REVIEW ARTICLE

Hemorrhagic Stroke in Chronic Kidney Disease

Vijoy Kumar Jha[1], Vivek Sharda[2], Salim A Mirza[3], Shashibhushan[3], KK Bhol[3]

Abstract

Hemorrhagic stroke is leading cause of death in Chronic Kidney Disease (CKD) population. Uremic patients are susceptible to hemorrhagic complications due to multiple reasons i.e platelet dysfunction, low platelet number, use of heparin during hemodialysis, use of anticoagulants for thromboembolic risk etc. Prevention and treatment of hemorrhagic stroke is complicated in CKD setting and if not managed properly can lead to several fold increased mortality and morbidity rate. In this brief review we will discuss about the magnitude of hemorrhagic stroke, important risk factors and outcomes in predialysis and dialysis setting and its important preventive and treatment strategy.

Introduction

Stroke is the third leading cause of cardiovascular disease death among persons with end-stage kidney disease (ESKD) on dialysis.[1] As compared with the general population, stroke incidence rates and stroke mortality rates are increased 6- to 10-fold among patients on dialysis.[2] The risk of hemorrhagic stroke has been reported to be higher than ischemic stroke in hemodialysis (HD) patients when compared to peritoneal dialysis (PD) patients, though this has not been consistently the case, especially in recent studies. Chronic kidney disease (CKD) is associated with an over representation of traditional cardiovascular risk factors and an increased risk of stroke. Hypertension continues to be the major modifiable risk factor for both ischemic and hemorrhagic stroke with risk increasing with worsening systolic and diastolic blood pressure control. In addition to shared risk factors, this higher cerebrovascular risk is mediated by several CKD-associated mechanisms including platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation and increased risk of atrial fibrillation (AF). Posterior circulation strokes involving the vertebrobasilar system occur more commonly in patients on dialysis than in the general population.[3] This suggests screening for carotid artery disease may not be as effective as stroke prevention strategy in patients on dialysis relative to the general population. Kidney transplantation is associated with 30% lower risk for stroke or transient ischemic attack (TIA) compared with patients remaining on the transplant waiting list, whereas allograft failure increases the risk for stroke or TIA by 50%.[4] Among patients who experienced an intracerebral hemorrhage, patients with CKD had a 2- to 3-fold higher likelihood of cerebral microbleeds, a marker of lipohyalinosis or amyloid angiopathy, compared to patients without CKD.[5] This association was stronger among blacks than among whites.

Platelet Dysfunction in CKD

In uremic condition there are various reasons which lead to platelet dysfunction. These are alterations in membrane fluidity, reduction in intracellular ADP and serotonin, enhanced intracellular cAMP, impaired release of β-thromboglobulin and ATP, increased NO production, increased intracellular Ca2+ (caused by secondary hyperparathyroidism), abnormal mobilization of platelet Ca2+,defective cyclooxygenase activity, reduced thromboxane A2 generation, decreased platelet factor 3 availability, reduced total GPIb content (with increased glycocalicin formation), reduced GPIIb/IIIa after stimulation and diminished responsiveness to platelet agonists. There may be decreased clot retraction, aggregation abnormalities (mostly hyperaggregation), abnormal platelet adherence, uremic toxins, anemia, vWF abnormalities, vessel abnormalities. Platelet dysfunction may also be drugs related (β-lactam antibiotics, nonsteroidal anti-inflammatory drugs, antiplatelet agents). Plasma vWF level is normal or elevated in uremia. The findings that the administration of agents which increase plasma vWF or the factor VIII–vWF complex results in a shortening of prolonged bleeding time and a transient reversal of bleeding tendency in uremia suggests abnormalities in vWF metabolism, structure, and/or function. Low GPIb expression on resting platelets obtained from patients with CKD correlates with the severity of impaired kidney function. However, GPIb expression in uremic platelets increases after stimulation. In contrast, GPIIb/IIIa expression on resting uremic platelets is normal but reduced after stimulation, indicating hyporesponsiveness of the uremic platelets. The ability to bind both vWF and fibrinogen to GPs is reduced in uremia because of a conformational change in the GPIIb/IIIa receptor. PD is more effective than HD in improving impaired platelet function and prolonged bleeding time in uremia, possibly because of better clearance of uremic middle molecules. Bleeding tendency in uremic patients is related to the increased platelet nitric oxide synthase (NOS) activity. The NOS substrate L-arginine inhibits platelet aggregation, whereas the NOS inhibitors NG-monomethyl-L-arginine (L -NMMA) and NG-nitro-L-arginine methylester (L-NAME) restore platelet adhesion and aggregation. Inhibition of NOS by L-NMMA restores the increased bleeding time in experimental uremia to normal. Renal anemia may be responsible for prolonged bleeding time in ESKD patients. Within the normal circulation

