Renal dialysis: biochemistry and haematology changes

1. The basis of the changes from normal that occur in the blood biochemistry and haematology during renal failure

Function of kidneys

The kidneys excrete metabolism wastes from the body, e. g. urea. They play an essential homeostatic role by regulating the fluid balance and maintain pH of the blood at a constant level. Moreover, the kidneys secrete important hormones into the bloodstream which include erythropoietin and angiotensin. Erythropoietin stimulates red blood cell production in the bone marrow while angiotensin helps to regulate blood pressure (Stephen, 1994, p. 260). Normal function of the kidneys depend on the integrity of the glomeruli and the tubular cells, normal blood supply, normal secretion and feedback control of hormones acting on the kidney (Zilva, 1988, p. 1).

Renal failure is when the kidneys fail to function normally with a resultant rise in the blood levels of urea and creatinine. It can be divided into acute renal failure and chronic renal failure. Acute renal failure may be due to injury to the kidney, such as acute glomerulonephritis, septicaemia, ingestion of certain drugs (e. g. sulphonamides, aminoglycosides) and nephrotoxic poisoning (e. g. mercury). Moreover, acute renal failure may be due to renal circulatory insufficiency, such as shock results from severe blood loss, heart failure, mismatched blood transfusion, intrarenal obstruction by calculi, neoplasms, etc (Zilva, 1988, p. 13). On the other hands, chronic renal failure may be caused by chronic glomerulonephritis, chronic obstructive uropathy, polycystic kidneys, hypertensive renal disease, reflux nephropathy, analgesic nephropathy and other kidney disease due to diabetes, systemic lupus erythematosus, etc (Bloom, 1994, p. 269).

Dialysis

Dialysis is used to replace the kidney filtration function of patients with renal failure, either acute or chronic. The principle of dialysis is the diffusion of solutes through semi-permeable membrane, so that, waste products such as urea and creatinine are removed out of the body, but larger molecules such as red blood cells are blocked. There are two different types of dialysis: haemodialysis and peritoneal dialysis. Haemodialysis involves passing the patient's blood through a dialysis machine where waste products are removed at the same time. It requires trained personnel, relatively expensive, and the patient must receive anticoagulants during the procedure to prevent bleeding which can be dangerous. Moreover, haemodialysis corrects electrolyte abnormalities rapidly and makes less risk of infection than peritoneal dialysis (Bloom, 1994, p. 267). On the other hand, peritoneal dialysis involves exchange of solutes and fluid by running dialysis fluid into the peritoneal cavity via catheter. The peritoneum acts as a dialysis membrane so that potassium and other waste products can diffuse into the dialysis fluid. Peritoneal dialysis is simple, cheap and can be carried outside hospital, such as continuous ambulatory peritoneal dialysis (CAPD). However, special attention must be paid to aseptic techniques when changing bags of dialysis fluid and to the peritoneal catheter site, to prevent the development of peritonitis complications (Gokal & Mallick, 1999).

Biochemistry and haematology changes during renal failure

Retention of nitrogenous wastes:

Urea and creatinine are the nitrogenous waste products of our body. During renal failure, serum urea and creatinine concentration increase. Urea is

derived in the liver from amino acid. A significantly elevated serum urea concentration, if it is above about 15 mmol/L (blood urea nitrogen 42 mg/dl), can be indicated as impaired glomerular function (Zilva, 1988, p. 18). Creatinine is derived from endogenous sources by tissue creatine breakdown from muscle metabolism. In severe renal failure, the serum creatinine concentration can reach to > 500 µmol/L (Lameire, Biesen, & Vanholder, 2005). However, in order to assess the ability of the kidneys to control the concentration of the substance in the extracellular fluid, measurement of the clearance of a substance, i. e. glomerular filtration rate (GFR) is used to determine the renal function (Price & Finney, 2000). It is the volume of fluid filtered from glomerular capillaries into Bowman’s capsule per unit time. In normal kidney glomeruli, about 180 litres of primary urine are filtered from the plasma daily (i. e. 125 ml/min), with almost no plasma protein loss (Tryggvason & Pettersson, 2003). During renal failure, glomerular filtration rate is reduced. In stage 5 chronic kidney failure (end stage renal failure), the GFR may decline to 15 ml/min (National kidney foundation, 2010). When the GFR decreases, nitrogenous wastes like urea and creatinine will accumulate in the body, leading to renal failure.

Proteinuria:

When the function of kidneys become abnormal, protein will appear in urine. Also, proteinuria is an independent risk factor for the progression of renal failure. Proteinuria can be classified as either glomerular, overflow, or tubular proteinuria. In glomerular proteinuria, large size proteins such as albumin (69 kDa) are excreted in the urine. However, in tubular proteinuria, small size proteins such as B-2 microglobulin (25 kDa) are usually found in the

urine, as a result of tubular damage. The most convenient and commonest way to detect proteinuria is by dipstick or reagent strip urinalysis. It is a simple and cost-effective method, however if positive in dipstick test, proteinuria should be confirmed with quantitative measurements, such as spot urine test. The quantitative test is important because the magnitude of proteinuria correlates with the severity of the glomerular disease (Tryggvason & Pettersson, 2003).

