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RENAL TRANSPLANTATION IN DIABETES MELLITUS: ANAESTHESIOLOGIST'S PERSPECTIVE

Vora KS, Shah VR

ABBREVIATIONS

CAD	coronary artery disease
CVP	central venous pressure
DKA	diabetic ketoacidosis
HNKC	hyperosmotic nonketotic coma
PFT	pulmonary function tests
CAPD	continuous ambulatory peritoneal dialysis
CVS	cardiovascular system
ESRD	end stage renal disease
HRV	heart rate variability

KEYWORDS

anaesthesia, diabetics, renal transplantation

INTRODUCTION

Diabetes mellitus (DM) is a leading cause of end stage renal disease (ESRD), about 30-40% of patients with ESRD have primary etiology of diabetic nephropathy (DN). Diabetic microangiopathy is the principal etiopathogenic factor for diabetic nephropathy in long standing diabetes mellitus (of 20-25 years duration) followed by hypertension, poor glycemic control and genetic factors. Literature has enough accumulated evidence for the protective role of angiotensin-converting enzyme inhibitors in type 1 DM, it is less convincing for type 2 DM [1].

Transplantation was not the treatment of choice for diabetic patients with ESRD before a decade, however with the better understanding and availability of superior therapeutic agents for controlling hyperglycemia, hypertension and rejection, now transplantation is a preferred modality over chronic maintenance dialysis for management of ESRD in diabetics [2]. The current understanding about importance of careful regulation of hypertension and hyperglycaemia has led to equal results in diabetic and nondiabetic patients. Advanced neuropathy, peripheral gangrene or therapy resistant cardiac decompensation are the only contraindications for transplantation.

Anaesthetic management of patients with DM undergoing renal transplantation presents significant challenge for the anaesthesiologist due to disturbed regulation of glucose metabolism and high incidence of complications. Nevertheless, with a thorough preoperative evaluation, skilled anaesthetic care and optimization of metabolic and haemodynamic status, majority of these patients can be managed well without mortality or serious perioperative morbidity [3].

Department of Anaesthesiology and Critical Care.

ADDRESS FOR CORRESPONDENCE

Kalpana S. Vora, MD. Asst. Prof., Department of Anaesthesiology and Critical Care.
Institute of Kidney Diseases & Research Centre and Institute of Transplantation Sciences
Civil Hospital Campus, Asarwa, Ahmedabad 380016, Gujarat, India
TEL: 0091 79 2268 5600/01/04/05 FAX: 0091 79 22685454 E mail: ikdrcad1@sancharnet.in

PREOPERATIVE EVALUATION

Diabetic patients with ESRD manifest microvascular, neuropathic and macrovascular complications of long standing disease which are a cause of special concern to the anaesthetist. Coronary artery disease (CAD), autonomic neuropathy and peripheral neuropathy are of particular importance since they have direct effect on perioperative morbidity and mortality. Preoperative assessment of target organ damage due to DM is as important as current metabolic status evaluation. Careful evaluation of cardiovascular status (CVS) is mandatory before renal transplantation since cardiac disease can affect haemodynamic stability intra-operatively and allograft survival subsequently. Lufft V. et al found that diabetic patients have four fold higher death rate from cardiovascular disease after renal transplantation versus carefully matched non-diabetics [4]. Significant asymptomatic myocardial ischaemia may be present in diabetic patients with autonomic neuropathy particularly with uremia. Apart from routine screening in the form of an ECG and echocardiography, thallium stress test and holter monitoring are also indicated. Prolonged QT interval, a predisposing factor for arrhythmias and sudden cardiorespiratory arrest have been reported in diabetic uremic patients [5]. Coronary angiography and appropriate coronary revascularization is recommended if other risk factors like advanced age, smoking, hyperlipidemia, and moderate to severe hypertension are also present. Advanced atherosclerosis due to DM as well as uremia warrants color doppler of iliac vessels and in some cases angiography, to avoid placement of renal allograft in the area of compromised arterial flow. Pulmonary function tests (PFT) are indicated in long standing uncontrolled type 1 DM as these patients have significantly decreased lung volume, lung diffusing capacity and cardiac stroke index during exercise [6].