[1]Physician and Nephrologist, [2]Neurophysician, [3]Physician, INHS Klayani, Vizag, Andhra Pradesh
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red blood cells increase platelet–vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall. Red blood cells also improve platelet function by releasing adenosine diphosphate (ADP) and inactivating prostacyclin. Vasodilating effects of prostacyclin and NO increase vessel luminal diameter and decrease peripheral dispersion of platelets and their contact with the vessel wall. Recombinant human erythropoietin (rHuEPO) improves platelet function mainly through increasing hematocrit, whereas an increase in blood viscosity may enhance the risk for thrombotic events. Platelet aggregation in uremia is increased by rHuEPO therapy even at a dose that does not influence hemoglobin and hematocrit by the release of young platelets into the blood. Low-dose rHuEPO therapy in patients with uremia also improves impaired platelet aggregation stimulated by ADP and ristocetin.

Platelet turnover in Chronic Kidney Disease

Reduced platelet half-life and low-normal platelet number in uremia suggest increased platelet turnover. Normal controls have a mean of 2.8% ± 0.2% reticulated platelets (a marker of platelet turnover), whereas PD and HD patients have a significantly higher percentage of 6.9% ± 0.7% and 8.2% ± 0.4%, respectively, suggesting enhanced platelet turnover in uremia. Shortened platelet survival in uremia may be the result of increased exposure of negatively charged phosphatidylserine. This signal is recognized by macrophages and promotes phagocytosis of the platelets.

Hemorrhagic stroke in dialysis patients.

There are also notable differences in the type of stroke in dialysis patients versus the general population with a higher prevalence of hemorrhagic stroke. A 22-year single center study of stroke in patients on maintenance HD compared HD patients with stroke to stroke with normal kidney function. It was observed that stroke patients receiving HD were younger (age 64 ± 10 vs. 67 ± 13 years, $P < 0.02$). In the HD group, hemorrhagic stroke was the major subtype of stroke (52%), whereas in the control group, ischemic stroke was more prevalent (68%).[6] This may be due to uncontrolled hypertension in this cohort as well as a genetic predisposition. There is a higher prevalence of hemorrhagic strokes compared to the general population (20% all events), a finding which was particularly marked in early Japanese studies that reported hemorrhagic stroke in up to 80% cases. This may relate to the degree of hypervolemia and hypertension seen in HD patients as well as the regular use of anticoagulation to maintain patency of the extracorporeal circuit. Majority of data about stroke in dialysis patients is derived from HD population from the United States and Japan. In a large single centre European study that has looked at stroke risk in maintenance HD patients revealed a first stroke rate of 14.9/1000 patient years (95% CI - 12.2–17.9) with a predominance of ischemic compared to hemorrhagic subtypes (11.2 vs. 3.7 per 1000 patient years).[7] Hemorrhagic strokes occurred more frequently in patients of South-Asian ethnicity compared to ischemic strokes which occurred predominantly in caucasian patients. Most studies with ESKD have focused on HD patients and less is known about the incidence, RRs, and subtypes of stroke in PD patients. In a retrospective cohort study data of >5000 PD patients was compared to 74,192 HD patients.[8] In comparison to the HD group, it was found that PD patients had a lower risk of hemorrhagic stroke (hazard ratio [HR] 0.75, 95% CI - 0.58–0.96), and there was no significant difference in risk of ischemic stroke between HD and PD patients after adjusting for all potential confounders and competing risk of death and matched by propensity scores. In both the general population and dialysis patients, diabetes and hypertension were risk factors for incident stroke. The conclusions reached were that "patients undergoing dialysis are at elevated risk of stroke, PD patients were at lower risk of hemorrhagic stroke, and comprehensive control of hypertension and diabetes is necessary when delivering dialysis treatment."US registry studies reported no differences in stroke risk in patients on peritoneal dialysis compared to those on HD.[16] In a Japanese study, 39% of ischemic and 35% of hemorrhagic strokes occurred during or within 30 min of concluding HD suggesting that the treatment itself may mediate stroke risk.[6] The association between renal dysfunction and bleeding has long been recognized, and morbidity and mortality from bleeding remain a significant clinical problem. While the usefulness of oral anticoagulation therapy for the primary and secondary prevention of stroke in patients with AF in the non-CKD population has been well documented, it has not been consistently seen in the dialysis population. Patients on HD are also regularly exposed to heparin anticoagulation during the course of their treatment and this can complicate matters. In a retrospective cohort study of incident ESKD patients with co-existing AF, warfarin use was associated with an increased risk of stroke presumably hemorrhagic stroke even after controlling for potential confounders.[9] Warfarin may potentiate vascular calcification to increase the risk of ischemic stroke.[10] Oral anticoagulants should therefore be carefully used in CKD patients with CHADS score ≥2 with careful monitoring. The role of newer non Vitamin K dependent anticoagulants such as dabigatran, rivaroxaban, and apixaban has not been tested in patients with eGFR <30 ml/min. Because of renal elimination, these have a prolonged half-life in CKD patients resulting in increased bleeding risk and have to be used cautiously. At present, there is little data about their use and safety in ESKD patients.

