Clinical Management of Renal Transplantation

Edited by

Mary G. McGeown

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Clinical Management of Renal Transplantation

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Clinical Management of Renal Transplantation presents The Belfast City and University Hospital experience in renal transplantation. Over the years, the Belfast Renal Transplant Unit has acquired considerable experience in all aspects of renal transplantation which have led to excellent results. The team working in the Belfast Renal Transplant Unit has built up an outstanding reputation which has become widely known.

This volume is a comprehensive, practical reference work for senior medical students and nurses as well as for the established nephrologist and transplantation surgeon. It provides a clear and concise picture of the care needed by patients who are being prepared for renal transplantation or who have recently received a kidney transplant.

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CHAPTER 13

Insertion of the kidney

P. F. KEANE and R. KERNOHAN

1. General principles

There are certain general principles which should be followed during the insertion of the kidney (Table 29).

2. The standard kidney transplant operation

With the exception of patients receiving a kidney from a live donor, the transplant patient is normally 'on call', and living at home. When a donor kidney becomes available and the tissue type results are known, the patient will be notified by phone to come immediately to hospital. Occasionally when the donor tissue type matches more than one patient several patients may be prepared, pending the cross-match results. Almost all of these patients are receiving either haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) and it is sometimes necessary to give a period of dialysis immediately pre-operatively to correct electrolyte and fluid imbalances in order to minimise the risks of surgery.

The operation of kidney transplantation is performed under general anaesthesia, although it would be technically possible to perform it under epidural anaesthesia. As these patients will receive immunosuppressive drugs, it is important that the highest standards of sterility are maintained to avoid complications of infection. The bladder is catheterised under strict aseptic conditions using a size 16 Ch. silastic catheter (silastic catheters have a lower incidence of infection compared to ones of latex) and the bladder drained of urine. The anastomosis of the ureter to the bladder is facilitated if the bladder is partly distended and it is customary to fill the bladder with 100 ml of saline. The catheter is spigotted for the duration of the surgery.

The abdomen is prepared with savlon, spirit and iodine and draped. It is customary to place a right kidney into the left iliac fossa and a left kidney into the right iliac fossa as this positions the kidney with the renal pelvis anterior to the artery and vein. It is then easier to puncture or explore the

Mary G. McGeown (ed.), Clinical Management of Renal Transplantation, 167–179.

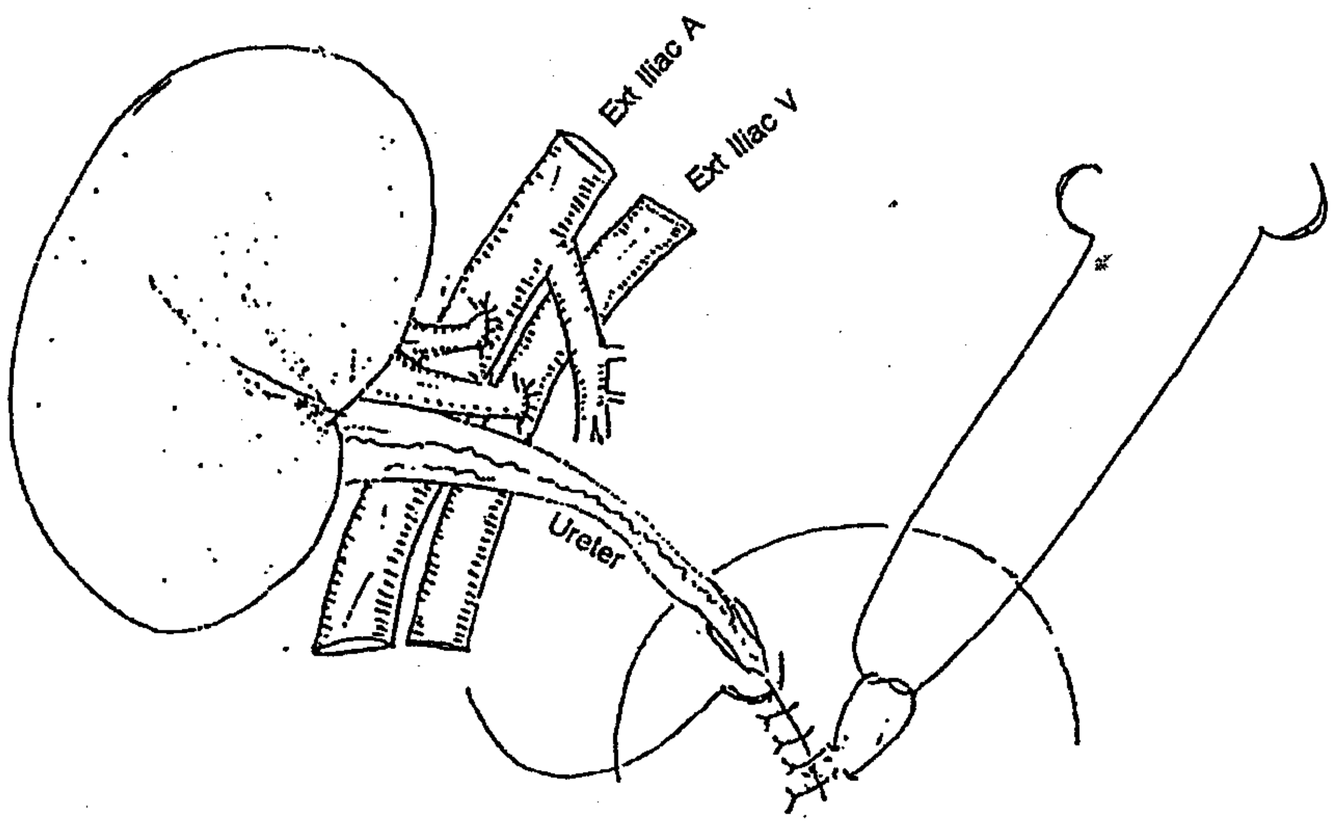

Figure 34. Renal transplantation: the muscle layer is approximated over the ureter.

changing from pale buff to pink in colour, becoming up to 30% larger in volume and pulsatile. If perfusion is sluggish this may mean a problem with the anastomosis, or spasm in the renal vasculature. The latter sometimes responds to an intravenous bolus of frusemide.

The next stage of the operation is to implant the ureter into the bladder. It is best to implant it in a position where the bladder is easily accessible and where the ureter can be kept reasonably short thereby maximising the blood supply to its end. The ureter is usually implanted onto the dome of the bladder in an anterolateral position. The bladder can be clearly identified by blunt dissection which has been facilitated by prior instillation of saline into the bladder. The dome of the bladder is held up between two stay sutures. With very careful use of diathermy, a 4 cm incision is made through the bladder muscle in the longitudinal or oblique plane. Careful dissection allows the bladder mucosa to bulge into the myotomy. The ureter is trimmed to a suitable length, and any bleeding points carefully ligated. The end of the ureter is spatulated over a distance of 1 cm and a double ended suture of polyglactin 2/0 is passed through the distal end of the ureter as shown in the diagram (Figure 34). A small hole is made in the bladder mucosa at the caudal end of the muscle incision and the needle coming through nearest to the spatulated part of the ureter is inserted through the hole in the bladder mucosa to enter as far as possible into the bladder. The needle coming through the distal end of the ureter is inserted through the hole in the bladder to exit from the bladder 1 cm proximal to the first needle. The ureter is passed through the hole in the bladder mucosa and pulled tight with this double ended suture. The suture is tied with the knot on the outside of the bladder. This causes the spatulated end of the ureter to assume the shape

3.5. *Alternative techniques for reimplanting the ureter*

There are many methods of ureteric reimplantation which may be employed; while some have advantages over others most operating surgeons have their own preference. Techniques include a "drop in" technique where the ureter is simply inserted into the bladder with 1–2 cm lying free in the bladder and the ureter secured to the bladder mucosa with 3–4 chromic catgut sutures. The Politano-Leadbetter type of reimplantation implants the ureter as close to the trigone as possible while forming a submucosal tunnel to prevent reflux. Both these techniques require a large cystotomy with the attendant risk of bleeding and catheter blockage.

The "lay on" technique involves suturing the mucosa of the ureter to the mucosa of the bladder after making a small cystotomy in the dome of the bladder. The bladder muscle is then sutured loosely over the anastomosis and distal 2 cm of the ureter to form an anti-reflux valvular effect.

The modified Lich technique as already described above and the "lay on" technique avoid formally opening the bladder and there is a lower incidence of bleeding and catheter blockage.

