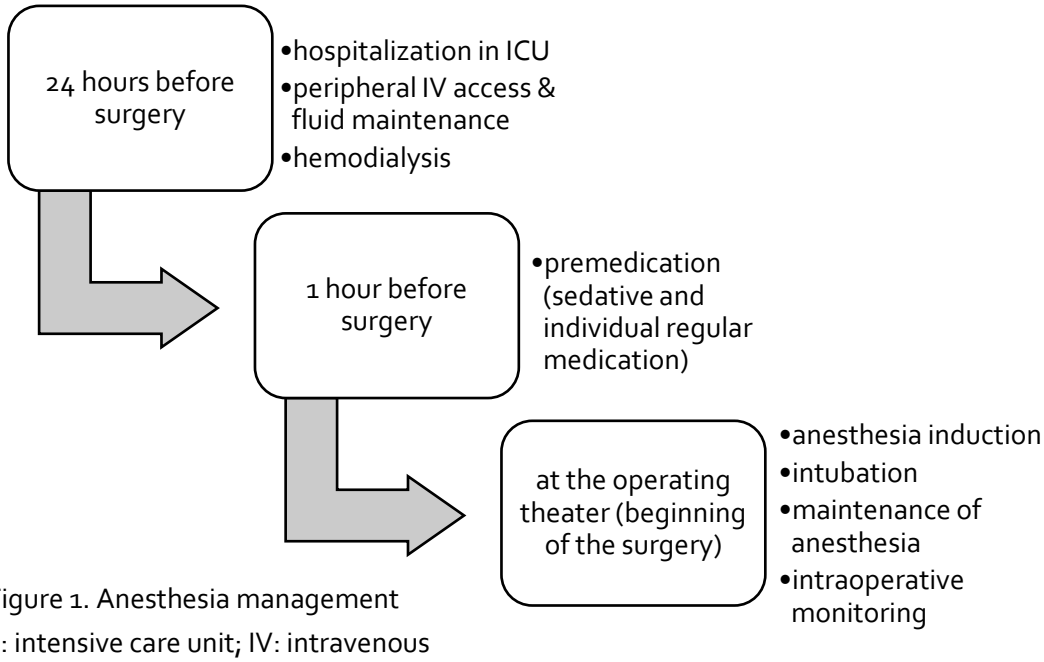

Figure 1. Anesthesia management

ICU: intensive care unit; IV: intravenous

coronary syndrome, heart failure, significant arrhythmia, and severe valve disease. A 12-lead electrocardiography and echocardiography examination are recommended.[2,4] In one study entailing 22 hospitals, several most common preoperative examinations include echocardiography, cardiopulmonary exercise testing, lung function test, and stress echocardiography. One hospital (4,5%) routinely instructs a cardiovascular review before transplantation, while other hospitals only conduct cardiovascular reviews in patients over 50 years old, diabetic patients, or patients with underlying cardiovascular diseases.[5,6,7]

Other comorbidities associated with end-stage renal disease include hypertension and diabetes mellitus. Hypertension prevalence was 90% in patients with glomerular filtration below 30 ml/min. Hypertension is the cause as well as the consequence of chronic kidney failure. Hypertension exacerbated chronic kidney failure through the renin-angiotensin-aldosterone system and volume overload.[2,4] Diabetes mellitus was observed in 30% of patients requiring renal replacement therapy and could occur concomitantly with hypertension and cardiovascular disease, further enhancing the risk of stroke and myocardial infarction[2,4].