Hemorrhagic Stroke Risk in Predialysis Chronic Kidney Disease

Hypertension, diabetes mellitus, dyslipidemia, and proteinuria are all highly prevalent in the CKD population. Moreover, factors specific to CKD include accelerated atherosclerosis, vascular calcification, effect of uremic toxins, prothrombotic tendency, and impaired cerebral autoregulation. Intracranial arterial calcification, which is associated with stroke risk in the general population increases in prevalence in patients with CKD. A graded and independent relationship between estimated glomerular filtration rate (eGFR) and stroke risk has been reported in some studies. A recent meta-analysis incorporating data from 33 studies reported a 43% independent risk of stroke with eGFR <60 ml/min.[11] This increased risk effect was further modulated by the ethnicity of the patient with a higher stroke risk seen in Asian compared to non-Asian populations (relative risk [RR] 1.96 vs. 1.26, $P < 0.0001$). The presence

of proteinuria is itself an important risk factor for stroke even in the absence of reduced GFR and after the adjustment for other vascular risk factor A meta-analysis of observational cohort studies observed that patients with proteinuria had an adjusted risk ratio of 1.71 (95% confidence interval [CI] 1.39–2.10, $P = 0.008$).[12]

Prognosis of hemorrhagic Stroke in Chronic Kidney Disease

CKD is an independent risk factor for hemorrhagic stroke. Following acute ischemic stroke, advanced CKD (eGFR <30 ml/min) has been associated with a higher risk of hemorrhagic transformation (odds ratio [OR] 2.90, 95% CI - 1.26–6.68, $P = 0.01$).[13] In one study among 128 patients with an Intracerebral hemorrhage (ICH) (mean age = 71.7 ± 12.3 years, 41.4% women) 46.1% had CKD (23.4% mild and 22.7% moderate/severe). Patients with moderate/severe impairment had >4-fold adjusted hazard ratio for mortality over 1 year (4.29; 95% CI = 1.69–10.90) compared to patients with no impairment. The hematoma volumes [median (25–75%)] were 15.3 ml (5.4–37.5) in patients with no impairment, 16.6 (6.8–36.9) in mild impairment and 50.2 (10.4–109.1) in moderate/severe impairment (p = 0.009). The location of the hematoma was lobar in 12% with no impairment, 17% with mild impairment and 39% with moderate/severe impairment (p = 0.02). Patients with moderate/severe impairment exhibited a 2.3-fold higher hematoma volume (p = 0.04) and a >6-fold higher odds of lobar location (95% CI = 1.59–24.02) as compared to no impairment. Further adjustment for antiplatelet use and for presence of leukoaraiosis attenuated the association with hematoma volume (p = 0.15), while moderate/severe impairment was associated with an adjusted OR of 5.35 (95% CI = 1.18–24.14) for lobar location.[14] These findings may represent the greater co-morbid profile of patients with CKD who experience a stroke or reflect subclinical cerebral vascular disease burden seen in patients with renal failure.