Occasionally the donor ureter has been damaged. In this case the patient's own native ureter can be used. An anastomosis can be formed between the donor renal pelvis and the recipient's ureter. However, the rate of anastomotic failure with this technique is much higher than reimplantation of the donor ureter into the bladder.

4. Post-operative care

In Belfast the patients are nursed in a purpose designed transplant unit complete with positive pressure ventilation etc. The staff are required to change into theatre garb. The patient's visitors are not allowed direct access to the patient but can see and communicate with him through a clean/dirty corridor arrangement. While it is accepted with current knowledge that these restrictions are excessive, we feel that it helps to maintain high standards of patient care and restricts the number of personnel coming into contact with the patient thus reducing the risk of infection.

The surgery is carried out in an operating theatre dedicated to transplantation and related procedures. It is situated within the transplant unit. On transfer to the ward routine observations are made, which include quarter hourly pulse, blood pressure and hourly estimations of CVP and urine output measurements. There may be occasional bleeding from the end of the implanted ureter. It is important that the catheter does not become blocked and if this occurs it should be cautiously washed out with saline, so that the anastomosis is not compromised.

Usually the patient can take oral fluids and medication after 24 hours and can take a normal diet on the second post-operative day. The patient should

be encouraged to become mobile as quickly as possible and should sit out of bed on day one. In this regard we have found that the abandonment of drains has been most beneficial.

5. Transplantation in children

Transplantation in children is more difficult than in adults and this bears a direct relationship to the age of the child. A fifteen year old is technically little different from an adult and presents little difference from an anaesthetic point of view, however, a two year old child presents more surgical and more anaesthetic problems.

Until recently transplantation in children younger than five years has shown poor results. Trumpeter et al. reported on 16 transplants performed in 15 children less than five years old in Guys Hospital, London. The mean follow up was 1–2 years with a 25% death rate.

The results of transplantation in children less than one year old remain poor and several centres have stopped transplanting children of this age, maintaining them on CAPD until they are old enough to reduce the risks. Miller et al. from Minnesota consider that live related donor transplants in the 1–5 age group give better results than cadaver transplants. Reports on these patients exhibiting catch-up growth remain at present contradictory.

5.1. *Problems in the under five age group*

The problems which may be encountered in children under five years are summarized in Table 30.

Table 30. Problems encountered in transplantation in children under five years

1. There will probably be disparity in size between the donor kidney and the recipient vessels and vice versa.
2. Vascular anastomosis is technically more challenging due to the small vessel size.
3. The kidney cannot usually be placed retroperitoneally in the pelvis due to inadequate space.
4. Fluid balance, particularly during initial perfusion of the kidney is more critical than in the adult due to the smaller intra-vascular volume and limited cardiac output in the small child.
5. Small children pose more difficult anaesthetic problems.
6. Post-operative care is more demanding than in adults.
7. Biopsy of the graft can be more hazardous due to the intra-peritoneal position of the graft.
8. Immunosuppression in children may lead to a greater incidence of malignancy.
9. Post-transplant hypertension is common.

5.1.1. *Disparity in size between the donor kidney and the recipient.* It is possible to transplant an adult kidney into a baby less than one year old. The kidney must be placed intraperitoneally and because the baby's iliac

vessels are of small calibre it is necessary to anastomose the graft vessels onto the aorta and vena cava. The anastomosis of the ureter to the bladder is not usually a problem and the same technique is employed as in adults.

Conversely a donor paediatric kidney 18 months old can be transplanted into an adult subject to the surgeon's ability to anastomose the small graft vessels satisfactorily. It is generally thought that a kidney from a paediatric donor older than 1.5 years can provide adequate function for an adult recipient. Kidneys from donors less than one year old should probably not be used routinely in adults due to the technical problems of vascular anastomosis.

5.1.2. *Vascular anastomosis*. When an adult kidney is transplanted into a child vascular anastomoses do not pose any technical difficulties, provided the graft vessels are anastomosed onto suitable sized recipient vessels such as the common iliacs, aorta or vena cava. However, it is good practice to use interrupted sutures rather than continuous so that the anastomosis can grow with the child.

When a paediatric kidney is transplanted into an adult the vascular anastomoses are usually straightforward provided that patches of aorta and vena cava are present on the donor vessels. If there are no patches difficulties can be encountered due to the small size of the donor vessels and artheroma in the recipient vessels. When a paediatric donor kidney becomes available for use in an adult it is important to transplant it into a relatively young adult to minimise the technical problems.

5.1.3. *Placement of the kidney*. In children the pelvis is shallow and underdeveloped. This means that generally, even in older children there is insufficient space to place the graft in the usual retroperitoneal position in the iliac fossa. This can result in compression and kinking of the vessels especially the vein resulting in graft thrombosis. The loss of some kidneys in children in Belfast was thought to be due to this cause. It is therefore advisable to place the kidneys intraperitoneally to avoid this risk.

5.1.4. *Fluid balance*. In babies and very young children where it is necessary to anastomose the graft vessels to the aorta and vena cava, it is usually necessary to cross clamp the abdominal aorta during the anastomosis. When the kidney is perfused metabolites from the ischaemic lower limbs are released into the circulation causing vaso-dilatation and relative hypovolaemia. In addition an adult kidney when reperfused will take up 250 mls of blood which in a baby represents a significant proportion of the blood volume. These two factors can cause significant hypotension and fall in cardiac output on reperfusion of the kidney. This can be counteracted by ensuring that there is adequate fluid replacement as judged by the central venous pressure before the kidney is perfused. If this is neglected the kidney may initially perfuse but the perfusion may not be maintained therefore placing the graft at risk of thrombosis.

5.1.5. *Anaesthetic problems*. Babies and small children pose significant anaesthetic difficulties which are discussed elsewhere.

5.1.6. *Post-operative care*. Babies and small children should be nursed in a paediatric intensive care unit to facilitate the monitoring of central venous pressure, arterial pressure etc. In general, while it may seem appropriate to perform the surgery in an adult transplant unit, there can be difficulties in the post-operative management of babies and small children mainly because the staff in an adult transplant unit do not have the requisite experience in managing paediatric cases. In Belfast, transplants under five years of age are performed in the Royal Belfast Hospital for Sick Children where adequate post-operative care facilities are available.

5.1.7. *Biopsy of the graft kidney*. When grafts are placed intraperitoneally, loops of bowel may lie anteriorly and may pose a problem when needle biopsies are performed. In general we have not found a problem in practice and would not regard intraperitoneal placement as a contraindication to routine biopsy when indicated. It has been said that grafts placed intraperitoneally may have a high incidence of ureteric complications due to the inability of the ureter to pick up a collateral blood supply from the peritoneum and some surgeons tunnel the ureter behind the peritoneum before implanting it into the bladder. As the ureter usually has an adequate blood supply from the blood supply to the kidney, this seems no more than a theoretical point. In Belfast we do not tunnel the ureter behind the peritoneum in intraperitoneal grafts and have not encountered an undue incidence of ureteric problems.

5.1.8. *Immunosuppression in children*. In children with kidney transplants receiving immunosuppression there have been a few cases of malignant lymphomas. This is of course worrying, but further experience and long-term follow up will be required before this can be evaluated.

5.1.9. *Post-transplant hypertension*. Hypertension in the immediate post-transplant period is common in paediatric recipients. The mechanism causing this is at present unclear. It would be tempting to believe that an adult kidney transplanted into a small child may suffer from relative ischaemia due to under perfusion. However, graft renal vein renin sampling has not shown this to be the case and at present the cause is undefined. In most patients hypertension is transient and responds to the new anti-hypertensives such as nifedipine.

CHAPTER 14

Management of the recipient during operation

J. P. ALEXANDER

Kidney transplantation has been performed successfully for over two decades and now lacks the newsworthiness of transplantation of other organs. Yet renal transplantation, when successful, is probably the most satisfying of all transplant procedures and can make remarkable improvements in the health of the patient and growth of the child which cannot at present be achieved by dialysis. In addition, transplantation for end-stage renal disease is much more cost effective than long-term dialysis. In an institution where multiple transplantation operations are performed simultaneously, responsibility for the conduct of the anaesthesia for renal transplantation may have to be delegated to relatively junior anaesthetic staff.

1. Historical

Early attempts to transplant kidneys were fraught with difficulties and frustration. Facilities for dialysis were limited and enthusiastic clinicians were forced to manufacture dialysis catheters in their spare time. Organs were removed after the donor heart had stopped and organ preservation was rudimentary, as was tissue typing. Little was known about immunosuppression and rejection was common. Operations were lengthy due to the time required to establish suitable vascular anastomoses, and the muscle relaxants used during anaesthesia were either gallamine or tubocurarine and either of these drugs may cause prolonged post-operative neuromuscular blockade. Although regional anaesthesia avoided some of the difficulties, patients found it unacceptable.