Metabolic acidosis is a common problem in a patient with ESRD. However, a large-scale retrospective study of more than 22,000 patients demonstrates a higher risk of delayed graft function in patients undergoing hemodialysis than CAPD. Routine usage of immediate hemodialysis before surgery is therefore not recommended, but it should be considered in patients with hyperkalemia due to potential potassium spikes during graft reperfusion.[2,6]

Most hospitals (63.6%) conduct preoperative dialysis on the recipients until their dry weight is achieved. Three hospitals (13.6%) set body weight post-dialysis 1-2 kg above the dry weight, while others do not precisely determine the target body weight before surgery.[5] In our study, all patients underwent preoperative dialysis to achieve their dry weight. Consequently, all patients had normal potassium levels and were not in a hypervolemic state preoperatively.[7]

ESRD patients are prone to infection due to uremia, comorbidities (such as hypertension, diabetes mellitus, and cardiovascular disease), infection from donors, and immunosuppressive drugs. As a result, broad-spectrum prophylactic antibiotics should be given before surgery, such as first-generation cephalosporin or vancomycin, and comorbidities should also be carefully controlled.[7]

ESRD patients generally have low albumin levels due to plasma volume expansion, albumin redistribution, exogenous loss (in peritoneal dialysis patients), and decreased synthesis of albumin. Hypoalbuminemia and uremia-induced blood-brain barrier amplify the fraction of over-the-counter medications. Hence, drug dosage adjustment is essential, and the drugs are administered at titration doses.[1,7] Induction choices of drugs, including thiopentone, propofol, or etomidate. Succinylcholine should be used cautiously because it can instigate hyperkalemia, particularly in patients with high initial potassium levels (>5 meq/l). Atracurium, cisatracurium, vecuronium, rocuronium, and mivacurium can be safely used, although rapid sequence intubation (RSI) may require appropriate modifications. Short-acting beta-blockers such as esmolol or short-acting opioids such as fentanyl or remifentanil prevent elevated blood pressure and hemodynamic disorders during laryngoscopy.[3,7]

Isoflurane, sevoflurane, desflurane, or intravenous propofol are some options for the maintenance of anesthesia. However, isoflurane is the agent of choice because it is metabolized in small amounts. Analgesia can be preserved using fentanyl or remifentanil. Morphine should be used cautiously because morphine-6-glucuronide, an active metabolite of morphine, can cause respiratory depression.[3,7]

Perioperative fluid management is crucial to

maintain sufficient intravascular volume and perfusion to the transplanted kidneys. After vascular unclamping, a large volume of blood enters the transplanted kidney, releasing mediators from the ischemic kidney tissue. There is also an excessive loss of fluid during dialysis and perioperative fasting. All these predispose the patients to hypovolemia which may lead to acute tubular necrosis and graft dysfunction.[1,4,7]

Optimal perioperative fluid management can be achieved by maximizing graft function with aggressive fluid management (up to 30 ml/kg/h and central venous pressure > 15 mmHg) with particular attention to cardiac patients. The restrictive hydration regimen demonstrated by Gasperi et al. with a CVP target of 7-9 mmHg is equally effective in maintaining graft patency (crystalloid 2400 ± 1000 ml, 15 m/kg/h). Some institutions recommend CVP as the parameter for fluid adequacy, with an increase of> 7 mm after the fluid bolus indicating the maximum intravascular volume. However, CVP and PAP are static markers of fluid responsiveness and therefore are generally less acceptable.[1,4,7]

The recommended fluid therapy for a kidney transplant is isotonic crystalloids such as ringer lactate, plasmalytes, and normal saline.[4,5] In our patients, 15 patients (75 %) patients got a combination of crystalloids (saline-based, non-potassium-containing fluids) and colloids (gelatin-based). Potura et al. compared 0.9% saline with buffered balanced acetate crystalline fluid in patients undergoing kidney transplantation. They found no significant differences in the incidence of hyperkalemia in both groups and a lower percentage of patients who needed inotropic in the crystalloid group. Hadimioglu et al. concluded that plasmalyte provides the best metabolic profile among the crystalloids.[4,5]

