Stroke, Chronic Kidney Disease and Dialysis

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Abstract: Chronic kidney disease, characterized by decreased glomerular filtration and proteinuria are associated with increased cardiovascular risk, and mortality as a result of those events. Stroke, in particular can be a debilitating event in a CKD patient's life due to limitations of standard treatment in this population even if the presentation is within the therapeutic time window. We discuss the traditional and non traditional risk factors associated with stroke in CKD patients and their pathophysiology. In addition, this article reviews the advantages and disadvantages of peritoneal dialysis and hemodialysis in the different subsets of stroke patients with CKD. We also talk about potential future areas of research in treatment and controlling for the risk factors associated with stroke.

Keywords: Stroke, Chronic Kidney Disease, Peritoneal Dialysis, Hemodialysis.

Introduction

The Cerebro-Renal Nexus

Chronic Kidney Disease (CKD) is defined by a glomerular filtration rate (GFR) below 60 ml/minute/1.73 m². There is an established body of clinical research [1] that shows an increased prevalence of CKD in patients with cerebrovascular disease (e.g. 20-35% in patients with acute ischemic stroke compared to 8-16% in the general population [2-5]).

Of course, part of the elevated prevalence is explained by correlation rather than causation: kidney disease and stroke have many common risk factors like ageing, diabetes, hypertension, dyslipidemia, obesity and smoking. Also, an interesting similarity between the kidney and the brain is that both are vulnerable to vascular injury from the same risk factors. The vasoregulation of the microvasculature of kidney and the brain is anatomically and functionally similar. They both share a low resistance vascular system allowing continuous high-volume perfusion.

However, according to several studies [6,7], the correlated risk factors alone are not sufficient to capture the extent of increased risk for vascular disease among patients with CKD. It appears that impaired kidney function results in a number of non-traditional vascular risk factors such as chronic inflammation, oxidative stress, sympathetic nerve overactivity, asymmetric dimethyl-arginine, thrombogenic factors and hyperhomocysteinemia. In addition, uraemia by itself leads to retention of uraemic toxins (e.g. indoxyl sulphate), sodium and water retention, anaemia and malnutrition, dyselectrolytemia leading to vascular calcification, secondary hyperparathyroidism, and decreased Klotho protein expression. All of the above mentioned risk factors lead to endothelial dysfunction and vascular damage.
[8-15]. This potentially results in strokes, white matter lesions, silent brain infarcts and microbleeds. In fact, kidney impairment seems to serve as a predictive marker for the presence and severity of small vessel diseases and white matter lesions in the brain. Further, there is ongoing debate regarding anemia (common in CKD) as a potential risk factor for stroke, and hence management of anemia has become an important quality index of dialysis therapy [26,27]. Last but not the least, findings from cross sectional studies [16-19] show an inverse association between intima media thickness of the carotid artery and renal function, which seems to be stronger in the Asian population compared to the white population.

The Problem and Motivation

It is difficult to find a research study on a single population which compares the incidence of stroke in the general population with the incidence of stroke among CKD patients. However, a study from South India [20] measured a 1.97% incidence of stroke among 1369 CKD patients, and an age-corrected incidence of 400 per 100,000 persons in a similar population in South and North India. Though the two numbers are not directly comparable, allowing for margin of error, we see that CKD roughly increases the incidence of stroke by a factor of 5, which is also in agreement with other studies from the developed world. Patients with CKD are at increased risk of cerebro-vascular events and have a 9-fold increase in mortality from stroke related events in patients with dialysis-dependent renal failure compared to the general population [21]. Another study from China [22] showed that the incidence of recurrent stroke in peritoneal dialysis patients was 73.1 per 1000 patient years. Stroke and subclinical cerebral abnormalities are associated with cognitive dysfunction in chronic kidney disease patients. 70% of hemodialysis and peritoneal dialysis patients more than 55 years of age show moderate to severe cognitive impairment [28,29]. Not to forget that health related quality of life (based on SF 36 and kidney disease quality of life) among CAPD patients and their caregivers is below the national norms with regards to physical and social functioning as well as mental health, suggesting the need for psychological and social support in these populations [34].

