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Update on the intraoperative management of adult cadaveric renal transplantation

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Key points

- In the UK in 2013, 1930 renal transplantations were undertaken: a 50% increase since 2005. NHS Blood and Transplant initiatives suggest that this number is set to increase.
- Chronic renal failure patients have severe comorbidities necessitating close attention to preoperative assessment.
- Patients on regular dialysis present the anaesthetist with significant challenges from complex fluid shifts, electrolyte disturbances, and rapid scheduling of emergency surgery.
- Achievement of physiological goals intraoperatively is associated with improvement in clinical outcomes.
- New immunosuppression regimes, particularly those including monoclonal antibodies, may be started perioperatively. They have side-effects which anaesthetists must be aware of.

Renal transplantation is increasing with 1930 transplants undertaken in the UK in 2013 compared with 1308 in 2005. This increase follows the NHS Blood and Transplant (NHSBT) 'Organs for Transplant' initiative, and should continue rising as part of their 'Taking Organ Transplant to 2020' programme. Renal transplantation confers almost immediate improvements in quality of life and improves morbidity and mortality compared with dialysis. There are also fiscal gains to the healthcare provider: renal transplantation being cheaper than ongoing dialysis. However, graft implantation is a complex surgical procedure with both short- and long-term outcomes directly attributable to intraoperative physiological status.[1,2] In future there will be a need to anaesthetize more elderly recipients, with more extensive comorbidities.

This article will discuss anaesthesia for implantation of cadaveric kidneys; alternative sources within this journal have discussed live related donor surgery in detail.[3]

Preoperative investigation and optimization

Comorbid illness

The commonest aetiology of renal dysfunction in the UK is diabetes mellitus, with an increasing prevalence since 2006 and projected to be 14 000 patients in 2014–15. This and other causes of end-stage renal failure (ESRF), such as IgA nephropathy and hypertension, each pose their own anaesthetic challenges.

Chronic kidney disease (CKD) is classified using glomerular filtration rate (GFR) to quantify the extent of failure. CKD Stage 1 disease (GFR >90 ml min^{-1} 1.73 m^{-2}) describes normal function but with urinary or structural renal abnormalities. Stage 2 (GFR 60–89 ml min^{-1} 1.73 m^{-2}), Stage 3 (GFR 30–59 ml min^{-1} 1.73 m^{-2}), and Stage 4 (GFR 15–29 ml min^{-1} 1.73 m^{-2}) describe mild, moderate, and severe impairment, respectively. CKD Stage 5 is defined as a GFR of <15 ml min^{-1} 1.73 m^{-2}. In this article, ESRF will refer to patients whose kidney disease is severe enough to warrant transplantation, typically a GFR <20 ml min^{-1} 1.73 m^{-2}, including both CKD Stage 4 and 5 patients.

Preoperative assessment of potential renal transplant recipients occurs as part of the listing process. This assessment identifies patients with scope for optimization and excludes patients with contraindications to transplantation. Though most patients will be adequately optimized, some travel significant distances to the transplant centre so investigations may not be readily available. Most will be in ESRF and dialysing, although some undergo pre-emptive transplantation before starting dialysis.

The commonest co-morbidity in adults with ESRF is ischaemic heart disease (IHD). This is accelerated in ESRF because of the complex interaction between CKD and risk factors for IHD such as diabetes mellitus, hypercholesterolaemia, and hypertension; and also through independent risk factors such as modulation of systemic inflammatory processes by dialysis, renal osteodystrophy, and hyperhomocysteinaemia.

Preoperative investigations

Patients are frequently anaemic, so a full blood count is mandated before operation with a group and save serum. Blood loss during renal transplantation is typically <500 ml, but unanticipated brisk bleeding is possible so transfusion should be consented for.

A raised white cell count is of concern and a source should be sought; the most likely foci being the chest, urinary tract, dialysis line, or peritoneal catheter. A decision must be made to proceed or cancel surgery as immunosuppression may render the patient susceptible to overwhelming sepsis.

An ECG should have been acquired at listing and a repeat preoperative ECG ensures there are no electrocardiographic sequelae from electrolyte imbalance, and provides a baseline should perioperative cardiac embarrassment occur. Many high risk or symptomatic patients will have more extensive preoperative cardiac investigations such as stress echocardiography, coronary angiography, or cardio-pulmonary exercise testing available.

