Impact of Correction of anemia in Anemic ESRD patients on Cerebral Circulation and Cognitive Functions

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Dedication

To all my teachers at kasr Alaini

Thanks alot.

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ABSTRACT

Background:

End stage renal disease patients undergoing hemodialysis has been associated with accelerated vascular disease and premature atherosclerosis of the cerebral circulation due to uremic toxins and augmentation of traditional risk factors of atherosclerosis. Also, anemia of chronic renal failure increases cerebral oxygen extraction fraction in hemodialysis patients, and the increased oxygen extraction fraction suggests that the cerebral vasodilatory capacity might be impaired in these patients.

Objective:

In this study we evaluate the effect of correction of anaemia on cerebral blood flow by measuring the mean blood flow velocity, resistance index (RI), and pulsatility index (PI) in the middle cerebral artery of twenty ESRD patients with anemia by transcranial doppler ultrasound and remeasuring it after correction of anemia in relation to cognitive functions.

Methods:

In this study we measured the mean blood flow velocity, resistance index, and pulsatility index in the middle cerebral artery of twenty ESRD patients when the haemoglobin range between 8.0 g/dl to 10.0 g/dl and after correction of anemia to two haemoglobin ranges; one between 10.0 g/dl to 11.5 g/dl and another between 11.5 g/dl to 12.5 g/dl in the same patients using transcranial doppler ultrasound in relation to cognitive functions assessment by Mini-Mental State Examination (MMSE).

Results:

We observed that there is a high frequency of mild to moderate cognitive impairment in hemodialysis patients especially if associated with anemia. Also, chronic anemia was associated with impaired cognitive function while gradual improvement of anemia will be associated with improvement of cognitive function. Improvement of blood flow of middle cerebral arteries with improvement of hemoglobin during the study appeared in decreasing of mean blood flow velocity, resistivity index and pulsatility index and increasing of end diastolic velocity which all indicate better blood flow with increasing of hemoglobin of cases during the study. There is correlation between improvement of cognitive function and improvement of cerebral circulation measured by transcranial Doppler of middle cerebral artery during the study. We have noted the lack of complications with increased hemoglobin to 12.5 g/dL such as a stroke, cardiovascular complications and uncontrolled hypertension, taking into consideration the short duration of the study and exclusion of other risk factors (as diabetes) that increase incidence of ischemia and blood clots. The improvement was obvious at stage 3 (Hb 11.5 to $\leq$ 12.5 g/dL) in comparison to stage 2 (Hb 10 to < 11.5 g/dL) with P value < 0.001 at all. This finding indicate that optimal hemoglobin for hemodialysis patients range from 11.5 g/dL to less than or equal 12.5 g/dL.

Conclusion:

The optimal hemoglobin for hemodialysis patients range from 11.5 g/dL to less than or equal 12.5 g/dL which associated with better improvement of cognitive function and cerebral circulation investigated by transcranial doppler ultrasound for middle cerebral artery.

Keywords:

Anemia, ESRD, cognitive, TCD.

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LIST OF ABBREVIATIONS

BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBF	Cerebral Blood Flow
CERA	Continuous Erythropoietin Receptor Activator
CHOIR	The Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	Confidence Interval
CKD	Chronic Kidney Disease
cm/s	centimeter per second
Cr	Creatinine
CREATE	The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
CVD	Cardio Vascular Disease
DOQI	Dialysis Outcomes Quality Initiative
e GFR	estimated Glomerular Filtration Rate
EPO	Erythropoietin
ESAs	Erythropoiesis Stimulating Agents
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
Fe	Iron
fTCD	Functional Transcranial Doppler sonography
g/dL	gram per deciliter
g/L	gram per liter
Hb	Hemoglobin concentration
HCT	Hematocrit
HDL	High Density Lipoprotein
HR	Hazard Ratio
HTN	Hypertension
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IU	International unit
IU/kg	International unit per kilogram
IV	Intravenous
K	Potassium
KDIGO	Kidney Disease Improving Global Outcome
KDOQI	Kidney Disease Outcomes Quality Initiative
LDF	Laser Doppler Flowmetry
LDL	Low Density Lipoprotein
MCA	Middle Cerebral Artery
MCV	Mean Corpuscular Volume
mg	milligram

mg/kg	milligram per kilogram
MHz	mega hertz
MI	myocardial infarction
ml	milliliter
ml/ min	milliliter per minute
mm Hg	millimeter mercury
mmol/L	mill mol per liter
MMSE	Mini Mental State Exam
MRI	magnetic resonance imaging
MV	Mean Velocity
Na	Sodium
ng/ml	Nanogram per milliliter
NHANES	National Health And Nutrition Examination Survey
NKF	National Kidney Foundation
NSAID	Non Steroidal Anti Inflammatory Drugs
OR	Odd Ratio
PI	Pulsatility Index
PRF	Pulse Repetition Frequency
PTH	Parathyroid Hormone
RBC	Red Blood Cell
RDW	Red cell volume distribution width
RI	Resistivity Index
RR	Relative Risk
SC	Subcutaneous
SD	Standard Deviations
sp Kt/V	Single pool Kt/V
SPSS	Statistical Package of Social Science
SSS	Superior Sagittal Sinus
TCD	Transcranial Doppler
TGs	Triglycerides
TIBC	Total Iron Binding Capacity
TLC	Total Leucocytic Count
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	Transferrin saturation
US	United State