Clinical trials testing rTPA for acute ischemic stroke did not specifically include patients with CKD and ESKD. The US National Get With the Guideline–stroke (GWTG-Stroke) registry analyzed the association of CKD with key hemorrhagic outcomes after IV TPA for acute ischemic stroke [15]. Out of 44, 410 patients with stroke treated with IV TPA, 34%.[15,19] patients had CKD. Presence of CKD was not associated with risk-adjusted symptomatic intracranial hemorrhage (adjusted OR 1.0, 95% CI - 0.80–1.18). However, the study found that compared to those patients with normal kidney function, those with CKD were more likely to die in hospital (OR 1.22, 95% CI - 1.14–1.32) and have an unfavorable discharge functional status (OR 1.13,95% CI - 1.07–1.99). The risk of symptomatic hemorrhage did not actually lead to increased mortality, and other CKD related factors were responsible. These findings suggest that the presence of CKD alone should not be a contraindication to administration of IV TPA for eligible patients Overall, the data suggest that CKD attenuates the therapeutic efficacy of alteplase, and in one study increased the risks of symptomatic intracranial hemorrhage after treatment. In the only available large, registry based study of US dialysis patients receiving thrombolysis for stroke (n = 1,042), there was no difference in the rates of symptomatic intracranial hemorrhage or disability at discharge although dialysis patients had a 2-fold higher risk of in hospital mortality following thrombolysis.[17] The prognosis following hemorrhagic stroke is particularly poor with case fatality rates reaching 90% in some series. It remains unclear whether ESKD patients have worse functional outcomes and quality of life following acute stroke. The risk of bleeding with prophylactic antiplatelet agents is increased in ESKD, and they have to be used with caution. Dual therapy with aspirin and clopidogrel increases the bleeding risk manifold and is therefore used with extreme caution unless there are other indications such as cardiac stent, which warrants their use. There have been no RCTs in CKD/ESKD patients and the anticoagulation targets for CKD patients are not known and guidelines applicable for the general population have been applied. Evidence-based answers in the form of a prospective clinical trial comparing dialysis patients with AF to placebo and oral anticoagulation therapy are urgently needed.

Prevention and treatment of hemorrhagic stroke in CKD

Control of hypertension is the cornerstone of primary and secondary stroke prevention in the general population as well as in patients with CKD including ESKD. The relationship between attained BP and stroke risk was shown to be linear in a recent RCT although prior, large, epidemiological studies suggested that in patients with CKD 3–4 this relationship was J shaped with a systolic BP <120 mm Hg associated with a 2.5 times greater risk.[18,19] To date, there are no compelling trial data to recommend one class of antihypertensives over another. Although retrospective studies have indicated that uncontrolled hypertension in dialysis patients is associated with stroke there are no studies defining an optimal target BP. The risk of bleeding with antiplatelet agents is augmented in ESKD and caution is advised. Treatment with oral anticoagulants needs to be tempered by the higher risk of bleeding seen in patients with renal impairment and especially in those with ESKD. Adequate dialysis (Kt/V > 1.2 in HD and Kt/V > 1.7 in PD patients by removal of uremic toxins improves platelet functional abnormalities. Heparin use should be stopped in case of intracerebral hemorrhage (using predilutional saline, 100 to 200 ml every 15 or 30 minutes, and a dialysis membrane with low thrombogenicity such as polysulfone). Beneficial effects of red cell transfusion on prolonged bleeding time are independent of changes in platelet function tests or in the level of vWF. Erythropoiesis-stimulating agent (ESA) therapy improves uremic bleeding tendency by several mechanisms including displacement of platelets closer to the vascular endothelium with the increase in circulating red blood cells, increase in reticulated (metabolically active) platelets, increase in platelet aggregation, improvement of platelet signaling (and thereby better response to stimuli) and scavenging of nitric oxide by hemoglobin, resulting in increased platelet adhesion.