A preoperative chest X-ray is essential to correlate with clinical evaluation of fluid status and to assess for radiological evidence of progressive heart disease.

Medication

Typically recipients are hypertensive and receiving antihypertensive therapy comprising an angiotensin receptor blocker or an ACE inhibitor. Hypertension is often refractory and patients may take several additional drugs such as calcium-channel antagonists, alpha antagonists, or beta-blockers. This impairs autoregulation and undermines their ability to respond to hypovolaemia under anaesthesia.

High doses of ACE inhibitors should be withheld perioperatively, unless there is evidence of left ventricular dysfunction. In contrast, beta-blockers, aspirin, and statins should not be stopped perioperatively.[4] Diuretics should not be stopped, as this may compromise native renal function after operation, and these patients must have serum potassium, chloride, and bicarbonate levels evaluated immediately before operation.

Although platelet number may be normal, the uraemic state and frequent use of antiplatelet drugs in this population may impair platelet function and prolong bleeding times without abnormalities in the coagulation profile.

Dialysis assessment

Volume status, acid–base, and electrolyte balance can be assessed from blood samples taken before and after dialysis, noting the volume of fluid removed at each session and the patient's native urine output. An anuric patient will be fluid restricted, and will have more fluid removed during dialysis to manage their water balance. This causes large fluid shifts and relative dehydration with possible cardiovascular instability under anaesthesia. Peritoneal dialysis patients undergo comparatively smaller fluid shifts.

An important decision is whether to dialyse a patient before transplantation. Absolute indications aside (hyperkalaemia, fluid overload, uraemia, acidosis), a subtle balance must be struck. Dialysis will reduce plasma potassium, correct acidosis, and potentially avoid the need for postoperative dialysis, even if graft function is delayed. However, it will render the patient intravascularly deplete necessitating greater i.v. filling to optimize conditions for graft implantation. Though dialysis renders the patient transiently anticoagulated, the short half-life of heparin obviates this problem perioperatively. Most transplant anaesthetists operate by the idiom: 'if in doubt dialyse'.

Anaesthetic techniques

Induction of anaesthesia

Good peripheral venous access is essential before induction, as there may be a requirement to give large volumes of fluid rapidly but insertion may be challenging because of previous repeated venepunctures.

Induction may proceed with a combination of an i.v. induction agent and a strong opioid, considering the renal elimination of the drugs used. Fentanyl is a suitable choice of opioid, as is remifentanil. Morphine is predominantly metabolized by the liver but its metabolites, which have analgesic properties, are excreted in the urine. This should not affect intraoperative morphine requirements (patients with ESRF require the same plasma concentration of morphine for analgesia), but maintenance doses should be reduced. Propofol is a safe choice of hypnotic agent, and thiopental is a suitable alternative (the dose of thiopental should be reduced in uraemia to correct for changes in its plasma protein binding). Both drugs cause severe hypotension if given in excess in this population.

Muscle relaxation

Neuromuscular block is mandated to facilitate tracheal intubation and allow modulation of acid–base status. An elevated Pa_{CO_2} will increase serum potassium concentrations. Rapid sequence induction (RSI) should be considered, particularly in patients who display autonomic dysfunction, as gastric emptying may be delayed. Should RSI be indicated, succinylcholine should be avoided in cases where the serum potassium is >5.5 mmol l^{-1}. Rocuronium 0.9 mg kg^{-1} provides a suitable alternative with only a slightly longer onset of action than succinylcholine. This dose will have a clinical duration in this patient population of around 90 min as rocuronium is 30% eliminated by the kidney.

Muscle relaxation can otherwise be achieved with drugs that are eliminated in the presence of renal failure, such as atracurium and cisatracurium which undergo Hofmann degradation and ester hydrolysis. Although rocuronium may be reversed with sugammadex at the end of surgery, excretion of the rocuronium–sugammadex complex is renally dependent (Fig. 1). It is not yet recommended on the product data sheet for these patients until further research has been carried out.[5]

Monitoring and positioning

A central venous cannula should be inserted after induction, to guide fluid administration and allow use of potent vasoactive