Introduction

End stage renal disease patients undergoing hemodialysis has been associated with accelerated vascular disease and premature atherosclerosis of the cerebral circulation due to uremic toxins and augmentation of traditional risk factors of atherosclerosis. The risk of stroke as a frequent complication of uremia, which can result from acute cerebral blood flow reduction, is a five times higher in dialysis patients than the general population. Decreasing of brain tissue perfusion has deleterious nature in uremic patients, as it increases the incidence of cerebral atrophy, especially in combination with a low hematocrit and in the presence of accelerated and premature atherosclerosis along with traditional risk factors ***[Mehdi F, et al. 2012].***

Anemia of ESRD increases cerebral oxygen extraction fraction in hemodialysis patients, and the increased oxygen extraction fraction suggests that the cerebral vasodilatory capacity might be impaired in these patients. In addition, some findings suggest a lowered metabolic demand of the brain tissue in patients with kidney failure on or before the start of hemodialysis therapy, that, the cause for depressed brain oxygen metabolism is considered to be either dysregulation of cerebral circulation or lower brain cell activity ***[Li H, et al. 2008].***

Transcranial doppler ultrasonography (TCD) is a noninvasive, safe, repeatable, simple procedure that obtains hemodynamic information related to brain circulation and shows continuously cerebral blood flow velocity in the basal and main brain arteries in dialysis patients ***[Skinner H, et al. 2005].***

Anemia in ESRD patients undergoing hemodialysis will be diagnosed when the hemoglobin concentration is less than 13.0 g/dl in males and less than12.0 g/dl in females. The following investigations include complete blood count (CBC), absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B12 ***[Kidney International Supplements 2012].***

Cognitive impairment is common among persons with ESRD and is associated with poor outcomes, Several ESRD- and dialysis-associated factors such as retention of uremic solutes, hypertension, hemodynamic instability during dialysis (intradialytic hypotension), and anemia may lead to stroke or cerebral ischemia and contribute to cognitive impairment and dementia in patients with ESRD ***[Murray A, et al. 2006].***

The evaluation of cognitive function involves the assessment of a range of cognitive domains, such as memory, language, attention, and executive function (i.e., the cognitive skill necessary for planning and sequencing tasks). Cognitive impairment that is caused by or associated with different neurologic or systemic illnesses may be characterized by impairments in specific cognitive domains, especially in early stages. For example, memory impairment is an early feature of Alzheimer's dementia, whereas vascular causes of cognitive impairment are frequently associated with diminished executive function. A few studies have suggested that impaired executive function is common among patients with ESRD but its correlates are unknown. Mini-Mental State Examination (MMSE) is the most widely used cognitive test. The examination takes approximately seven minutes to complete. It tests a broad range of cognitive functions including orientation, recall, attention, calculation, language manipulation, and constructional praxis ***[Prohovnik I, et al. 2007].***

Aim of the work

In this study we are aiming to evaluate the effect of correction of anemia on cerebral blood flow by measuring the mean blood flow velocity, resistance index (RI), and pulsatility index (PI) in the middle cerebral artery of 20 ESRD patients with anemia by transcranial doppler ultrasound and remeasuring it after correction of anemia in relation to cognitive functions.

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Anemia of chronic kidney disease patients

- **Introduction and definition:**

Anemia has been defined as a reduction in one or more of the major red blood cell (RBC) measurements obtained as a part of the complete blood count: hemoglobin concentration, hematocrit, or RBC count ***[Shamir M, et al. 2012].***

Hemoglobin concentration (Hb) measures the concentration of the major oxygen carrying pigment in whole blood. Values may be expressed as grams of hemoglobin per 100 ml of whole blood (g/dL) or per liter of blood (g/L). Efforts are underway to determine Hb levels non-invasively, allowing continuous monitoring of this parameter. Hematocrit (HCT) is the percent of a sample of whole blood occupied by intact red blood cells. RBC count is the number of red blood cells contained in a specified volume of whole blood, usually expressed as millions of red blood cells per micro liter of whole blood ***[Causey M, et al. 2011].***

One set of "normal ranges" (95 percent confidence limits) for Hb, HCT, and RBC count is shown in the table ***[Camaschella C. 2013].***

Red cell parameter	**Adult men**	**Adult women**
Hemoglobin, g/dL	15.7 ± 1.7	13.8 ± 1.5
Hematocrit, percent	46.0 ± 4.0	40.0 ± 4.0
RBC count, million/µL	5.2 ± 0.7	4.6 ± 0.5
Reticulocytes, percent	1.6 ± 0.5	1.4 ± 0.5
Mean corpuscular volume, fL (MCV)	88.0 ± 8.0	88.0 ± 8.0
Mean cell hemoglobin, pg/RBC	30.4 ± 2.8	30.4 ± 2.8
Mean cell hemoglobin concentration, g/dL of RBC	34.4 ± 1.1	34.4 ± 1.1
Red cell volume distribution width, percent (RDW)	13.1 ± 1.4	13.1 ± 1.4

Table (1) shows normal values for red blood cell parameters in men and women