KIDNEY FAILURE AND ITS MANAGEMENT WITH DIALYSIS AND NEPHROPROTECTIVE HERBAL DRUGS

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Introduction

Kidney failure is the clinical syndrome that occurs when kidneys are no longer able to maintain their regulatory, excretory and endocrine function resulting in retention of nitrogenous solutes and derangement of fluid, electrolyte and acid-balance. Renal failure occurs when 75% or more of nephron population is non functional (Di Bartola, 2005). So it refers to a complex of clinical signs attributable to dysfunction of many body systems.

Kidneys are one of the vital organs in the body which performs multiple functions to keep the body in homeostasis. It maintains the salt and water balance and control the osmolality and acidity of the body. They also maintain the plasma potassium, calcium and phosphate ions level. They enable the body to retain essential plasma constituents like glucose; amino acids etc and excrete the metabolic waste products from the body like urea, uric acids, sulphates, ammonia, creatinine and guanidine derivatives.

The clinical signs associated with acute and chronic renal failure may be similar therefore differentiation of ARF from CRF is important for both prognostic and therapeutic reason. It is more likely that an animal with acute renal failure (ARF) will recover than an animal with chronic renal failure (CRF) (Vaden, 1997; Cogwill and Francy, 2005 and Di Bartola, 2005), because ARF is potentially reversible. Accurate and early identification of ARF is crucial to allow the institution of aggressive treatment, thereby affording the best chance of animal survival (Vaden, 2000).

Acute renal failure (ARF) is a clinical syndrome characterized by rapid decline in renal function over a period of hours to days (Kraje, 2002). The causes of ARF may be divided into pre-renal, renal, post renal categories. Pre-renal causes include any condition resulting in decreased renal perfusion such as shock or dehydration; post-renal causes include obstruction to urine flow or tear in the urinary tract. Renal causes are various and most commonly encountered are nephrotoxins and ischemia. Nephrotoxins can be therapeutic or non therapeutic agents. Under therapeutic nephrotoxic drugs include indiscriminate use of aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDS), angiotensin-converting enzyme (ACE) inhibitors, amphotericin-B, cisplatin and non-therapeutic nephrotoxic agents like heavy metal (Mercury, uranium, lead, Bismuth salts, chromium, arsenic, gold, silver, nickels, antimony etc) and organic compounds (carbontetrachloride, ethylene glycol, chloroform, pesticides, herbicides etc). Specific causes of ischemia include shock, dehydration, low cardiac output, thrombosis of renal vessels, hypotension. Other causes of acute renal failure include leptospirosis, ehrlichiosis, pyelonephritis etc. (Kraje, 2002; Cogwill and Francy, 2005).

The kidneys are susceptible to ischemia and toxicants because of their unique anatomical and physiological features (Labato, 2001). The kidneys receives about 20% of cardiac output and the renal cortex receives 90% of that blood flow (Lane *et al*., 1994 and Grauer, 1996) which results in increased delivery of blood born toxicants to the kidneys compared with other organs (Labato, 2001). Within renal cortex, proximal tubules and thick ascending loops of henle's epithelial cells are most frequently affected by ischemia and toxicants because of their transport functions, high metabolic rates and vulnerable to hypoxia (Gleadhill, 1994, Bhatt and Patra, 2000). Hypoxia cause cellular damage by decreasing blood flow to the kidneys, which leads to depletion of tubular cells ATP reserve and dysfunction of Na^+, K^+ ATPase pump. This leads to cellular swelling and cell death (Kraje, 2002).

ARF, classically proceeds through three clinical phases initiation, maintenance and recovery (Grauer, 1998). The initiation phase is the period during which animal is subjected to the renal insult (DiBartola, 2005). During this phase, therapy to decrease the renal insult can prevent established ARF (Kraje, 2002). The maintenance phase ensues after a critical amount of irreversible epithelial

damage (DiBartola, 2005) characterized by tubular lesions and established nephron dysfunction (Grauer, 1996). This phase may last 7 to 21 days (Labota, 2001) and most animals will die (Krajae, 2002). The recovery phase is the periods where renal tissues undergo regeneration and repair with restoration of renal function (DiBartola, 2005). During this phase resolution of azotemia, nephron repair and functional compensation occur (Lane *et al*., 1994).

Acute renal failure (ARF) may or may not be reversible depending on the degree of damage (Gleadhill, 1994). As long as basement membranes are intact and viable epithelial cells are present, tubular injury can be repaired (Kraje, 2002).

The best time to intervene and stop the progression of ARF is the initiation phase where the initial injury can be minimized (Labato 2001). Fluid therapy remains the mainstry of treatment for ARF. The goal of fluid therapy is to correct fluid and electrolyte imbalances improve renal haemodynamics, increase tubular flow and initiate dieresis (Lane *et al*., 1994). When fluid therapy alone is in effective to promote dieresis routine use of dieresis and vasodilators have been advocated (Cogwill and Francy, 2005).