2. Pharmacokinetics in renal failure

A number of factors alter drug disposition in end-stage renal failure patients.

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of distribution are large (large reservoirs in major organs and peripheral tissues) and are difficult to remove by dialysis.

2.4.3. *Protein Binding*. Again, highly bound drugs are difficult to remove by dialysis.

3. Drugs used in anaesthesia in the renal failure patient

The importance of over- and under-hydration, electrolyte shifts and acid-base disturbances on the pharmacokinetics of drug action cannot be over-emphasized. Drugs which act mainly on the central nervous system must be fat-soluble and hence are normally reabsorbed during passage through the kidneys. The duration of action of such agents therefore depends on redistribution, metabolism or excretion via the lungs (for volatile agents), and not on renal function. This applies to the intravenous induction agents, narcotic analgesics and inhalational agents, but not to the water-soluble non-depolarizing muscle relaxants which are highly ionized at body pH.

3.1. *Pre-operative medication*

Virtually all the standard premedicant drugs have been used, although the dosage schedules may need to be modified in view of the increased sensitivity to the undesirable effects of medication that is seen in renal failure patients. When oral diazepam is used the amount of unbound drug is increased and the clearance of a single dose decreased. In spite of these theoretical disadvantages the drug has been widely used. The shorter acting temazepam or triazolam, may have some advantages. In view of their occasional unpredictable effects, narcotic drugs, in particular morphine, may be best avoided. Pethidine should also be avoided. Metoclopramide and cimetidine or ranitidine may be given. The latter does not interfere with the cytochrome P 450 hepatic metabolism of certain drugs.

3.2. *Induction agents*

At one time it was thought that the dose of thiopentone necessary to induce sleep was about half that required in the normal subject. However, with a relatively slow rate of drug administration in line with modern practice, the dose required for induction is only slightly less than that required in healthy patients, because the free drug volume of distribution and drug clearance are unchanged. The induction dose of other agents, and of hypnotic and sedative drugs may need to be reduced. The response to neuroleptic agents appears to be normal. Propofol has a profound effect on arterial blood

procedure. Non-invasive monitoring with electrocardiogram, blood pressure, pulse oximeter and end-tidal carbon dioxide measurement are routine. Arterial and central venous cannulae may be *in situ*. Muscle relaxants are used to aid surgery and to blunt spinal reflexes. A high proportion of cadaveric organ donors respond to surgical incision with abdominal muscle contraction (a spinal arc reflex) and autonomic nervous system responses, suggesting that even though irreversible brain-stem damage has occurred from which death is inevitable, some brain-stem function remains. The surgeon may call for a bolus dose of phentolamine shortly before the aorta is clamped. When this is done, the time is noted, monitors and infusions are turned off and the donor disconnected from the ventilator.

6. Anaesthetic management of the recipient

Successful renal transplantation is very dependent on haemodialysis which allows preoperative preparation to be accomplished rapidly, particularly in the patient who has been maintained on a chronic dialysis program. Unlike other major organ transplants, the patient can be maintained in reasonable health if the graft is slow to function or fails.

6.1. *Pre-anaesthetic evaluation*

Management of the recipient is similar regardless of the source of the donor. With improved techniques for preservation of the graft, the need to perform the operation as an emergency has passed. One noticeable recent trend has been to extend the transplant program to include the quite young and the relatively elderly, and to include patients with severe chronic disease of other organs. These require careful evaluation. Behavioural, mental or neurological changes and peripheral neuropathies are all common.

6.2. *Fluid and electrolyte status*

Most centres prepare recipients for live donor transplants with dialysis 12–24 hours prior to surgery. The recipient of a cadaver kidney is dialysed for several hours before the operation. If this is not done, there may be a certain amount of fluid retention, not necessarily disadvantageous, because patients dialysed to "dry weight" may respond to induction of anaesthesia with vasodilatation and associated hypotension.

Metabolic acidosis should not be a problem in the patient maintained on an adequate dialysis regimen. The serum potassium level is critical. Apart from dangers associated with the use of suxamethonium, potassium can be released from ischaemic muscle if the external iliac artery is used for vascular

end-stage renal disease have accelerated atheroma formation; some workers routinely perform coronary arteriography and will consider coronary artery bypass grafts in selected patients prior to transplantation.

6.5. *Diabetes*

An increasing number of diabetics with end-stage disease are being offered transplantation. The diabetic state which may be destabilized by steroids requires careful control. Regular injections of insulin can be stopped on the day of surgery and replaced by an infusion of 5–10% dextrose containing 10–20 units of regular insulin per litre. This is infused at a rate of 100 ml/h in a modified Alberti regimen that does not include the use of potassium, combined with frequent measurement of blood sugar. Fine control over blood sugar can be achieved using a sliding scale of additional insulin administration (Table 31).

A high incidence of difficult laryngoscopy may be anticipated in diabetic patients who have limited joint mobility. This joint rigidity is probably due to glycosylation of tissue proteins from chronic hyperglycaemia and may involve laryngeal and cervical areas.

Table 31. The sliding scale of insulin dosage. Blood glucose is measured 2- or 4-hourly as appropriate.

Blood glucose mmol l^{-1}	Soluble insulin dosage
0–10	Nil
10–15	5 units subcutaneously
15–20	10 units subcutaneously
20 or more	Intravenous bolus of 5 or 10 units or constant infusion at 1–2 units hourly

6.6. *Monitoring*

Apart from the presence of a skilled and vigilant anaesthetist, certain basic monitoring procedures are considered necessary for all patients undergoing anaesthesia and surgery. Major surgery demands more sophisticated techniques. The single precordial lead electrocardiogram gives information on the heart rate, cardiac rhythm, and conduction disturbances. The CM5 configuration may give early warning of myocardial ischaemia. Modern automatic non-invasive blood pressure recorders measure systolic, mean and diastolic blood pressure at regular intervals. They can be set to cycle at one minute intervals during induction of anaesthesia and during release of vascular clamps, but should not be left to cycle at this frequency for prolonged periods since both nerve and arterial damage have been reported.

The anaesthetic machine should be fitted with an oxygen analyzer to monitor the inspired oxygen concentration and a respirometer should be available to check tidal and minute volumes. A disconnect alarm should be fitted and switched on. Breath sounds may be monitored with a precordial or oesophageal stethoscope (or both). Since both hypercarbia and hypocarbia decrease renal perfusion, monitoring of expired carbon dioxide is valuable. The aim should be normocarbia with an end-tidal concentration at about 5% (5 kPa or approximately 40 mm Hg). Pulse oximetry has become a valuable method of confirming the adequacy of oxygenation. Many patients with renal failure require substantially higher concentrations of inspired oxygen than have been used conventionally to maintain satisfactory arterial oxygen saturation (SaO_2). This may reflect some degree of heart failure or of pulmonary oedema. Measurement of central venous pressure via an internal jugular catheter is becoming popular. Not only will this allow a more accurate assessment of the degree of hydration, but in addition, early function of the graft appears to be improved if venous pressure is maintained at between 10–12 cm of water. The use of pulmonary artery catheters is thought to be undesirable in patients who are soon to become immuno-compromised and increasingly susceptible to infection.

A nerve stimulator is useful, particularly where a short-acting muscle relaxant such as atracurium is being used. Determination of the train-of-four twitch fade allows for proper titration of subsequent doses. It also gives the anaesthetist an idea of the amount of curarization remaining at the end of surgery.

During prolonged surgery, core temperature will fall and should be measured. Humidification of inspired gases may limit the temperature fall and, where appropriate, a heat and moisture exchanger will conserve heat and water vapour and protect the airway against bacterial and viral contamination. Laboratory facilities for rapid determination of electrolytes, blood gases, haemoglobin or haematocrit and glucose are essential for renal transplantation.

6.7. *Choice of anaesthesia*

The first patient ever to receive a living related donor kidney transplant had a spinal anaesthetic. Spinal or epidural anaesthesia held certain attractions in the early days of transplantation in America. Patients often came to surgery with heart failure, uncontrolled hypertension and high serum potassium levels. Some developed life-threatening arrhythmias, particularly while being intubated. Regional anaesthesia also avoided the unwanted effects of muscle relaxants and may have reduced the risk of pulmonary aspiration. An epidural catheter could be used for postoperative pain relief although recent heparin dialysis would be a contraindication to its insertion. However, many of the early operations were prolonged and spinal anaesthesia was not

well tolerated. The sympathetic block associated with spinal or epidural anaesthesia created difficulty in maintaining an adequate systolic blood pressure. Local anaesthetics have a shorter effect when the circulation is hyperdynamic. The introduction of newer inhalational drugs and muscle relaxants has given the anaesthetist much greater control over the patient having general anaesthesia and this has become the method of choice in most transplant units.