Patients on dialysis tend to have frequent medical contact and therefore often present with stroke within the therapeutic “golden hour”. We believe this makes a good case for proactively managing stroke, and researching novel treatment options for CKD patients.

Comparison Of Peritoneal vs Hemo-Dialysis For Stroke Patients

Pros of Peritoneal Dialysis

1. Patients undergoing intermittent hemo-dialysis experience more intra-dialysis hemodynamic changes, fluctuations in body fluid content, electrolyte and acid-base homeostasis than patients undergoing peritoneal dialysis [23]. These fluctuations can result in higher risk of brain injury [24,25] and concomitant ischemic strokes. Hence, peritoneal dialysis may be a better option in patients with significant risk factors for stroke or prior stroke, and in patients with labile blood pressures.

2. Additionally, routine heparin use in hemo-dialysis could potentially increase the risk of hemorrhagic stroke when compared to peritoneal dialysis.

3. Research [30,31] has identified glutamate as the most abundant neuro-transmitter in the peri-infarct zone in mammals. Glutamate has been shown to play a critical role in the propagation of ischemic brain damage via excitotoxicity. Glutamate causes sustained activation of postsynaptic receptors leading to massive influx of calcium,
sodium and water into neurons. This influx leads to production of reactive oxygen species and uncoupling of oxidative phosphorylation, thereby resulting in apoptosis. In the study by Godino Mdel et al [30], peritoneal dialysis was able to lower the blood levels of glutamate in rats, thereby preventing progression of ischemic brain damage. In this study, rats on PD were evaluated two weeks after the ischemic event using functional MRI and limb use asymmetry. Both techniques demonstrated significant improvement in tissue viability and functional outcomes, reducing the degree of disability.

4. Elderly patients with CKD and acute stroke are predisposed to delirium. The sleep-wake cycle plays a major role in helping to prevent delirium. A Chinese study has shown that patients undergoing peritoneal dialysis have a better sleep quality than patients undergoing hemodialysis, likely a result of reduced incidence of hyperphosphatemia [32].

**Pros of Hemo-Dialysis**

1. Most patients in the developing world undergoing peritoneal dialysis use a glucose-based dialysate. This might disregard glycemic control and result in metabolic side effects like hyper-insulinemia, peripheral insulin resistance and obesity. This disadvantage does not exist for hemo-dialysis [35-39].

2. Peritoneal dialysis involves manual intervention by the patient or caregiver. Developing countries mostly employ continuous ambulatory peritoneal dialysis over automated dialysis owing to cost reasons. Hence, patients debilitated with stroke may have a much harder time performing the procedure. This can also significantly increase caregiver burden.

3. The levels of asymmetric dimethylarginine are lower in hemodialysis patients due to better clearance of this metabolite via hemodialysis than peritoneal dialysis. It has been observed that ADMA is one of the non traditional risk factors for stroke in CKD patients on dialysis.

**Overall Conclusion: Which Dialysis Modality To Employ?**

Weighing the pros and cons of peritoneal vs hemo-dialysis listed above, we believe that peritoneal dialysis might still be a better overall option for patients at high risk of stroke in developing countries. The cons of manual intervention could be mitigated using cost-effective techniques. For example [33], a study from China and Hong Kong, utilized an ultrabag connecting device for patients who were visually impaired or had hand tremors. The study showed superior performance after this empowerment process.

One other thing to keep in mind is that overhydration or propensity for heart failure, low serum albumin and poor cardiac function increase the morbidity and mortality associated with peritoneal dialysis. Also, peritonitis incidence and catheter exit site/tunnel infection attacks were higher in patients with amyloidosis especially in the first 2-3 years [33]. Hence, careful patient selection is warranted for either of the two dialysis modalities keeping in mind all the above factors.