Acid-base balance:

The normal extracellular fluid pH is 7. 4. The kidneys are responsible for balancing hydrogen-ion gains and losses so as to maintain plasma hydrogen-ion concentration relatively constant. This can be done by either excrete bicarbonate or contribute new bicarbonate to the blood. When renal functions impair, the mechanism becomes imbalance, thus metabolic acidosis results due to excessive loss of bicarbonate or inability of bicarbonate reabsorption by the kidneys (Gluck, 1998).

Potassium homoestasis:

Potassium is the most abundant cation in the body. 98% of total body potassium ions are in the intracellular fluid, but only 2% being in the extracellular fluid. Negative voltage is the major force to keep potassium ions inside cells. Since the kidney regulates potassium ions balance, impaired renal function therefore decrease in GFR, and in turn decrease excretion of potassium ions, finally result in development of hyperkalaemia (serum potassium ion concentration > 5 mmol/L). An increase in extracellular potassium concentration depolarizes plasma membrance,

triggering action potentials and cause serious abnormalities of heart rhythm, cardiac arrhythmias (Halperin & Kamel, 1998).

Anaemia:

Anaemia, which is common in renal failure patients, is an important factor that predisposes such patients to bleeding complications (Sohal, Gangji, Crowther, & Treleaven, 2006). The value of red cell count, haematocrit, MCV and MCH will be decreased in renal failure patients. It is because kidneys play an important role in the production of erythropoietin, which is a hormone controlling the red cell production. In renal failure, the production of erythropoietin is decreased; together with blood losses during haemodialysis and blood sampling, so iron deficiency is common in renal failure patients. In the absent of erythropoietin therapy, haemoglobin levels will drop to 5-7 g/dL (normal haemoglobin level in adult male is 14-18 g/dL). Therefore, renal failure patients due to insufficient erythropoietin production can result to anaemia (Eschbach, 2005).

Coagulopathies:

Acute renal failure can lead to renal vasoconstriction and ischaemia. Platelet aggregation is found to be significantly decreased in renal failure patients, and platelet count is also lower. It is because uremic retention products can cause platelet dysfunction and inhibit blood coagulation and fibrinolysis. Moreover, patients with acute renal failure show impaired platelet sensitivity to collagen. Thus, abnormalities of platelet function and platelet-endothelial interaction are probably the major cause of coagulopathies. So, patients with

renal disease may encounter haemostatic abnormalities that causing bleeding diathesis and a hypercoagulable state (Malyszko et al., 1996).

2. Possible scenario which could result in the pattern of deaths

Nowadays, haemodialysis has been increasingly used for the treatment of acute renal failure and end-stage renal failure. However, it remains potentially hazardous, both as a result of machine malfunctions and human error. Haemodialysis replaces kidney function by using a semi-permeable membrane inside a dialyzer to filter wastes and water from the blood into the dialysate fluid. Water is used in haemodialysis to prepare dialysate. If dialysis water contains contaminants such as bacteria, endotoxins, metals or chemicals, these contaminants may enter the patient’s bloodstream through the dialyzer membrane and cause disease. Some substances can cause conditions such as anaemia or pyrogenic reactions, while some substances can build up to toxic levels, causing long-term physical harm, and other substances are immediately toxic and can cause death (Tong, Wang, Kwan, Chan, & Au, 2001).

Scenario of deaths due to cardiovascular disease

Dialysis patients have a substantial increased risk of death. Cardiovascular disease (CVD), i. e. heart failure, coronary disease, peripheral vascular disease and cerebrovascular disease, remains the most common cause of sudden death, the diseases include myocardial infarction, cardiac arrest, or other cardiac causes in haemodialysis patients especially for end-stage renal disease (ESRD). There are additional factor that can increase the risk of sudden death in ESRD, such as hypertension, atherosclerosis, anaemia,

volume overload, autonomic dysfunction, left ventriculary hypertrophy, dyslipidaemia, hyperchomocysteinemia, inflammation, etc. Moreover, in dialysis patients there is an additional factor that uncontrolled blood pressure is associated with rapid loss of renal function. It is estimated that half of all haemodialysis-related deaths are due to cardiovascular disease (Karnik et al., 2001).

Scenario of death due to microbial contamination of dialysate

Dialysis fluids used in haemodialysis need to fulfil certain microbiological quality criteria. One of the most widespread standards and recommendations of dialysate for haemodialysis is published by the Association for the Advancement of Medical Instrumentation (AAMI). From the above standards, water used for dialysis should contain no more than 200 CFU/mL, and dialysate itself should contain no more than 2000 CFU/mL (AAMI, 2010). No matter how stringent of the standards, the water systems of dialysis equipment may become contaminated with microorganisms due to inadequate maintenance of tanks, dead spaces, and tubing within the dialysis machine. It can be concluded that the dialysis machine is the main source of contamination. Tubing within the machine may be the site of biofilm development, resulting in contamination of dialysate. Even if dialysis machines are disinfected regularly, biofilm contamination may not be completely eradicated (Oie et al., 2003). When the contaminated dialysate enter the body, bloodstream complications would lead to patient morbidity and mortality (Nystrand, 2008).