About 50 % patients with DM and hypertension have autonomic neuropathy. Many pathogenic mechanisms have been suggested, including local ischemia, tissue accumulation of sorbitol, altered function of neuronal Na+/ K+- ATPase pump activity and immunologically mediated damage. Only a small proportion of these patients are symptomatic so the anaesthetist must specifically inquire about symptoms like dizziness on standing, unrecognised hypoglycemia, hypotension on initiating dialysis, oesophageal dysmotility, nausea and intermittent diarrhoea, early satiety, lack of sweating, heartburn, bloating etc. Asymptomatic patients with autonomic dysfunction should be detected by lack of beat to beat heart rate variability (HRV) during deep breathing, response to valsalva maneuver, resting tachycardia and arterial pressor response to standing [7-10]. Detection of diabetic neuropathy is of particular importance, as it can lead to cardiac arrythmias and severe hypotension during anaesthesia, sudden death during recovery from anaesthesia. This could develop due to altered autonomic response to hypoxia and refractory bradycardia after neostigmine administration due to denervation of cardiac acetylcholine receptors [11, 12].

Diabetics with gastroparesis from neuropathy of vagus nerve can lead to delayed gastric emptying which is further aggravated by uremia [13]. The increased risk of aspiration during induction of anaesthesia strongly warrants anti-acid prophylaxis with non-particulate antacid, H2 blockers and metoclopropamide. Due to decreased skin-capillary blood flow and decreased sweating, these patients are also prone to intraoperative hypothermia [14].

Motor and sensory peripheral neuropathy is common in diabetic uremic patients. Sensory neuropathy presents as nocturnal sensory discomfort of the lower extremities and carpal tunnel syndrome. Severe motor neuropathy from diabetes or uremia although rare, may place patients at risk for hyperkalemia after succinylcholine administration. Diabetics are more likely to develop postoperative neuropraxis, probably owing to impaired vascular supply to peripheral nerves. A detailed preoperative neurological examination should document pre-existing deficits, to avoid alleged perioperative nerve injury and litigation.

Assessment of airway is very important because chronic hyperglycemia causes abnormal cross linkage of collagen by non-enzymatic glycosylation in connective tissue which is potentiated by renal insufficiency. This tissue becomes stiff resulting in limited joint movements (Stiff joint syndrome). Involvement of joints of head and neck, particularly atlanto-occipital joint, limits visualization of glottis during laryngoscopy, making intubation difficult. Mary et al found that 4.8 % of recipients with long standing DM undergoing transplantation are difficult to intubate as compared to 1 % of non-diabetics [15]. However we have rarely come across this problem. Preoperatively difficult intubation can be predicted by Prayer sign- inability to approximate palmer surfaces of fingers due to stiffness of 4th & 5th interphalangeal joints or alteration in palm print [16].

Finally, preoperative glycemic control should be ascertained by frequent blood glucose monitoring and adjusting the dose and timing of anti-diabetic therapy. Glycosylated hemoglobin estimation to evaluate preoperative glycemic control is of no value in uremics, since these patients accumulate it in toxic amounts, not reduced to normal by hemo or peritoneal dialysis; but fall sharply to normal range after successful transplantation [17]. Many patients have poor glycemic control which is further complicated by concurrent administration of thiazide diuretics, diazoxide and b blockers. Treatment and correction of hyper/hypoglycemia can begin while the remaining preoperative evaluation continues. In advanced renal failure, renal clearance of insulin is decreased, effect of short acting insulin is prolonged and there is a peripheral insulin resistance. Episodes of hyper/hypoglycemia occur in spite of dose adjustment due to slow change in the size of insulin pool. Risk of coma is increased as hypoglycemia may develop with few, late or different warning symptoms due to autonomic neuropathy. Similarly inadequate insulin, starvation or insulin antagonism can lead to diabetic ketoacidosis (DKA) or hyperosmotic nonketotic coma (HNKC) characterized by dehydration and electrolyte deficits. There may be glucose induced hyperkalemia probably due to hypoaldosteronism and hyporeninism. It has also been observed that poor glycemic control can impair anastomotic healing and increase the incidence of wound infection by altering neutrophil function [18]. Any preexisting infection or sepsis should be aggressively treated with proper antibiotics as it can flare up postoperatively under the cover of immunosuppresssants.

ANAESTHETIC CONSIDERATIONS

The combination of DM and uremia presents a major challenge in the perioperative period. Adjustment in treatment plans must be made prior to, during and after transplantation procedure to accommodate unique problems imposed by DM and its vascular complications. Pre-transplant evaluation is a vital step facilitating outcome which has been already discussed. Since metabolic care of patients with severe DM under anaesthesia is often difficult, it seems prudent to convert patients taking oral hypoglycaemic agents to insulin several days before transplantation. The dose, type and timings of the last dose of insulin should be ascertained. Blood glucose should be obtained on the day of surgery and if the patient is extremely hyperglycemic (blood sugar level >500 mg/dl) and has not received insulin recently, blood gases must be obtained and blood analyzed for ketones. Although ketoacidosis is rare, surgery may need to be delayed until the patient's metabolic status is stabilized. Patient should be asked about the time of last dialysis and hyperkalemia should be treated before the beginning of surgery. If patient is on continuous ambulatory peritoneal dialysis (CAPD), it should be continued till 1 hour before surgery and dose of insulin should be reduced in the final exchange before operation.