A large-bore intravenous cannula is required. Peripheral venous access may be difficult in the patient who has been receiving haemodialysis for years. The intravenous infusion and blood pressure cuff must not be placed on the arm which has a functioning dialysis fistula or shunt. This arm must be carefully protected during surgery and the presence of a bruit noted before and after operation. Episodes of hypotension and the hypercoagulable state that can occur in the perioperative period may lead to loss of a functioning fistula. Induction of anaesthesia is hazardous for the transplant patient. The majority of deaths and serious arrhythmias have been related to hyperkalaemia and levels over 6.0 mmol/l are dangerous. Pre-oxygenation and correctly applied cricoid pressure should be used in patients at risk of regurgitation and aspiration. An intravenous bolus injection of fentanyl, alfentanil or lignocaine (which may depress the heart) will reduce the cardiovascular response to oral intubation. The uses of beta-adrenergic receptor antagonists (beta-blockers) as bolus injections prior to induction is best avoided. All the currently available beta-blockers are long-acting and some are eliminated by the renal route. Esmolol, a short-acting beta-blocker, may establish a place in this regard when it becomes available, but on no account should this type of drug be given to patients with obstructive pulmonary disease or a history of asthma. Chewing a 10 mg capsule of nifedipine which can then be absorbed through the buccal mucous membrane will often give satisfactory control of high blood pressure during the induction.

6.8. *Induction and maintenance*

Unless the timing of organ availability allows time to curtail oral intake, full-stomach precautions are taken during induction. After pre-oxygenation, a rapid-sequence induction with cricoid pressure and oral intubation is performed. Thiopentone (3–5 mg/kg) is given intravenously. If the pre-operative serum potassium concentration is normal, laryngoscopy and endotracheal intubation are facilitated with suxamethonium (1.0–1.5 mg/kg). If the serum potassium is raised, vecuronium 0.1 mg/kg or atracurium 0.6 mg/kg is used in preference to suxamethonium. Isoflurane, nitrous oxide in 50% oxygen and supplementary doses of non-depolarizing muscle relaxant and fentanyl is the current choice for maintenance. A urinary catheter and, if required, a central venous pressure cannula are inserted. Central venous pressure will be high in well hydrated patients and in those with a good functioning arterio-

venous fistula. The electrocardiogram is closely observed for evidence of hyperkalaemia. Washout hyperkalaemia may occur when vascular clamps are released. Blood loss averages 200–400 ml and should be replaced with whole blood (which has been previously ordered). Crystalloid solutions should be potassium free. Compound sodium lactate (Ringer's or Hartmann's solution) is not used. Isotonic sodium chloride, dextrose 5% in 0.45% sodium chloride or dextrose 4% in 0.18% sodium chloride (solution 18) are acceptable. Losses of blood not requiring transfusion can be replaced by plasma or isotonic sodium chloride. Transfusion may be required if excessive bleeding occurs when the vascular clamps are released. Blood should be warmed prior to transfusion to reduce the infused serum potassium level. Intravascular volume is titrated using central venous pressure and systolic arterial pressure measurements rather than making use of any standard formula. Maximum hydration short of precipitating pulmonary oedema encourages early graft function. Intermittent positive pressure ventilation during anaesthesia can mask pulmonary oedema until after resumption of spontaneous breathing and extubation.

Individual transplant teams vary in the pharmacological agents which may be used to encourage graft function. Frusemide (10–20 mg) has been shown to be effective in many animal models of acute renal failure and in clinical studies provided it is given at the time of injury and that the subject is not dehydrated or hypotensive. Mannitol (25–50 g), in addition to its osmotic action on the renal tubules, is a renal vasodilator. It can also cause a rise in serum potassium (0.4–0.7 mmol/l). Upon release of the clamps the kidney should turn from grey to pink. Sometimes hypotension results which should be treated by cautious administration of volume expanders, although use of low dose dopamine (not more than 10 μg/kg/min) has been described. Less commonly, clamp release may result in renin release by the ischaemic kidney, resulting in a transient hypertensive episode.

If significant hyperkalaemia (greater than 6.5 mmol/l) is present at the end of the operation, it may be wise to continue artificial ventilation into the post-operative period to maintain a respiratory alkalosis. Otherwise, the neuromuscular block is reversed with neostigmine (0.035 mg/kg) and glycopyrrolate (0.01 mg/kg) or atropine (0.02 mg/kg) and the patient extubated. Although the slow elimination of anticholinesterase agents in anuric patients may facilitate the reversal of muscle relaxants, there is an increased incidence of delayed unwanted effects such as bradycardia.

For the first 24 hours post-operatively, the patient is nursed in a high dependency area in the transplant ward or in an intensive care environment. Monitoring of heart rate, arterial blood pressure and arterial oxygen saturation should continue during this period, while the patient receives adequate oxygen by disposable face mask. The central venous pressure commonly falls to near zero within a few hours after renal transplantation as the kidney begins to function and adequate fluid replacement is essential. Good oxygenation is important. The medullary thick ascending limb of the loop of Henle

has a high oxygen demand and low oxygen supply from the medullary counter current exchange system. The medullary thick ascending limb is thus particularly vulnerable to relatively mild hypoxic insults.

6.9. *Post-operative complications*

In terms of graft function, three scenarios can be imagined. Firstly, there may be good immediate function, and elimination of drugs is undistinguishable from that which occurs in patients with normal renal function. Another common pattern is a high flow of urine but with accumulation of toxic metabolic products resembling the diuretic phase of acute tubular necrosis. Thirdly, there may be delayed graft function requiring haemodialysis but without evidence of rejection.

Cardiac complications remain the most serious cause of post-operative morbidity and mortality. Cardiac death occurs in about 1% of patients, myocardial infarction in 0.5% and serious arrhythmias in 5–10%. Hypertension may require vigorous attention as it threatens both patient and graft survival, especially in diabetic patients. Complications which may lead to other surgical procedures in the early postoperative period include problems with ureteral obstruction or fistulae, vascular problems from haemorrhage, kinking of the renal artery, or thrombosis, and acute rejection (see Chapter 16).

7. Renal transplantation in children

Renal transplantation is now established as the treatment of choice for older children; however, the approach to the infant and young child remains controversial, despite the introduction of dialysis procedures suitable for the very young. The results of transplantation in children under the age of two years were particularly discouraging although there have been recent improvements with greater emphasis on live related donor allografts. Management of anaesthesia for these patients does not differ in detail from that in adults. It should be remembered that children with end-stage renal disease may have severe growth retardation and that due allowance should be made when calculating drug dosage, tracheal tube size and gas requirements for ventilation. Intermittent positive pressure ventilation is used and the intravascular volume maintained steady with a central venous pressure between 10 and 15 cms of water.

Intraoperative volume losses are replaced with a combination of packed cells and plasma, maintaining adequate blood pressure. The immunosuppressive therapy used in Belfast for paediatric recipients is described in Chapter 15. If there is no diuresis within 30–60 min, intravenous frusemide is given over 10–15 min in the dose of 2–5 mg/kg. In the small patient receiving an

adult kidney the organ may need to be placed within the abdomen; the renal vessels can be anastomosed directly to the aorta and vena cava. Meticulous attention to peri-operative management and fluid and electrolyte balance is required; intra-transplant scquestration can occur when the vascular clamps are released and a significant proportion of blood volume and cardiac output is diverted to the newly transplanted kidney.

Post-operatively, hourly urine volumes are replaced as 0.45% sodium chloride. Electrolyte measurements are carried out 4 hourly. Insensible loss is replaced by 5% dextrose and other fluid loss by half volume 0.9% sodium chloride and half volume 5% dextrose. If urinary volume is very large potassium loss should be replaced by giving potassium chloride 30 mmol per litre of intravenous fluid.

Organ transplantation in children is fraught with emotional problems. Patients often cope better with their illness than do their parents who may require particularly sensitive and tactful handling.

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CHAPTER 16

Nursing care of the patient with a renal transplant

MARY G. McGEOWN

The nurse plays an important part in the management of all stages of chronic renal failure.