Cryoprecipitate is a blood product rich in factor VII, vWF, and fibrinogen. The effect of cryoprecipitate is apparent 1 hour after infusion, but maximal effects on the bleeding time are obtained 4 to 12 hours after the infusion. By 24 to 36 hours, the effect of cryoprecipitate is no longer detected. Desmopressin acetate (1-deamino-8-D -arginine-

vasopressin, DDAVP) is a synthetic derivative of the antidiuretic hormone vasopressin. This is useful in a variety of inherited and acquired hemorrhagic conditions. Moreover, DDAVP shortens bleeding time and APTT of patients receiving heparin. It is therefore helpful for the management of hemorrhagic complications during treatment with heparin. Desmopressin shortens the prolonged APTT and bleeding time by an increase in plasma levels of factor VIII and vWF. The increase in larger vWF–factor VIII multimers after infusion of DDAVP is associated with shortening of bleeding time. It also increases platelet GPIb expression. The recommended doses range from 0.3 to 0.4 μg/kg administered intravenously in 50 ml normal saline over 20 to 30 minutes as a single infusion. Subcutaneous (0.3 μg/kg) or intranasal (2-3 μg/kg) routes of administration are also effective. One important advantage of DDAVP is its rapid onset of action in the setting of acute bleeding. Desmopressin decreases bleeding time within approximately 1 hour after administration. Disadvantages of DDAVP include tachyphylaxis caused by depletion of vWF from endothelial stores even after one single dose, headache, facial flushing, and rare thrombotic events. Conjugated estrogens can be given intravenously, orally, or transdermally. The intravenous route of administration at a cumulative dose of 3 mg/kg divided over 5 consecutive days produces a long-lasting reduction in the bleeding time of uremic patients. At least 0.6 mg/kg of a conjugated estrogen is needed to reduce bleeding time. A single oral dose of 25 mg normalizes the bleeding time for 3 to 10 days. Low-dose transdermal application of a conjugated estrogen (50 to 100 μg of estradiol per 24 hours) as a patch twice weekly also improves bleeding time and reduces bleeding complications. Conjugated estrogens are safe and well tolerated. Side effects include flush, increase in blood pressure, and abnormal liver function tests. Tranexamic acid (TXA) is an antifibrinolytic lysine analog that shortens bleeding time in uremic patients. TXA prevents the binding of plasminogen to fibrin and the activation of plasminogen to plasmin. Bleeding time improves or normalizes in uremic patients within 6 days of treatment with TXA (20 to 25 mg/kg/day) administered intravenously or orally. Improvement of bleeding time is already observed as soon as 24 to 48 hours after initiation of TXA therapy. TXA may be combined with DDAVP to prevent or treat bleeding in uremic patients, if other treatment options do not elicit the desired response. The use of surgical methods to treat ICH remains controversial, particularly for chronic renal disease patients. Open craniotomies and removal of hematomas were avoided whenever possible. Free hand aspiration and stereotactic aspiration of a hematoma are beneficial because platelet dysfunction due to uremia and coagulopathy caused by systemic anticoagulation therapy may result in difficulty in maintaining hemostasis and an increased risk of additional complications after surgery. Severity of renal function, initial neurological status, hematoma volume, and uncontrolled blood pressure are considered as significant prognostic factors in ICH patients with CKD.

Conclusion

Hemorrhagic stroke is not so uncommon in setting of chronic kidney disease and risk increased in patient on dialysis. HD patients may be at higher risk of hemorrhagic stroke compared with PD patients, although this needs further study. The benefit of antiplatelet therapies and oral anticoagulants must be balanced against the real risks of bleeding that are most evident in dialysis cohorts.

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