On the day of surgery, preparation for difficult intubation should be made and all patients should receive aspiration prophylaxis. Undue anxiety may affect metabolic control, hence an appropriate dose of a short acting drug like midazolam are preferred to allay anxiety. Also patient should be taken in to confidence regarding pros and cons of anaesthetic technique, and the consent should be obtained. In view of neuropathy, adequate care of pressure points and precautions against hypothermia should be taken.

ANAESTHETIC TECHNIQUE

Surgery evokes the 'stress response' which causes release of catabolic hormones like catecholamines, cortisol, growth hormone and glucagon having 'anti-insulin' effect, and inhibition of insulin secretion leading to hyperglycemia, increased metabolic rate and negative protein balance. Shamoon has shown that catecholamines play major role in insulin resistance and increased sensitivity of diabetic tissues to the action of catecholamines leads to hyperglycemia [19]. Gluconeogenesis is stimulated and peripheral glucose uptake is depressed. All these factors lead to increased insulin requirement during perioperative period [20].

Both regional and general anaesthesia can be administered to diabetic patient undergoing renal transplantation. Regional anaesthesia is preferred in patients with good left ventricular function, normal coagulation profile and absence of autonomic or peripheral neuropathy. The doses of local anaesthetics need to be decreased and adrenaline containing local anaesthetics should be avoided in view of atherosclerosis. Advantages of regional anaesthesia include better metabolic control, easy diagnosis of hypo/hyperglycemia, early resumption of postoperative oral intake, decreased incidence of aspiration and good postoperative pain relief; hence early ambulation. It also decreases the incidence of deep vein thrombosis as blood viscosity is increased in patients with DM due to production of macroglobulins by the liver. Profound hypotension, increased

risk of nerve injury, epidural abscess, vascular damage and anterior spinal artery syndrome due to marked increase in epidural pressure by non-compressible collagen tissue are the disadvantages of regional anaesthesia.

General anaesthesia enables more predictable control of blood pressure and ventilation if cardiovascular function is compromised by coexisting diseases, surgery or volume expansion. At the same time, it can mask signs and symptoms of hypoglycemia, necessitating more frequent estimation of blood glucose. In view of delayed gastric emptying, rapid sequence induction should be planned to protect against aspiration. Studies on handling of anesthetic drugs which affect glucose homeostasis in diabetics with ESRD are limited; however majority of drugs used in non-diabetics undergoing renal transplantation can be used in these patients. Usually patients are induced with a small dose of intravenous narcotic and thiopental or etomidate. Propofol can be safely used for induction but should be avoided for maintenance as diabetics show decreased ability to clear lipid from circulation. Exaggerated decrease in blood pressure on induction may occur due to peripheral vasodilatation, myocardial depression, effect of antihypertensive therapy and presence of autonomic neuropathy. This should be managed with slow injection rate of induction agent, fluid challenge and use of vasoconstrictors. Intubation is accomplished with succinylcholine but rocuronium is a better choice in presence of neuropathy and hyperkalemia. Increased response to intubation is expected reflecting super sensitivity to catecholamines and loss of autonomic control [21]. Fentanyl, 2 ug/ kg BW attenuates and protects against arrhythmias during intubation, and in high doses it provides hormonal and metabolic stability. Anaesthesia is maintained with N2O, oxygen, atracurium and inhalation agents. Inhalational agents inhibit the insulin response to glucose in a reversible and dose dependent manner [22]. This technique allows rapid adjustment of anaesthetic depth during periods of potential haemodynamic instability at the time of revascularization of the graft. Patients with autonomic neuropathy may develop severe bradycardia after vascular unclamping which can be treated with atropine, isoproterenol or dobutamine.

PERIOPERATIVE METABOLIC CONTROL

Euglycemia is the principal goal for anaesthesiologist in perioperative period, avoiding harmful hypoglycemia and excessive hyperglycemia. Corticosteroids, adrenergic agonists and mannitol worsen the diabetic state, making glycemic control difficult. Poor skin blood flow and intraoperative circulatory disturbances interfere with absorption of subcutaneously administered insulin, hence intravenous tight control regime is imperative with an aim to maintain blood glucose between 6-10 mmol/L [23].