Scenario of deaths due to chemical contaminants and other substances

It is found that organic and inorganic chemicals in the water used to prepare dialysate could diffuse through the dialyzer membrane and enter the patient’s blood. The contaminants could affect the health of haemodialysis patients. Metal contaminants such as aluminum, zinc and copper can be found in the plastic tubing of the dialysis machines. The phenomenon of deposition of trace metal elements is possibly due to adsorption-desorption processes. For example, aluminum toxicity in the haemodialysis patients can cause many clinical disorders such as demineralising osteodystrophy, dialysis encephalopathy and anaemia (Milacic, Benedik, & Knezevic, 1997). Fluoride can cause fatal intoxication in haemodialysis patients. In 1993 Chicago, fluoride was released from the deionization system after the ion exchange resin inside was exhausted. The incident was caused by errors in maintenance of the deionization system (Arnow, Bland, Garcia, Fridkin, & Fellner, 1994). In 1996 Brazil,

60 out of 126 haemodialysis patients died from the toxin microcystin, which are produced by blue-green algae. Microcystin are hepatotoxins, neurotoxins and inhibitors of protein phosphatases. It was found that the outbreak was due to inadequate water treatment at both the municipal water plant and the dialysis centre (Pouria et al., 1998). On the other hand, the water purification system and the circulation piping system of the dialysis machine should be cleaned and disinfected regularly in order to prevent the formation of biofilm. Disinfection may be achieved by heat or by chemical, such as formalin, peracetic acid or sodium hypochlorite. However, if the delivery system is not adequately rinsed before subsequent use, any residue of

formalin may cross the dialyzer membrance into patients' blood. A scenario happened in 1999 Hong Kong, formalin residue was left behind into the circulation piping system and accidentally delivered to six patients, who were receiving haemodialysis treatment. Formalin quickly passed into the bloodstream of these patients through the dialysis membranes in the dialysis machines. Finally, three patients died and three patients were seriously injured in this tragedy (Mok, 1999).

Scenario of deaths due to the problem of machinery

In 1970, there had been reported death after exposure of patients' blood to overheated dialysate. The cause of this accident was due to failure in the thermostat on the dialyzer. At this time, the temperature of dialysate in the dialyzing machine was 55oC. Such a high temperature can cause heat-induced haemolysis to release cardiotoxic potassium ions and/or systemic injury resulting from the rapid infusion of overheated blood. In order to prevent this tragedy happens again, certain measures should be done such as installation of alarm to alert any rise in temperature of dialysate, and the heater should be turned off during replenishing of dialysis (Fortner, Carter, & Knepshield, 1970).

3. Role of pathology in management of patients on renal dialysis

Management of the quality of water for dialysis

Water used for renal dialysis may be contaminated with microorganisms or other substances, such contaminants found in water are toxic to haemodialysis patients. To prevent harm from these contaminants,

standards for the quality of water used to prepare dialysate have been proposed. The most widely used standards for water and dialysate in dialysis settings is come from AAMI. Sampling for microorganisms of dialysis fluids is necessary because gram-negative bacteria can grow rapidly in the water and dialysate in haemodialysis systems. Overgrowth of these organisms can cause pyrogenic reactions in haemodialysis patients. They recommend that bacterial culture for water and dialysis fluids should be performed monthly and during outbreaks using standard methods (spread plate assay, use of tryptic soy agar, incubation for 48 hours at 35oC). After incubation, bacterial colonies (if any) should be enumerated. The colony count of microorganisms should be less than 200 CFU/mL (AAMI, 2010). However, biofilm on the surface of the pipes may escape bacterial culturing technique and show no viable colonies on the agar plates. So, another assay to monitor of the bacteriological quality of water and dialysate has been introduced. It is the measurement of endotoxins by Limulus amoebocyte lysate assay. There are two different methods, one is kinetic test method (e. g. colorimetric or turbidimetric), the other is gel-clot method. Endotoxin is actually a complex lipopolysaccharide derived from the cell wall of gram-negative bacteria (e. g. Escherichia coli and Pseudomonas aeroginosa). If endotoxin enters into human bloodstream, it can cause pyrogenic reaction, coagulation and circulatory disturbances, and severe consequences such as bacteraemic or endotoxic shock. Gram-negative bacteria have been shown to multiply rapidly in supply water for haemodialysis (e. g. distilled water and RO water) and in dialysate (Sehulster, 2003). CDC has highly recommended testing of endotoxin monthly together with bacterial culture of the water, because the activity of endotoxin may not correspond to the bacterial plate counts. For

routine haemodialysis, the upper limit for endotoxin testing on RO water should be less than 0. 25 EU/mL. While for on-line haemodiafiltration, the maximum allowable level for endotoxin should be lower, at 0. 03 EU/mL. (Hong Kong College of Physicians & Central Renal Committee, 2002). Moreover, sample testing should be performed monthly on the water treatment system; and at least annually on dialysis machines (Northwest Renal Network, 2005).