In other studies comparing Ringer lactate fluid and normal saline of 0.9% during kidney transplantation, researchers showed that patients who were given a lactic ringer solution had a lower incidence of hyperkalemia and acidosis. Saline infusion can cause acidosis due to dilution of the bicarbonate or hyperchloremia, lowering the strong ion difference. Metabolic acidosis of hyperchloremia triggers hyperkalemia by shifting potassium into the extracellular space. However, the volume of crystalloids used during surgery in those studies was approximately 3 liters.[1,5,6]

Colloids can also be used for volume replacement. In recent decades there has been a shift in clinical practice from the use of natural colloids to synthetic colloids. These colloids include natural colloids such as albumin and synthesis such as dextrans, gelatin, and others. However, the safety of gelatin and dextran has yet to be established. Hence their usage should be done with caution.[4,5] There are also some concerns regarding the use of hydroxyethyl starch (HES) due to osmotic lesions, such as nephrosis shown in transplanted kidneys taken from deceased donors transfused with HES200/0.62.[1,6]

The timing of fluid administration is also crucial. Othman et al. compared a CVP biphasic regimen of 5 mmHg in the pre-ischemic phase and 15 mmHg in the ischemic phase with a constant infusion of 10-15 ml/kg/h. They found better initial graft function with the biphasic regimen.[4,5]

In our study, intraoperative monitoring was conducted in most patients. Intraoperative monitoring is divided into the static method, such as transesophageal echocardiography (TEE) and central venous pressure (CVP), and the dynamic method, such as systolic volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation (SVP). Dynamic measurements of patient fluid responsiveness are better predictors than static methods. SVV predicts fluid responsiveness better in patients undergoing kidney transplantation than in CVP. Hence more commonly used. However, SVV usage is limited to mechanically ventilated patients.[4,1,7]

In our study, a 40 mg of furosemide injection was administered to all patients, and four patients

were also given mannitol and an additional dose of furosemide. Mannitol has a protective effect on the tubule cells of the transplanted kidney against ischemia. It prompts the release of prostaglandin vasodilators in the kidneys, therefore accommodating the removal of free radicals. Mannitol is generally given at the time of anastomosis release in some hospitals, but the effect of mannitol on graft function still needs to be determined. Furosemide can also lower kidney oxygen consumption by inhibiting Na-K ATPase in the thin loop of Henle, but its clinical effect on improving renal function has not been proven.[4]

General anesthesia is generally used for kidney transplants, although there are cases of kidney transplants performed under regional anesthesia.[1,3,7] All patients in our study had continuous epidural anesthesia, and there were no significant complications in our cases. However, Lauretti and Gabriela Rocha reported frequent complications of continuous epidural anesthesia, such as respiration and rupture of renal anastomoses caused by coughing, hiccups, and agitation. Endotracheal intubation or laryngeal mask airway is an alternative to maintain airway patency during continuous epidural anesthesia.[1,7]

Acute graft rejection was witnessed in 2 patients in our study. Both showed good clinical responses to tacrolimus, immunosuppressant, and plasmapheresis. The risk of acute rejection is the highest in the first week and several months after kidney transplantation. This risk can be lowered by prescribing rapid-acting and strong immunosuppressive drugs with minimal side effects (induction agents). The drugs of choice are anti-lymphocyte antibodies (polyclonal and monoclonal) and interleukin-2 receptor antagonists with IL-2 antagonists mediated by cell proliferation. This induction strategy allows early steroid discontinuation and delayed initiation of calcineurin inhibitors when there are concerns about slow or delayed graft function.[2,8,9,10]

Conclusion

Improvements in anesthesia, surgical techniques, and immunosuppressive drugs enable patients to receive transplants that were deemed unsuitable at first. Optimization of preoperative status, proper anesthesia management, and good postoperative care with a solid collaboration of nephrologists, urological surgeons, and anesthesiologists are compulsory to manage kidney transplant patients successfully.

Acknowledgment

Thank you to all hospital staff who have helped care for the patients. We declare no potential conflict of interest relevant to this article. This study did not receive specific grants from funding agencies in the public sector, commercial, or non-profit section.

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