"TIGHT CONTROL" REGIME

Insulin adsorption over surface of intravenous fluid bags and intravenous set is an unavoidable problem; insulin delivery by syringe pump is preferred to achieve consistent delivery of more concentrated solution. Mix 50 units of regular insulin in 50 ml of normal saline (1unit/ml) and flush the line with 10 ml of infusion mixture. Start the infusion at the rate of 1unit/ hour, measure blood glucose at least hourly or more frequently if necessary by glucometer and adjust the infusion rate using following equation:

Insulin (U/hr) = plasma glucosa (mg/dl) / 100.

Administer 5 % dextrose at the rate of 50ml/ hour/ 70 kg BW and all other intravenous fluids to be administered during surgery should be non-dextrose containing.

MONITORING

Standard monitoring includes continuous ECG [lead II and V], pulse oxymetry, noninvasive blood pressure, inspired and end tidal gas analysis, temperature, peripheral nerve stimulator, arterial blood gases and serum electrolyte estimation. All patients need CVP monitoring for assessment of volume status, provision of central access for immunosuppressive drugs and blood sampling. Use of further invasive monitoring is guided by preoperative cardiovascular evaluation as stress on CVS may follow intentional volume expansion during surgery. For patients with history of cardiac disease or autonomic instability, arterial catheter is placed before induction of anaesthesia to allow rapid detection of blood pressure changes, increased need for intra-operative blood pressure support and aggressive treatment of hypotension with vasoconstrictors. Pulmonary artery catheter or trans-esophageal echocardiography should be considered in all patients with significant cardiac or pulmonary disease since reduced cardiac output can result in poor graft perfusion and subsequent graft thrombosis.

Post Operative Care

Post- transplant management of diabetic recipient is complex

requiring close supervision. ECG and oxygen saturation monitoring should be continued for at least two postoperative days after renal transplantation, since these patients may develop profound bradycardia due to hypoxia [24]. Adequate metabolic control can be achieved by frequent measurement of blood glucose and serum electrolytes. Administration of intravenous glucose and insulin infusion of 1-4 units/hour is continued in the postoperative period. Postoperative pain can be managed without significant impairment of ventilation by careful titration of potent opioids, which helps in achieving better glycemic control.

Protracted gastric atony from gastroparesis may delay resumption of oral feeding, requiring administration of metoclopramide with bethanechol. Both constipation and diarrhoea may occur, requiring symptomatic treatment. Indwelling urinary catheter should not be kept longer than necessary to avoid infection. Early detection and treatment of infection is imperative.

Diabetic renal allograft recipients require longer hospitalization than non diabetic patients due to problems of infection, cardiac disease and allograft failure. Wide swings in glucose concentration including alternating hypo / hyperglycaemia upto HNKC are life threatening particularly immediately postoperatively and during the time of high dose steroid administration for rejection treatment. Frequent adjustment in insulin dose is required till metabolic control is achieved .When insulin clearance improves after successful transplantation, glycemic control becomes easier. Strict follow up by endocrinologist and nephrologist is required to achieve tight control of glucose, hypertension and hyperlipidemia, failing which recurrent diabetic nephropathy in renal allograft may be detectable as early as five years after transplantation [25]. Combined pancreas and kidney transplantation is becoming popular as the optimal therapy for type I DM with ESRD [26, 27].

SUMMARY

Safe anaesthesia for kidney transplantation candidates with DM is a challenging goal. Supranormal haemodynamic state and metabolic control must be provided to ensure optimal renal allograft function and survival. Meticulous preparation and anticipation of serious problems will help in preventing allograft or patient loss.

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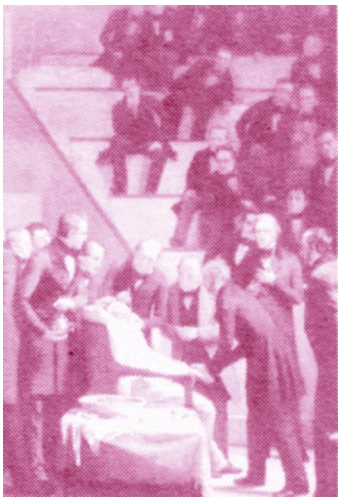

Anesthesia and Pain Management

Local anesthesia began with topical cocaine which was first isolated from the coca leaf in 1860 but not clinically used till1880. Endotracheal anesthesia was introduced in 1932 using hexobarbitone; and intravenous anesthesia in 1942 using curare. These developments made many major operations painfree, and were the direct result of increasing interaction between physiology, pharmacology, technology and medicine-associations that have led to many other important developments in modern surgery.

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