Chronic renal failure, once established persists for the remainder of the patient's life and may need to be treated in different ways at different times. In the early stages control of diet, and treatment of hypertension if needed, may be sufficient to keep the patient feeling reasonably well and at work, but as renal function continues to decline a plan for the future needs to be made. This plan may include a renal transplant at some time, usually after a period of some form of dialysis treatment. The patient must be made aware that the transplant may not succeed, or may fail after months or years of good function and dialysis may become necessary again (Figure 47). The patient needs to be informed that there are different types of dialysis and understand the reasons why one type may be suitable for the present but another may be better as circumstances change over a longer period of time. In planning it is important to preserve blood vessels which may be needed in the future for haemodialysis. The object is to restore reasonable health with as little disturbance to ordinary existence as possible and the initial choice of treatment may need to be changed with time in pursuit of this goal.

The renal team includes doctors, nurses, technicians, artificial kidney assistants, the pharmacist and the social worker as well as secretaries and transplant co-ordinators all working together for the treatment and support of the patient. Ideally the same staff should continue to look after the patients as they progress through different modalities of treatment, but this is often not possible.

The role of the nurse is not confined to the physical care of the patient. It includes psychological support, counselling and education about the nature of the illness and its treatment.

1. Nursing care in the immediate post-operative period

In the Belfast Unit after transplantation patients are nursed in protective isolation until sutures, drains and catheter are removed. The patient has a single room and toilet with positive pressure ventilation. All nursing and

Mary G. McGeown (ed.), Clinical Management of Renal Transplantation, 231–241.

2. Fluid and electrolyte balance

On return from theatre the patient has a urethral catheter attached to a urinometer bag. The urinary output is recorded hourly. The urine is usually heavily blood-stained and occasionally, especially if the output is low, the catheter may become blocked with clot in which case the patient will usually complain of pain (bladder spasm). A bladder lavage may be needed, with full aseptic technique using sterile water for flushing. This is uncomfortable and the patient needs reassurance that the bladder spasm will be relieved as soon as the catheter is unblocked.

The initial prescription for intravenous fluids assumes that the urinary output may be modest in amount, but it should take into account any output from the patient's own kidneys prior to operation. If substantial quantities of urine are produced the intravenous fluid prescription must be increased accordingly, tailoring it to the previous 12, later 24 hour output. The intravenous fluids are given through a peripheral line, if possible ensuring that the fistula arm is not used for this purpose. Intravenous fluids are usually not necessary after bowel sounds become audible, unless the new kidney produces so much urine that the patient is unable to drink sufficient fluids to keep up with the output.

The patient is always very concerned if the urinary output is low, especially if this continues for more than a day or two. The situation should be discussed frankly with the patient, explaining that it is not unusual for function of the new kidney to be delayed, and that there is good reason to hope that it will do well.

Blood samples are taken each morning for monitoring urea, creatinine, electrolytes, full blood picture and 24 hour creatinine clearance. The laboratory treats as urgent specimens from recently transplanted patients, which enables early decisions about treatment to be made.

A rising serum potassium concentration is particularly important, and if above 6.5 mmol/l requires urgent action. If this occurs during the first 48 hours after surgery an intravenous "cocktail" of dextrose and insulin, sometimes with sodium bicarbonate or calcium chloride, is given to delay the need for dialysis for a short period, during which the urinary output may be improving. If this does not happen quickly enough dialysis, either haemodialysis or CAPD according to the patient's previous method of treatment, will become necessary.

The patient may become very anxious if dialysis should be necessary and may think that the graft has failed. Reassurance is needed that this is a common occurrence at this stage and does not mean that the kidney has failed.

CHAPTER 17

Graft dysfunction and its differential diagnosis

C. C. DOHERTY

The quality of clinical management in the early post-operative phase has an important influence on the outcome of renal transplantation. This chapter deals mainly with graft dysfunction as manifested by deteriorating renal function, but also examines post-transplant proteinuria. Some problems special to renal transplantation in children and the elderly are discussed.

It is convenient and practical to consider renal transplant dysfunction in two main clinical settings – firstly, the early post-operative phase prior to discharge from hospital and secondly, the patient who is re-admitted from the outpatient clinic because of later transplant dysfunction. The point of this distinction is that there are certain causes of graft failure which occur in the first but not the second of these two settings. The initial approach to graft dysfunction in all cases requires a careful assessment of the clinical background, the symptoms and physical signs, and preliminary laboratory investigations. The differential diagnosis requires a knowledge of the general principles of renal failure and of the urological and infectious complications of renal transplantation. Where the diagnosis remains uncertain, ultrasound, isotope renography and graft biopsy are the most valuable investigations.

1. Early post-transplant graft dysfunction

Some transplanted kidneys function immediately, graft dysfunction does not occur and clinical management is straightforward. This is exceptional and it is more common for one or more episodes of graft dysfunction to occur. Thus the kidney may (1) never function; (2) function for a short period and then lose function or (3) show delayed onset of function. Important clues may be found in the antemortem history of the kidney (e.g. cardiac arrest in the donor, prolonged total or operative ischaemia), the peri-operative events (e.g. intra-operative hypotension, sub-optimal perfusion on removal of clamps) or the early post-operative pattern of vital signs and fluid balance charts (a good diuresis of heavily bloodstained urine followed by sudden anuria not attributable to hypotension suggests clot obstruction).

Mary G. McGeown (ed.), Clinical Management of Renal Transplantation, 243–262.

Table 45. Causes of early post-transplant graft dysfunction

1. Hypovolaemia
2. Obstruction
3. Acute tubular necrosis
4. Urinary leak
5. Vascular complications
6. Infection
7. Cyclosporin nephrotoxicity
8. Nephrotoxicity due to other drugs
9. Rejection

The common causes of abnormal renal function in the early post-transplant period (defined here as the first 3 weeks) are listed in Table 45. The clinical presentation may be a rising serum creatinine in an otherwise well patient, or there may be additional features which aid the differential diagnosis.

1.1. *Hypovolaemia*

Assessment the volume status of the dialysis patient admitted for renal transplantation is critically important. The patient's target 'dry weight' must be compared with body weight on admission. If the patient has been kept fasting for a significant period awaiting the transplant procedure and continues CAPD during this time, negative balances must be assessed. The average 24 hour volume of urine produced by the patient's own kidneys, if any, must be taken into consideration. This is particularly important in children who may have salt-wasting and polyuria (often 1.5–3 litres) as a feature of their primary renal disease. Central venous pressure monitoring is essential in children and the elderly and should also be used in cases where clinical assessment of volume status is difficult. Blood loss in theatre should be replaced volume for volume with blood and in patients in whom the CVP is monitored, adequate isotonic saline should be given to ensure a CVP of at least 10–12 cm of water at the time the arterial clamps are released. For the first 12–24 hours post-operatively the CVP should be maintained above 5 cm of water and during this initial period when urinary volume may vary from zero to torrential diuresis (which may be 1 litre or more per hour) hourly urinometer readings should be kept and the fluid prescription revised every 3–6 hours if necessary. For those patients with immediate allograft function, adequate fluid balance can usually be maintained by replacing hourly urine volumes plus 30 ml, using alternative dextrose 5% and normal saline. Intravenous fluids can usually be discontinued by 24–48 hours. The cardiovascular response to hypovolaemia can be masked by beta-blockade and this may contribute to dangerous delay in diagnosis of post-operative haemorrhage. Therefore beta-blockers should be omitted prior to renal transplantation and alternative agents used to control hypertension. In the Belfast

Later haemorrhage may occur associated with perinephric abscess or mycotic aneurysm. Iliac artery involvement may produce catastrophic bleeding. Occasionally, significant post-operative bleeding arises in the retroperitoneal space with acute flank pain, and a drop in haemoglobin. A large haematoma extending up the psoas gutter may be visible on ultrasound. This type of bleeding is often self limited but can be a potential site of sepsis.

1.5.2. *Arterial thrombosis*. This event may produce complete or segmental infarction of the kidney and may result from multiple renal arteries, technical difficulties or atherosclerosis of recipient or donor vessels. Complete infarction of the graft is suggested by absence of renal function and continued need for post-operative dialysis. There may be significant urine production from the patient's native kidneys and surprisingly little systemic disturbance. The kidney may appear small in size on ultrasound with increased echogenicity and reduced cortical thickness. There may be a sensation of little resistance on needle graft biopsy and the tissue core may be a pale muddy colour on naked eye inspection. Concern has been expressed that CYA may increase the risk of primary graft non-function due to arterial thrombosis (especially in children). This increased risk may be due to the significant renal vasoconstriction and decrease in renal blood flow induced by CYA. I^{131} hippuran renography will aid assessment of blood flow to the kidney. If there is a normal vascular phase one can assume that the arterial supply is intact. Duplex doppler scan and arteriography may also be used to confirm the diagnosis. Operative salvage of such kidneys is unlikely and nephrectomy is indicated.