**General Considerations in Management of Stroke in CKD Patients**

Patients with CKD have both high thrombo-embolic risk and high bleeding risk. Thrombo-embolic risk is secondary to increased risk for atherosclerosis, volume overload with concomitant heart failure resulting in atrial fibrillation, and dyslipidemia. Bleeding risk is secondary to dysfunctional platelets arising out of uremia and hypertension, common to CKD patients. There are small-scale studies that document a high rate of intracerebral hemorrhage (ICH) and death in patients with renal dysfunction treated with intravenous (IV)
thrombolytics, but no large-scale studies have addressed this issue [48,49].

Pharmacotherapy in stroke is limited in such patients by the need for special dosage requirements to account for reduced glomerular filtration. There is also an enhanced bleeding complication with anti-thrombotic treatment for stroke. Due to dysfunctional platelets in CKD, there is reduced responsiveness to anti-platelet drugs like aspirin and clopidogrel. There is conflicting evidence for benefit of stroke prevention from warfarin in dialysis patients. The newer oral anticoagulants seem to be of limited use in patients with advanced renal impairment due to renal elimination, since current evidence in this regard is lacking.

The use of contrast agents is impaired in CKD and therefore endovascular stroke treatment, which relies on these agents, cannot be employed effectively. Owing to enhanced carotid calcifications in CKD patients, endovascular treatments can also pose the risk of embolic events. Carotid endarterectomy is another surgical option, but has high operative mortality in patients with an estimated GFR below 30 ml/minute/1.73 m$^2$ [40].

Hyperhomocysteinemia, associated with CKD, is known to increase carotid intima media thickness, resulting in carotid artery stenosis and increased stroke incidence. Biochemically, folic acid supplementation should decrease the levels of homocysteine. However, the ASFAST trial [41] has not shown a significant reduction in carotid intima media thickness.

Since patients with diabetic nephropathy develop more severe strokes and also at a younger age [42], achieving euglycemia and treating diabetic nephropathy is critical in CKD patients.

Routine use of body composition monitors in dialysis centres is another useful modality: it helps to assess the hydration status of dialysis patients, thereby achieving euvoeemia and preventing overhydration, a big factor that results in hypertension, left ventricular hypertrophy and congestive heart failure, all of which are risk factors for stroke [43].

An observational study from Japan finds that low protein diet (0.8 g/kg) and sodium restriction (5g per day) in peritoneal dialysis could help reduce the risk of peritoneal hyper-permeability and thereby improve the cardiovascular risk of PD patients (50). Dietary sodium restriction enhances the efficacy of Renin Angiotensin Aldosterone (RAAS) blockade in hypertensive, diabetic and non diabetic CKD. It enhances the responses of blood pressure and proteinuria to RAAS blockade by a shift of the top of the dose response curve so a larger maximum effect is obtained [51].

Lower BMI and malnutrition is an independent predictor of recurrent stroke risk [47]. One observational study to predict short term survival in peritoneal dialysis patients showed that non-Chinese race, low serum albumin, elevated alkaline phosphatase from chronic hypocalcemia, echocardiogram findings of reduced ejection fraction and regional wall motion abnormalities were associated with cardiovascular mortality, but a predictive model could not be built [44-46]. Treating for these risk factors might be useful.

Conclusion and Future Directions

For many patients, a single blood pressure reading in the outpatient clinic may not truly reflect their blood pressure throughout the day. Hence, research studies on the effect of BP control via Ambulatory Blood Pressure Monitoring (ABPM) can help provide insight on the effects of better BP control in CKD and its consequent effect on stroke rates. Future research using pulse wave velocities and pulse pressures can lead to better use of this tool for assessing the effect of BP related changes on the cardiovascular system.
Another critical area would be in discovering alternative acute therapies like intra-arterial thrombolysis and mechanical thrombectomy. This could help improve stroke outcomes in patients with renal failure on dialysis. Analysis of secondary outcomes from large randomized control trials argue against aggressive reduction of BP in certain patient population, though the inferences are retrospective in nature. Dedicated research to identify the appropriate lowest blood pressure target in CKD patients with varying co-morbidities will help in individualizing treatment accordingly. Paying greater attention to socioeconomic and environmental issues related to race and ethnicity will help in better cardiovascular outcomes as the scientific community makes advancements in understanding the relationship between BP, CKD, race, ethnicity, genes and epigenetics.

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