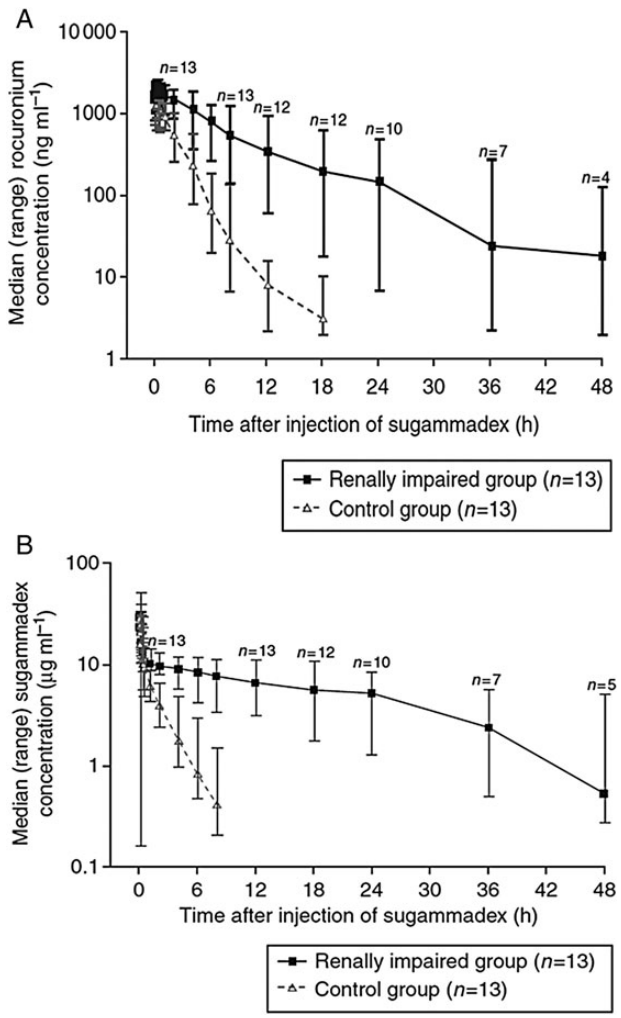

Fig 1 Semilog plots of the plasma concentrations of rocuronium (A) and sugammadex (B) in health and chronic renal failure.[5] Both drugs persist in the plasma for up to 48 h in patients with renal dysfunction.

medication such as metaraminol, ephedrine and norepinephrine. It may be appropriate to site a haemodialysis catheter at this stage for postoperative use in anticipation of delayed graft function; an assessment best made by the transplant surgeon. Ultrasonographic assessment of the central vasculature before attempting cannulation is essential as there is a high incidence of pre-existing venous stenosis from the use of long-term indwelling catheters (particularly at subclavian and internal jugular sites). Central venous cannulae should not be sited where there is a potential for steal from an established arteriovenous fistula (AVF), or where post-procedural stenosis may undermine future attempts to form one.

Monitoring of cardiac output may be warranted in cases where cardiovascular instability is expected, particularly if there is evidence of significant cardiac co-morbidity or large volume fluid administration is anticipated. There is little evidence to guide therapy using oesophageal Doppler in this cohort, but it remains the most useful tool in practice. Avoidance of unnecessary arterial cannulation renders pulse contour analysis devices less appropriate. If there is a strong comorbid indication for arterial cannulation (e.g. severe valvular heart disease or poor ventricular function), then a site should be selected that will not impede future AVF formation, or undermine existing fistula function. Femoral cannulation is contraindicated because of surgical vascular access concerns, and the increased incidence of catheter-related bloodstream infection.

Care of the AVF is of paramount importance perioperatively and involves avoiding cannulating the AVF limb, wrapping it with cotton wool, and carefully positioning it alongside the patient or on an arm board to prevent traction and compression injuries. Positioning is typically supine with lateral roll as necessary with the arms easily accessible using boards. Patient and fluid warming should proceed according to NICE Clinical Guidance 65 standards.

Maintenance of anaesthesia

Anaesthesia may continue using inhalation agents, with sevoflurane being the agent of choice for shorter, uncomplicated cases. Isoflurane is an alternative and neither drug has been shown to be associated with postoperative renal dysfunction, despite peak plasma fluoride levels in excess of 50 μM litre^{-1} having been documented with use of sevoflurane. Should anaesthesia run to over 4 MAC hours then desflurane has a more favourable emergence profile and results in less fluoride ion production (although this has not been shown to be clinically significant).[6] Total i.v. anaesthesia is a suitable alternative technique using target-controlled propofol and remifentanil infusions. Safety is ensured as esteratic metabolism of remifentanil is renally independent.