1.5.3. *Venous thrombosis*. This may occur as a primary event or in association with severe acute rejection. It causes graft swelling and tenderness and is usually – but not always – associated with signs of iliac vein thrombosis in the form of marked swelling of the leg on the side of the transplant. Lesser degrees of ipsilateral leg swelling are not uncommon post-transplant and are probably due to extrinsic pressure of the kidney on the iliac veins. Diagnosis may be aided by absence of uptake of isotope on renography (suggesting graft infarction) and duplex doppler ultrasound scanning can also be useful to assess blood flow in the renal vein. Selective contrast venography to image the renal vein is often technically difficult and carries a risk of damage to the venous anastomosis if carried out in the early post-operative period. Arteriography with venous phase films may be preferred. Salvage of the kidney by operative intervention is rare. However, a Belfast patient developed venous thrombosis three weeks after transplantation. The thrombus was removed, and the kidney continued to function until death from myocardial infarction over 21 years later.

CHAPTER 19

Surgical complications of renal transplantation

R. A. DONALDSON

Surgical complications following renal transplantation may be defined as those which require operative intervention for alleviation. Non specific surgical complications such as wound sepsis, peptic ulceration and gastro-intestinal haemorrhage to which the immunosuppressed recipient may be more susceptible than normal are not described in this chapter. The surgical complications are usually technical in origin. Since the early days of renal transplantation their incidence has fallen dramatically. This is in part due to better technique and a fuller understanding of the anatomy, both normal and anomalous, of the kidney and excretory tract. The introduction of synthetic suture materials for vascular anastomoses has reduced the incidence of complications. The vast worldwide experience of renal transplantation shared at conferences and through publications has been most helpful in managing surgical complications. The number of surgical complications has been dwindling and as a result they may now seem to be more complicated, but with the help of a shared experience, a remarkable number of innovative techniques have been used to salvage allografts which would otherwise have been lost. Nevertheless, life threatening and graft threatening situations still arise and an awareness of these situations is still essential. Apart from haemorrhage and wound sepsis, the surgical complications of renal transplantation usually come to light during the investigation of early anuria or graft failure. A combined medical and surgical approach to the investigation of anuria and early and late renal failure, using minimally invasive techniques is essential.

The surgical complications of renal transplantation may be conveniently described under the following headings:

1. excretory tract
2. vascular
3. fluid collections
4. miscellaneous

Mary G. McGeown (ed.), Clinical Management of Renal Transplantation, 277–290.

becomes lodged at the suture line of uretero-vesical junction, it may become organised and very adherent to the ureteric orifice sufficient to cause complete obstruction for days or weeks. Eventually it will be dislodged spontaneously if renal replacement therapy by dialysis has been maintained. It can be diagnosed earlier if ureteric obstruction is suspected and cystoscopy is carried out, at which time the clot can be dislodged easily with small biopsy forceps.

2. Vascular complications

2.1. *Haemorrhage*

During operation serious and uncontrollable haemorrhage may occur when the vascular clamps are released. Haemorrhage from the arterial anastomosis is more frequent but may also occur from the venous anastomosis or from small veins in the hilum of the kidney which have been inadvertently damaged or over-looked at the time of renal retrieval. Carefully constructed anastomoses will reduce the incidence of haemorrhage. Continuous suturing of the arterial anastomosis has been facilitated by the use of a Carrel patch without risk of subsequent stenosis of the renal arteries. If a patch is not available for anastomosis, as is usual in the case of living related donors, then end to end anastomosis of the internal iliac artery to the renal artery is recommended, using interrupted sutures rather than a continuous suture with risk of subsequent stenosis at the suture line. The technique of suturing and the suture material used is very important. Suture should be from within the lumen of the recipient artery (which may be somewhat atheromatous) passing the needle through the media and adventitia. In this way, small atheromatous plaques are tacked down to the media and produce a smooth suture line. In the early days of renal transplantation silk was used, but the introduction of synthetic suture materials has vastly improved the results. Modern sutures ensure that the suture material is wider than the needle used and this means that the needle holes are completely plugged by the suture and needle hole bleeding is completely avoided. Some surgeons advocate wrapping the anastomotic line with synthetic haemostatic material such as Surgicel or Haemocel prior to removal of the clamps. When haemostasis is secured, the material can be picked off from the suture line.

It is very rare to have completely uncontrollable haemorrhage requiring re-clamping of the main recipient vessels and removal of the donor organ. Smaller bleeding points can be oversewn. Small veins within the hilum of the kidney which have been overlooked can be ligated and, as long as one main renal vein remains intact, this can be carried out without detriment to the venous drainage of the kidney.

When the wound is closed, significant haemorrhage may occur in the first few hours after operation and is usually reactionary in nature occurring in

those recipients who have been hypotensive during surgery, as the blood pressure rises post-operatively. A drain, if used, may not reveal the full extent of blood loss. In such situations immediate exploration is mandatory. Bleeding tends to be from the anastomoses, especially the arterial anastomosis, or from damaged veins within the hilum of the kidney. The donor organ can usually be salvaged by oversewing the anastomosis if necessary and ligation or oversewing of open veins within the hilum of the kidney.

2.2. *Arterial complications*

2.2.1. *Renal artery thrombosis*. The arterial complication which occurs earliest is thrombosis at the site of anastomosis. This is usually technical in origin as a result of an irregular suture line predisposing to clot. Rarely conditions such as protein C or protein S deficiency predispose to early arterial thrombosis. Intrarenal thrombosis may occur in acute rejection and is not considered to be one of the surgical complications. If arterial thrombosis occurs it is rarely possible to make the diagnosis in time to salvage the kidney by exploration and thrombotomy. If the kidney is anuric or oliguric from the beginning, then the diagnosis will not be suspected. If early function occurs and it is noticed that urine output is declining, then by the time catheter drainage is fully investigated and DTPA renography and arteriography carried out, the ischaemic time has been far exceeded for exploration and remedial surgery to be carried out. A few cases of renal artery thrombosis have been described after the administration of antilymphocyte globulin and after the administration of CYA in the immediate post-operative period. The precise reason why CYA therapy should be implicated in renal artery thrombosis is still a mystery and requires further observation and research. Arterial thrombosis is more common in those kidneys which have multiple vessels requiring bench surgery prior to implantation. If multiple renal arteries arising from the aorta are present, best results are achieved by using several Carrel patches rather than trying to anastomose smaller vessels to the main renal artery.

2.2.2. *Renal artery stenosis*. Renal artery stenosis occurring months to years after transplantation is very uncommon and is usually detected on the investigation of hypertension. This condition is investigated by the use of intra-arterial digital subtraction angiography and by conventional angiography. Stenosis of the arterial supply to the kidney may occur at various sites. The most common site of stenosis is at the suture line where a short segment of stenosis can be identified. There may be stenosis in the common iliac artery proximal to the anastomosis or if the internal iliac artery has been used there may be stenosis within this vessel. The aetiology of stenosis within these vessels may be dense peri-arterial fibrosis or atheromatous plaques within the vessels. Treatment of common iliac internal iliac and suture line stenosis is bypass grafting or venous patch grafting after the vessels have been

CHAPTER 20

Early medical complications after renal transplantation

P. McNAMEE

1. Fluid balance

1.1. *Early post-operative management*

In the immediate post-operative period it is essential that monitoring of fluid balance begun in the operating room is continued. There is evidence that hypotension and hypovolaemia occurring in an ischaemic kidney may lead to more prolonged acute tubular necrosis. It is our policy to monitor central venous pressure (CVP), blood pressure and urinary output in the post-operative period to ensure optimum hydration and blood pressure.

A CVP catheter is inserted at the time of surgery and is maintained between 5 and 12 cm H_2O. Urinary output is measured hourly and fluid administered according to the CVP and the previous hour's output. The standard regime is to administer the previous hour's output +30 ml if the CVP lies within the normal range. If the CVP is below 5 cm H_2O the previous hour's output +50 ml (or sufficient to raise the CVP to within the normal range) is administered. If the CVP is greater than 12 cm H_2O then the previous hour's output is administered without supplement. If the patient has evidence of pulmonary oedema, fluid intake is decreased and if the graft is functioning a loop diuretic is administered.

The fluids administered are usually 0.9% saline and 5% dextrose in roughly equal proportions, although if the patient has diabetes or severe acidosis this regime may be altered accordingly.