Furosemide probably increase renal blood flow through activation of renal prostaglandin system, however, a dieresis often occurs without improvement of glomerular filtration rate (GFR). Although, dieresis in general is thought to be beneficial. Low dose dopamine with minimal systemic effects has been effective in some experimental model of ARF in dogs (Grauer, 1989).

Dopamine has a direct dilator effect on afferent arteriole in dogs. Recently, a combination of dopamine and furosemide is being considered to manage the ARF cases in a better way it seems that dopamine and furosemide together have a synergistic effects. When conservative therapy fails to initiate diuresis, the prognosis is grave. Then haemodialysis and peritoneal dialysis are the only option to manage the cases of ARF (Labato, 2001).

Haemodialysis and peritoneal dialysis have been used extensively in human medicine as method of extra-renal means of excretion of metabolic waste products in the recent year but to a limited degree in the dogs. **Haemodialysis** is the therapeutic process of diffusion of substances across semi permeable membrane to or from blood. (Dhein 1981). It uses physical principle of :- (Cowgill 2003) Diffusion, Convection, Ultra filtration.

Peritoneal dialysis is simple procedure, equally effective and comparatively less expensive than haemodialysis which is expensive and requires trained technician and sophisticated instruments (Lane *et al.,* 1994).Peritoneal dialysis should not be regarded as cure for renal failure. It should be considered as temporary life saving measures, which keeps the body chemistry in comparative balance until such time that, the damaged kidney regain adequate function (Jackson, 1964). The main objective of peritoneal dialysis is to transfer the uremic solutes from blood to the dialysate as a partial substitute for renal recovery from ARF. Blood urea nitrogen, serum creatinine, phosphorus and many other uremic solutes can be removed by this technique of dialysis (Mahajan, 2000).

Continuous Ambulatory Peritoneal Dialysis (CAPD) has the following descriptive details.

C- Continuous- The dialysis fluid is always inside the peritoneum cleansing the blood in a continuous manner.

A- Ambulatory- Ambulatory means that between exchanges, animal can move about freely and continue their normal activity.

P- Peritoneal- This type of dialysis makes use of a membrane that covers peritoneal cavity in order to cleanse wastes and excess water from the blood, using the peritoneal membrane as a filter.

D- Dialysis- Dialysis constitutes the process of removing all waste and excess water from the blood using the peritoneal membrane as a filter. Once the patient is on CAPD, it requires to perform daily "exchanges". An exchange consists of draining the dialysis solution that peritoneal cavity is holding once it has served its purpose and introducing new solution.

In spite of tremendous advance in modern medicine there are not many effective drugs available that stimulate the liver and kidney function, offer protection to this organ from damage (Chattopdhyay R.R , 2003).

Medicinal plants are part and parcel of human society to combat diseases, from the dawn of civilization (Bandyopadhyay *et al.,*

2003). It is greatly to the credit of people of India, that they were acquainted with a far large number of medicinal plants than the natives of any other country on the face of the earth.(Kirtikar K R & Basu B D, 1991). Many Indians fruits, grains and vegetables employed as useful dietary articles forms a chief factor in the cure of diseases, as well as preservation of health and good nutrition. (K M Nadkarni & A K Nadkarni, 1992). Herbs have always been the principle form of medicine in India and they are becoming popular throughout the world, as people strive to stay healthy in the face of chronic stress and pollution and to treat illness with medicine that works in concert with the body's own defences. Thus medicinal plants play an important role in the lives of rural people. A plant is said to be medicinal when "at least one part possesses therapeutic properties". (Singh & Mani, 2011).

In the absence of reliable and effective modern medicine employed for the disease treatment or prevention (Adeneye *et al.* 2008). In the research of some of these medicinal plants for pharmacological intervention in progressive renal injuries as well as the potential for nephrotoxicity from other Chinese herbal medicine (Farombi E.O , 2003). However the herbal medicine has recently attracted much attention as alternative medicines useful for treating or preventing life style related disorders of nephrotoxicity but relatively very little knowledge is available about their mode of action (Saisree *et al.* 2011).

Till today there are no drugs available which could effectively prevent the incidence of renal damage or cure the renal damage caused by various agents such as some drugs, industrial/environmental chemicals. Search for nephroprotective agents has resulted in exploration of medicinal plants which were claimed to be useful in the treatment of renal disorders in folklore medicine (Shirwaikar, A. & Setty, M.M., 2004, Mustea, *et al.,* 1997).

Herbal medicine claims that herbs can be used to both treat and prevent diseases. The appeal of herbal medicines is even greater because patients are often dissatisfied with traditional treatments due to disappointing rates of success or unfavorable side effects. (Sudhavani V , 2010).