Intraoperative analgesia

This can be provided with i.v. paracetamol, and incremental doses of morphine (0.05–0.1 mg kg^{-1}) or fentanyl (up to 1.0 mcg kg^{-1}). Non-steroidal anti-inflammatory drugs are contraindicated because of deleterious effects on kidney function by interruption of blood flow in the renal vasa recta. Given the nature of the surgical technique and incision site, transverse abdominus plane blockade, either post induction or surgically under direct vision, provides a useful opiate-sparing effect.

Neuraxial techniques may be suitable depending on the anticipated duration of surgery. The increased risk of haematoma formation in these patients must always be appreciated. Use of spinal anaesthesia with local anaesthetic agents will provide dense intraoperative analgesia, reducing initial opioid requirements. Addition of intrathecal opioids may aid postoperative analgesia. Epidural catheter techniques are less appropriate because of the possibility of dialysis and anticoagulation in the immediate postoperative period.

Physiological goals under anaesthesia

A mean arterial pressure (MAP) of 90 mm Hg is warranted for all patients undergoing renal transplantation (adjusted upwards for untreated hypertensives).[1] This preserves residual renal function and reduces delayed graft function and the need for postoperative dialysis. Normotension at the time of graft arterial clamp removal is essential to optimize graft perfusion.

I.V. fluids

Fluid balance during renal transplant surgery is contentious. Fluid loading to maintain cardiac output, optimize renal perfusion, and reduce blood viscosity (to improve rheology) may improve outcomes.[2] However, sensible goals should be set, as postoperative pulmonary oedema must be avoided.

There is good evidence that a CVP of 12–14 cm H_2O at the time of graft perfusion leads to improvements in graft survival and

function.[2] One trial suggested that fluid regimes where <2500 ml were administered intraoperatively seem to have better outcomes.[1] Therefore, a liberal fluid administration strategy at the beginning of surgery is likely to be beneficial, whilst avoiding high total infusion volumes. Cardiac output monitoring allows more accurate assessment and management of the fluid regime. Several trials have suggested that normal saline in this population is detrimental to postoperative serum potassium indices and acid–base balance, and instead a balanced crystalloid such as Hartmann's solution should be used.[7] Hydroxyethyl starch must be avoided due to the risk of renal injury. Alternative colloids include gelatins and human albumin solution (which has a growing evidence base).

Mannitol

Mannitol is used as an adjunct to intraoperative fluid therapy: combining a well-established colloid with a free radical scavenging effect, but there is little evidence of improved graft survival.[8] Many centres infuse mannitol 0.5 g kg^{-1} at the time of arterial clamp removal. This should be accounted for when planning fluid administration.

Dopamine

Dopamine is used by a diminishing number of centres during renal transplantation, as there is no evidence to support improvements in patient or graft outcomes after use of this drug.

Blood transfusion

A transfusion target of 70 g $litre^{-1}$ should be used before operation, in line with current critical care recommendations. Though the recently dialysed patient will be volume deplete and blood transfusion may seem appropriate to reduce haemodilution and improve oxygen delivery to the graft, such improvements are not immediate. Other risks of transfusion include hyperkalaemia, increased blood viscosity, allosensitization, and transmission of infection. Consequently, transfusion of allogenic CMV negative blood should be used judiciously and, in cases of high blood loss, consideration should be given to intraoperative cell salvage.

Immunosuppressant regimes

Early immunosuppressant regimes for renal transplantation were reliant on corticosteroids and azathioprine. They were superseded in the 1980s by cyclosporin, which has a more acceptable side-effect profile. Current immunosuppressant regimens comprise two phases: induction and maintenance. The induction phase is typically administered pre- and intraoperatively.

If induction of immunosuppression begins after induction of anaesthesia, it should be agreed with the transplant surgeon before operation, and recognized during the WHO surgical safety 'sign in'. Modern intraoperative regimes include a biological agent and high dose methylprednisolone.

Methylprednisolone is a potent i.v. corticosteroid, administered around the time of venous anastomosis. Whilst many centres avoid use of long-term steroids for maintenance immunosuppression, almost all induction regimes include a perioperative dose.