Hourly measurement of the urinary output and appropriate replacement with intravenous fluids is continued for 24 hours post-operatively. At that time, if the patient has normal bowel sounds oral fluids may be administered. Urinary output is measured on a 12 hourly basis and fluids prescribed appropriately. Central venous pressure is monitored for a 24 hour period. Then unless there is concern about the patient's haemodynamic status, the central line is withdrawn.

Mary G. McGeown (ed.), Clinical Management of Renal Transplantation, 291–304.

1.2. *Late post-operative management*

Following withdrawal of the central line, the patient's daily fluid requirements are assessed on clinical parameters i.e. daily output, blood pressure, jugular venous pressure, presence or absence of oedema and weight. The daily intake and output of fluids is recorded on a fluid balance chart. The patient is assessed on a daily basis with particular regard to blood pressure, presence of peripheral and pulmonary oedema and charted fluid balance. The patient is weighed regularly so that excessive weight gain is recognised early. Fluids are prescribed initially on a daily basis appropriate to the previous day's losses and the clinical state of hydration.

2. Electrolyte disturbances

Plasma electrolyte levels are reviewed one hour post-operatively and daily thereafter unless there is an indication for more frequent monitoring. Hyperkalaemia is the most frequent disturbance in the immediate post-operative period.

2.1. *Hyperkalaemia*

If hyperkalaemia is detected management depends on a number of factors:
1. the severity of hyperkalaemia
2. the state of renal function
3. the patient's volume status

The plasma potassium concentration is normally maintained between 3.5 and 5.0 mmol/l. If the concentration is greater than 6.5 mmol/l then action is necessary. There may be great variation in patient response to hyperkalaemia, due to whether factors such as acidaemia, pulmonary oedema, or hyperglycaemia are present, and whether digoxin is being given. It is therefore essential that in addition to the plasma potassium level, an ECG is carried out and muscle strength is tested.

ECG monitoring is commenced if the potassium concentration is greater than 6.5 mmol/l. If there is broadening of the QRS complex or significant tenting of the T waves then calcium gluconate is administered intravenously (10 ml, 10% solution). This will counter adverse membrane effects of hyperkalaemia although it will not remove or redistribute potassium.

The use of a cocktail of sodium bicarbonate, 50% dextrose and insulin administered intravenously leads to a shift of potassium from the extra- to the intra-cellular space and helps stabilise the membrane potential. The amount of intravenous fluids which can be given safely is related to the state of the patient's hydration. If there is evidence of pulmonary oedema and no sign of established renal function then urgent dialysis is necessary to remove

excess potassium. If on the other hand the patient is euvolaemic and if renal function has been established conservative management is all that is necessary.

2.2. *Hyponatraemia*

Hyponatraemia occurs frequently in renal transplant patients as in most surgical patients. It is important to attempt to identify the factors responsible for the development of hyponatraemia since appropriate therapy depends upon correct diagnosis. Hyponatraemia may result from true total body sodium depletion, normal total body sodium with increased total body water or increased total body sodium with proportionately greater increase in total body water. Appropriate management of hyponatraemia hinges upon correct clinical assessment of the patient.

Since sodium is the principal determinant of extracellular volume, decreased total body sodium can be identified clinically by assessment of volume status. A patient who is truly sodium deficient will have a relatively contracted extracellular volume, characterised by hypotension (particularly postural hypotension) and an absence of peripheral oedema. The patient who has normal total body sodium but increased total body water leading to the development of hyponatraemia will have normal blood pressure without postural hypotension. There may or may not be mild oedema. The patient with increased total body sodium and even greater increase in total body water will have normal or high blood pressure and moderate to severe oedema.

If the patient is sodium deficient appropriate amounts of sodium chloride should be administered to return plasma sodium concentration to normal. This can be judged by:

1. normalisation of blood pressure
2. return of plasma sodium concentration to normal
3. when the patient has a functioning graft, increased urinary sodium excretion.

In the case of the patient with increased total body water but normal total body sodium, water intake should be restricted.

In the patient with increased total body sodium and increased total body water, restriction of sodium and water intake combined with loop diuretic therapy is appropriate, provided that the graft is functioning. If the graft is not functioning and the clinical situation demands it, dialysis therapy combined with ultra-filtration may be needed.

Hyponatraemia rarely develops in the early post-operative period unless inappropriate amounts of free water – from 5% dextrose – have been administered. Hyponatraemia developing later in the post-operative period is most often due to excessive water intake and decreased ability of the transplanted kidney to clear free water.

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Editorial

Postoperative hyponatraemic encephalopathy following elective surgery in children

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Introduction

In the United States, there are an estimated 15 000 deaths per year as a consequence of postoperative hyponatraemia (1) (Figure 1). There have been a number of recent studies which have described postoperative hyponatraemic encephalopathy with death or permanent brain damage (2–6). From these studies, it appears that brain damage associated with postoperative hyponatraemic encephalopathy primarily affects menstruant women (1) and prepubertal children (6).

Postoperative hyponatraemic encephalopathy in prepubertal children

There are multiple reports of prepubertal children suffering brain damage from postoperative hyponatraemic encephalopathy (6–9). The aetiology of the hyponatraemia usually involves a combination of: a) intravenous hyponatraemic fluids; b) elevated plasma antidiuretic hormone (ADH); c) respiratory insufficiency secondary to hyponatraemic encephalopathy. It has been demonstrated in several series that plasma levels of ADH (vasopressin, antidiuretic hormone) are elevated in virtually every postoperative child (7,10–13). If such patients are given intravenous free water (any solution with a sodium concentration below 140 $mmol \cdot l^{-1}$), there will always be a tendency towards postoperative hyponatraemia (14). When compared with other groups, prepubertal children are far more susceptible to brain damage from hyponatraemia than are adults (6), and recent experimental evidence demonstrates why this may be the case.

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Effects of hyponatraemia on the paediatric central nervous system

Nattie & Edwards (15) studied the effects of acute hyponatraemia on the brain of puppies. They found that acute lowering of plasma sodium from 140 to 120 $mmol \cdot l^{-1}$ resulted in severe hypoxaemia (arterial PO_2 fell from 11.4–6.9 kPa (88 to 53 mmHg)) and cerebral oedema. In contrast to adults, the brains of paediatric animals (three day old puppies and neonatal rats) were unable to adapt to hypo-osmotic stress by extrusion of cation (15,16).

Adaptation of the brain to hyponatraemia occurs as a consequence of the following sequence of events. First, hyponatraemia leads to a movement of water into brain cells as a result of osmotic forces. In addition, vasopressin which is usually elevated in the plasma of hyponatraemic patients (17) may lead to a direct movement of water into brain cells independent of the effects of hyponatraemia (18). The early response of the brain to this hyponatraemia-mediated oedema is the loss of blood and cerebrospinal fluid, followed by extrusion of sodium from brain cells by several pathways (19). Loss of potassium and possibly organic osmolytes follows later, in an attempt to decrease brain cell osmolality without a gain of water (20).

Effects of hormones and physical factors on brain adaptation to hyponatraemia

There is a significantly higher intracellular brain water content in prepubertal rats in comparison with adult rats, suggesting that the brain occupies a greater percent of the available intracranial volume in young rats (16). Such physical factors may be important determinants of outcome in hyponatraemic rats. As individuals age, there is a progressive decline in the volume of brain, while skull size remains constant in adult life (21). Thus, elderly individuals of both

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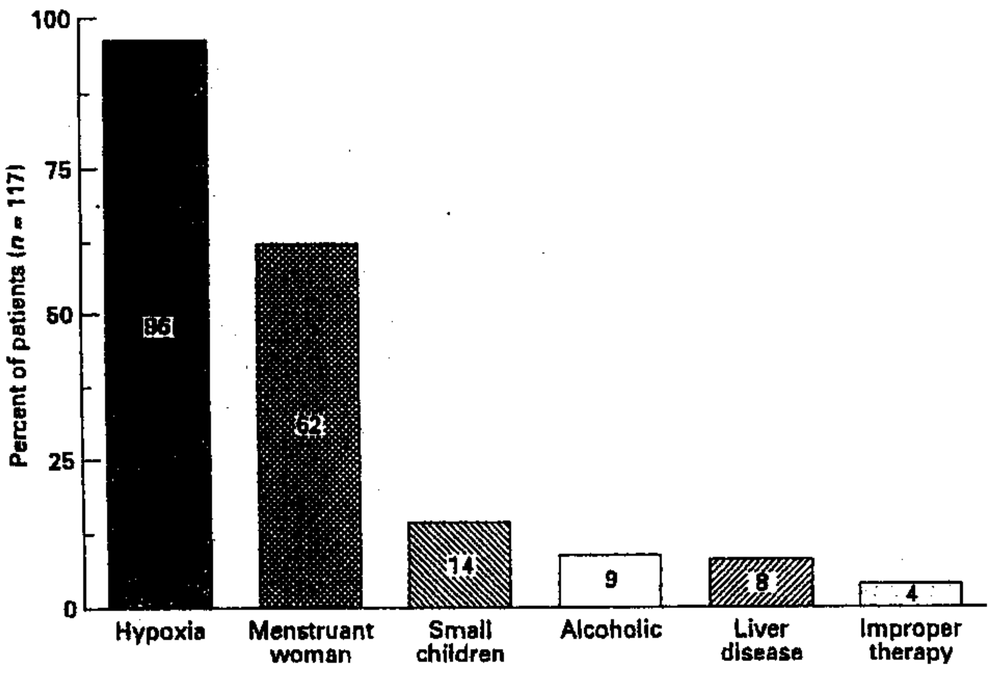