Medicinal plants can be important source of previously unknown chemical substances with potential therapeutic effects. The medicinal use of plants is an ancient tradition, far older than the contemporary sciences of medicine, pharmacology and chemistry. The world health organization has estimated that over 75% of the world's population still relies on plant derived medicines, usually obtained from traditional healers, for its basic health care needs (Herrera *et al.,* 2008). Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological and medicinal activities, higher safety margins and lesser costs (Chaudhary *et al*., 2010).

Herbal drugs have shown their potent nephroprotective effect due to their antioxidant, diuretic, anti inflammatory, antispasmodic properties.(Gaikwad *et al.* 2012).

Among the nephroprotective plants some plants are described in brief:

1. Olagunjua *et al*., (2009) evaluated nephroprotective activities of the aqueous seed extract of *Carica papaya* Linn. in carbon tetrachloride induced renal injured Wistar rats: a dose- and time-dependent study. Study showed that CP*E* (*Carica papaya* Extract) has nephroprotective effect on Carbon tetra chloride renal injured rats, an effect which could be mediated by any of the phyto components present in it via either antioxidant and/or free radical scavenging mechanism(s).

2. Sarumathy *et al*., (2011) evaluated protective effect of *Caesalpinia sappan (CS)* on acetaminophen induced nephrotoxicity and oxidative stress in male *albino* rats. The aim of this study was to examine the nephroprotective and antioxidant activities of ethanol extract of *CS* at two dose levels of 100 and 200 mg/kg B/W on acetaminophen (APAP) induced toxicity in male *albino* rats. APAP significantly reduced levels of uric acid and increased levels of serum urea, creatinine. Ethanolic extract CS significantly increased activities of renal superoxide dismutase, catalase, and glutathione peroxidase and decreased. Malondialdehyde content of APAP treated rats.

3. Ghaisas *et al*., (2010) evaluated Antidiabetic and Nephroprotective effect of *Tectona grandis* linn. In Alloxan induced Diabetes. Ethanolic extract of bark of *Tectona grandis* Linn. (TG) was evaluated using alloxan induced diabetes and associated renal complication. The diabetes was induced by administration of alloxan to the rats at the dose

of 140 mg/kg, i.p. TG was administered to diabetic animals for six weeks and various biochemical parameters in blood and urine (plasma glucose, serum albumin, total protein, and creatinine, urine total protein, urine albumin), tissue parameters (cholesterol and triglyceride in kidney homogenate) and % change in body weight were evaluated along with histopathological study. In present study diabetic animals treated with TG showed significant reduction in the elevated level of plasma glucose ($p<0.01$) when compared with diabetic control.

4. Palani *et al*., (2009) evaluated effect of the ethanolic extract of *Indigofera barberi (L)*

in acute Acetaminophen - Induced nephrotoxic rats. Nephrotoxicity was induced in rat by administering single dose of paracetamol (750 mg/kg). The degree of nephroprotective activity was measured by renal functional parameters such as serum urea (UR), uric acid (UA) and creatinine (CR).and hematological profile was concluded that the ethanol extract of *I-barberi* is an effective nephroprotective agent.

5. Sarumathy *et al*., (2011) evaluated biochemical studies show that there is an increase in the levels of serum urea and creatinine along with an increase in the body weight and reduction in the levels of uric acid in acetaminophen induced groups. These values are retrieved significantly by treatment with *Clitoria ternatea* extracts at two different doses. The antioxidant studies reveal that the levels of renal SOD(Superoxide dismutase), CAT(Catalase), GSH(Glutathione) and GPx(Glutathione peroxidase) in the APAP(acetaminophen) treated animals are increased significantly along with a reduced MDA content in ethanol extract of *Clitoria ternatea* treated groups. The study suggest that the ethanol extract of *Clitoria ternatea* can prevent renal damage from APAP induced nephrotoxicity in rats and it is likely to be mediated through active phytoconstituents and its antioxidant activities.

6. Pratibha *et al*., (2009) evaluated nephroprotective activities of root extracts of *Andrographis paniculata (Burm f.)Nees* in gentamicin induced renal failure in rats: A time-dependent study. The extent of nephroprotection offered by various extracts under study increased with the increasing time of treatment and polarity of the solvents. The signs of Gentamycin nephrotoxicity in rats are significantly mitigated by petroleum ether and Chloroform extracts whereas the maximal alleviation of Acute renal failure was caused by Methanolic root extract; hence, the methanolic root extract of AP can be advocated as a nephroprotective agent.

7. Yogesh *et al*., (2011) evaluated preventive and curative effect of *Ficus religiosa* (L) latex for against cisplatin induced nephrotoxicity in wistar rats. The level of brush border enzymes like*) a+ / K+ ATPase, Ca++ ATPase and Mg++ATPase* were found significantly reduced after single dose cisplatin injection. It was overcome by treatment of same extract in curative and protective groups. Finally it is concluded that the present study data conformed nephrotoxicity induced by cisplatin due oxidative stress and methanolic extract of *Ficus religiosa* L. latex may have nephroprotective and curative activity.

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