Biological immunosuppressants

There is good evidence that induction of immunosuppression with a biological agent reduces the incidence of early cellular rejection,[9] but this is balanced against the risks of these extremely potent drugs, which are summarized in Table 1.

Table 1 Recognized complications of depleting biological immunosuppressants (e.g. alemtuzumab)

Infusion-related side-effects
Fever
Nausea and vomiting
Anaphylactoid effects
Pruritus
Rash
Dyspnoea and bronchospasm
Angioedema
Hypotension, both transient and sustained
Cytokine release syndrome
Cardiac effects
Angina
Arrhythmia
Heart failure
Cardiac tamponade
Cutaneous effects
Stevens–Johnson syndrome
Toxic epidermal necrolysis
Infectious complications
Susceptibility to opportunistic infection
Hepatitis B infection and reactivation
Tuberculosis reactivation
Progressive multifocal leucoencephalopathy

Agents may be divided into two groups: T-cell depleting and non-depleting agents. Lymphocyte depletion is associated with cytokine release and potential drug reactions. It results in chronic immunosuppression in some patients putting them at risk of infectious complications and malignancies in the longer term.[10] For this reason, depleting agents are used when potent immunosuppression is required (e.g. ABO or HLA incompatibility between donor and recipient, in young recipients with potent alloreactivity or where there are adverse pro-inflammatory graft factors).

Depleting agents

The commonest depleting agents in transplant practice are antithymocyte globulin (ATG) and alemtuzumab. Both cause profound lymphocyte depletion.[11] ATG is first line in the USA, with alemtuzumab being the agent of choice in the UK. Intraoperatively, alemtuzumab 30 mg is given by i.v. infusion over at least an hour, or by subcutaneous injection.

Non-depleting agents

These drugs do not cause lymphocyte depletion but oppose the pathways that result in alloreactive T-cell activation. They include the CD-25 (IL-2 receptor) antagonist basiliximab. The benefit of non-depleting agents is reduced immunoparesis and improved side-effect profile whilst reducing the risk of acute rejection compared with regimens where induction agents are not used.[12] Intraoperatively, basiliximab 20 mg is given by slow i.v. injection.

Anaphylaxis

Biological agents are manufactured after inoculation of animals with human T cells. The polyclonal sera produced are purified, chimerized and humanized, to a greater or lesser degree, but all carry a risk of anaphylaxis and cytokine release syndrome. This syndrome, characterized by bronchospasm, hypotension, and tachycardia initially indistinguishable from anaphylaxis, can cause vasodilatation and bronchospasm lasting for many hours or days. Survival after cytokine release syndrome is variable but severe reactions are

associated with poor outcomes. Management is initially that of anaphylaxis, with ongoing organ support as required.

Biological agents are also associated with cardiac events intra- and after operation, ranging from coronary work perfusion mismatching (cardiac ischaemia) to idiosyncratic cardiac tamponade.

Postoperative management

Analgesia

A patient-controlled analgesia (PCA) device is appropriate for pain control. As renal function may improve only slowly after operation a reliable regime is morphine 0.5 mg boluses with 5 min lockouts. The inherent safety of a PCA means that standard dosing regimes should be safe but the risk of respiratory depression is greater than in healthy patients due to the renal excretion of active metabolites of morphine. Other suitable pain management strategies utilize oxycodone (19% excreted unchanged in urine) or fentanyl (despite increased risks of respiratory depression).

Fluid balance

Monitoring of CVP after operation can guide fluid administration but evidence suggests that suboptimal MAP rather than suboptimal CVP increases the incidence of DGF.[13]

Level of care

There is no indication to admit transplant recipients to Level 2 or 3 care routinely, although this should be considered if there are perioperative concerns. A dedicated post-transplant unit is essential and staff who routinely care for this cohort are vital to early identification and prevention of postoperative complications.

Summary

Renal transplantation is a complex surgical procedure. Anaesthesia for these cases is challenging and optimal physiology can significantly improve graft and patient outcomes. Many of these cases occur outside of normal working hours, but senior anaesthetic input is essential.

Immunosuppression commences in the pre- and intraoperative phase and it is imperative that anaesthetists have an awareness of the agents used. Immunosuppressant drug selection should be discussed by the anaesthetic and surgical team, and units must have strict protocols regarding drug handling and administration.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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