Figure 1
In nine published series from our laboratory comprising 847 hospitalized patients with postoperative hyponatraemia, 19% (158/847) developed hyponatraemic encephalopathy and 117 developed permanent brain damage or died. The major risk factors associated with permanent brain damage in these 117 patients with hyponatraemic encephalopathy are shown. Most patients (96%) suffered an hypoxic episode because of failure to initiate active therapy in a timely manner. In 4% of patients suffering permanent brain damage, improper therapy for hyponatraemia was implicated in the outcome.

genders have more room in the rigid skull for the brain to expand than do younger ones. This finding is more marked in males (21).

If adaptation of the brain is not adequate, pressure of the swollen brain on the rigid skull leads to a decrease in cerebral blood flow (22) and cerebrospinal fluid production (23). If the ability of the brain to adapt is impaired, there will be increasing oedema, with eventual tentorial herniation and secondary cerebral ischaemia (24). This often leads to respiratory insufficiency (4), with reduced delivery of oxygen to brain because of the further decrease of cerebral blood flow, thereby exacerbating the existing cerebral ischaemia (22).

Sex steroid and certain neuropeptide hormones may influence brain adaptation to hyponatraemia. Male rabbits and cats are more efficient than females in extruding sodium to decrease brain cell osmolality during hyponatraemia, resulting in significantly less brain swelling in male than in female hyponatraemic animals (16,25). Oestrogens have also been reported to stimulate, and androgens to suppress, vasopressin release (26,27). Virtually all hyponatraemic patients have increased plasma levels of vasopressin (17,28), a neuropeptide which may exert multiple potentially deleterious cerebral effects. In normonatraemic animals vasopressin results in water accumulation in the brain (18), a significant decline in brain synthesis of ATP (29), and a decline of brain pH (29,30). Vasopressin also impairs the function of several important adaptive pathways to hyponatraemia (31,32).

Recent studies have demonstrated that the brains of prepubertal rats are unable to adapt to hyponatraemia (16). The greater mortality with hyponatraemia in prepubertal rats is associated with a greater accumulation of water in the intracellular space of the brain than in rats belonging to other age groups, as well as an inability of the prepubertal brain to extrude sodium from brain cells. The baseline intracellular sodium content in the prepubertal rats was greater by almost 50% than in control adult rats, a finding consistent with previous studies in newborn dogs (15,33).

Biochemical differences in paediatric vs *adult brain with hyponatraemia*

There are several possible reasons for the increased brain intracellular sodium in prepubertal rats. The Na^+-K^+ ATPase system appears to be the major early adaptive pathway for extrusion of sodium from brain cells during hyponatraemia (19,34) and its impairment results in decreased ability to pump sodium out of the brain. In prepubertal rats, the brain Na^+-K^+ ATPase activity is significantly lower than that observed in adults, both *in vitro* (35) and *in vivo* (36). Coupled with the higher brain sodium, these differences may reflect a limited ability to pump sodium out of the prepubertal brain. The increased intracellular sodium content may be a consequence of limited cerebral Na^+-K^+ ATPase function in young rats compared to adults. The decreased cerebral Na^+-K^+ ATPase activity may be responsible for the impaired adaptation to hyponatraemia in prepubertal rats. Testosterone stimulates Na^+-K^+ ATPase activity in rat brain (37,38). Pretreatment of prepubertal rats with testosterone resulted in a significant decrease in the brain intracellular content of both sodium and water while also reducing the mortality associated with acute hyponatraemia from 84% to zero (16).

Clinical effects of hyponatraemia in children vs *adults*

If one can extrapolate the above experimental findings to paediatric patients, then the implications would be that children are more susceptible to brain damage from postoperative hyponatraemia than are adults. The reasons include: a) decreased available

room for swelling of the paediatric brain in the rigid skull, leading to a propensity for brain herniation with what might appear to be a small decrement of plasma sodium (39); b) impaired ability of the paediatric brain to adapt to hyponatraemia when compared with adults (15,37); c) severe systemic hypoxaemia secondary to respiratory insufficiency frequently occurs in children with only modest hyponatraemia (6,15,39). The respiratory insufficiency is a consequence of increased intracranial pressure (3).

Gomola *et al.* have described a prepubertal (10 years old) female child with middle face hypoplasia who underwent elective maxillary reconstruction (40). The surgery went well and postoperatively, she was given primarily free water intravenously (280 mM glucose in 51 mM NaCl) at a rate of 2 l per day. The child weighed 30 kg with estimated total body water of 18.5 l. On the first postoperative day, the child became confused and developed headache and vomiting. Renal function was apparently normal on the basis of normal plasma urea and creatinine. The plasma sodium was found to be 117 $mmol \cdot l^{-1}$. She was initially treated with sodium supplementation, but on the second post-operative day, the plasma sodium was still low at 120 $mmol \cdot l^{-1}$. The urine and plasma osmolalities were 342 and 255 $mOsm \cdot kg^{-1}$. An MRI of the brain was normal. The authors proposed three possible explanations for the hyponatraemia: a) dilutional hyponatraemia secondary to IV hypotonic fluid; b) pituitary insufficiency; c) inappropriate secretion of ADH. Pituitary insufficiency was ruled out by normal values for ACTH, cortisol, thyroid hormone and growth hormone. The ADH was 4 to 5 $pg \cdot ml^{-1}$, which is 'normal' but inappropriately high for the extracellular hypoosmolality (41) and is essentially a universal finding in both paediatric and adult postoperative patients (7–13). The child received 2 l per day of hypotonic IV fluid in the presence of elevated plasma ADH. Although neither initial plasma sodium, urine output or total volume of IV fluids are provided, given the child's weight and rate of infusion, the plasma sodium of 117 $mmol \cdot l^{-1}$ appears very likely to have been the consequence of retention of about 3 l of IV hypotonic fluid over two days (6). The expression inappropriate secretion of ADS (SIADH) was originally used for elevated plasma ADH related to lung cancer (42) and has become a catch all term for virtually any patient with elevated plasma ADH. In particular, postoperative patients as well as those with heart failure or hepatic cirrhosis have elevated plasma ADH levels but are functionally hypovolaemic as well (41). Postoperative subjects are functionally hypovolaemic, so that the term SIADH may not be appropriate in this patient (11). There is also a perception that ADH, and by association SIADH, can somehow lower the plasma sodium. Although ADH leads to increased retention of ingested or infused water, in the absence of increased water intake, ADH by itself will have no effect upon the plasma sodium. Thus, the most likely explanation for the hyponatraemia in this patient is infusion of hypotonic fluid (51 mM NaCl/280 mM glucose) in the presence of the expected postoperative increase in plasma ADH. Adrenal insufficiency is ruled out by the normal plasma cortisol and the fact that she remained normal for six months without any steroid replacement therapy. Exactly why the plasma sodium rose following IV hydrocortisone is uncertain, but may have been related to the expected decline of ADH values to normal after four to five postoperative days. Pituitary insufficiency is ruled out by normal values for ACTH, IGF1 and growth hormone.

Symptomatic postoperative hyponatraemia carries a mortality of at least 15% (43), particularly in children and respiratory arrest is a frequent occurrence, but once this complication occurs, the morbidity is substantial (6,7). There is no obvious rationale for the administration of hypotonic fluid to a postoperative patient, unless the individual is hypernatraemic (14). If the patient becomes symptomatic, therapy with hypertonic NaCl is indicated (39). The syndrome can be prevented by administration of primarily isotonic fluids to postoperative patients.

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