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An 8 week prospective study on the relationship between major depressive episode and serum brain derived neurotrophic factor in a Nigerian tertiary hospital

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ABSTRACT

Background: Current views on the etiology of Major Depressive Diorder(MDD) emphasizes environmental and biological interplay. Recent studies have implicated reduction in Brain Derived Neurotrophic Factor (BDNF) in the pathophysiology and as a biomarker of major depression (Neurotrophin Hypothesis of Depression). This study aimed at showing that the Neurotrophin hypothesis of depression is relevant in the pathophysiology of Major Depressive Episode in Southern Nigeria.

Methods: Consecutive consenting patients diagnosed with Major Depressive Episode (MDE) using the Structured Clinical Interview for DSM (SCID) and age and sex matched controls were enrolled into this study. Serum BDNF was measured prior to commencement of treatment as baseline and 8 weeks after treatment. Depression severity was rated with the Hamilton Depression Rating Scale (HAM-D) and Patient Health Questionnaire (PHQ-9).

Results: Seventy-five cases and 75 age and sex matched controls were recruited. The mean ± SD of serum BDNF of depressed patients (26.09 ng/ml ± 1.96) was significantly lower than those of age and sex matched controls (28.13 ng/ml ± 1.47) $P < 0.01$. The study had a follow up rate of 48% after 8 weeks of treatment. Serum BDNF post treatment was significantly higher than baseline.

Limitations: This was a single center study with a high drop-out rate.

Conclusion: The result of this study adds to the mounting evidence in support of the neurotrophin hypothesis of depression.

1. Introduction

Depression is a highly prevalent disorder affecting over 120 million of the world's population (Lépine & Briley, 2011). It is one of the leading causes of disability worldwide and is estimated to be the 2nd cause of disability worldwide by 2020. It is associated with increased morbidity, mortality, suicide rate and cognitive impairment (Ojagbemi, Oladeji, Abiona, & Gureje, 2013). Prevalence rates globally are highly variable ranging from 1.5%–19% (Weissman et al., 1996). In Nigeria, the point prevalence of Major Depressive Episode (MDE) ranges between 3.1%–5.2% (Amoran, Lawoyin, & Lasebikan, 2007; Gureje, Uwakwe, Oladeji, Makanjuola, & Esan, 2010).

Brain Derived Neurotrophic Factor (BDNF) is a member of the neurotrophin (NT) family along with Nerve Growth Factor (NGF), Neurotrophin 3 (NT3) and neurotrophin 4 (NT4) found in the mammalian brain. It was first purified in 1982 where its function was thought to promote cell survival (Adachi, 2014; Barde, Edgar, & Thoenen, 1982; Dwivedi, 2013). The neurotrophin family of which BDNF is a member is important in the regulation of cell survival and cell differentiation during development (Bramham & Messaoudi, 2005). BDNF has emerged as a crucial mediator in neuronal plasticity and also has a positive impact on neurogenesis in the adult brain (Calabrese et al., 2014).

The neurotrophic hypothesis of depression proposes that depression is associated with reduced brain BDNF levels and that antidepressant treatments alleviate depressive behaviour and increase BDNF levels (Duman & Li, 2012; Lee & Kim, 2010). This hypothesis postulates that a reduction in BDNF plays a direct role in the pathophysiology of depression and that Major depression is associated with impaired neuronal plasticity. Antidepressant treatment promotes several forms of neuronal plasticity such as neurogenesis, synaptogenesis neuronal maturation and increases BDNF activity. Karege et al. demonstrated that

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serum BDNF was significantly decreased in patients with MDE than healthy controls and that BDNF correlated negatively with depression severity. Further clinical studies have replicated these findings. A systematic review and meta-analysis of clinical studies on MDE and BDNF level found the mean serum BDNF in depressed patients to be significantly lower pre-treatment than in the control group. These findings support the neurotrophin hypothesis of depression (Diniz et al., 2010; Bocchio-Chiavetto et al., 2010; Brunoni, Lopes, & Fregni, 2008; Karege et al., 2002).

Recent studies have shown that BDNF is not only associated with the presence of MDE but also with depression severity. Depression severity measured using various depression rating scales has been shown to correlate negatively with serum BDNF concentration (Gonul et al., 2005; Kreinin et al., 2015; Shimizu et al., 2003).

There are several commonalities of function in the central nervous system for BDNF and serotonin in terms of their effect on synaptic plasticity, neurogenesis and cell survival (Mattson, Maudsley, & Martin, 2004). Substantial evidence suggests that BDNF promotes the development and function of serotonergic neurons, highlighting its role in treatment response following anti-depressant use. This brings to light the role of BDNF as a possible biomarker for the presence of Major Depressive Disorder.

There is, however, no data supporting or refuting this hypothesis from the sub-Saharan region of Africa.

This study aimed to show that the neurotrophin (BDNF) hypothesis of depression is relevant in the pathophysiology of depression in adults in Southern Nigeria, and has the specific objectives of comparing serum BDNF level in patients with MDE with controls at baseline and to assess the effect of Selective Serotonin Reuptake Inhibitor (SSRI) treatment on serum BDNF level. This is the first study of its kind to be carried out in the West African region and thus adds to the gap in data on the role of BDNF in Major Depressive Episode (MDE).

2. Methods and materials

2.1. Subjects

Seventy-five patients with MDE, who had been anti-depressant free for at least 1 month (the effect of antidepressant on serum BDNF level is minimal) and presenting at the Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital were recruited into the study after written informed consent and meeting the eligibility criteria of the study which included,

Inclusion criteria for cases of depression

1 Subjects aged 18 years and over
2 Subjects who met the DSM-IV criteria for Major Depressive Episode (MDE).
3 Subjects who gave written informed consent

Exclusion criteria for cases

1 Subjects previously diagnosed as having other major mental disorders
2 Subjects with cognitive impairment (assessed using the Mini Mental State Examination and having a score of < 24)
3 Subjects who at the time of interview were receiving antidepressant medications for over 1 week
4 Subjects who had chronic medical conditions such as epilepsy, diabetes mellitus, hypertension, heart disease, etc. excluded by clinical history.
5 Subjects who were smokers, with drug abuse problems and recent physical injuries during the time of the study.

This information was obtained from structured patient interviews, measurement of physical parameters and examination of patients' case notes.

All patients were diagnosed with current MDE using the Structured Clinical Interview for DSM diagnosis (SCID) (Michael, Spitzer, Miriam, & Williams, 2002) following the administration of the study's socio-demographic questionnaire. For each case recruited into the study, a control of same sex and similar age (+/− 2 years) was selected for recruitment into the study, from the pool of administrative staff of the hospital meeting the eligibility criteria.

Inclusion criteria for controls

1 Subjects are 18 years and over
2 An administrative staff of UPTH without a mental illness (GHQ-12 score of ≤3, plus PHQ-9 score < 5).

Exclusion criteria for controls

1 Presence of cognitive impairment (MMSE score < 24)
2 Subjects who had chronic medical conditions such as epilepsy, diabetes mellitus, hypertension, heart disease, etc. excluded through personal history.
3 Subjects, who were smokers, had drug abuse problems and recent physical injuries during the study period.

Each eligible control was administered the socio-demographic questionnaire.

The severity of the depressive episode for each subject with MDE was assessed using the PHQ-9 and Hamilton Depression Rating Scale (HAM-D). Patients with MDE were treated with Selective Serotonin Reuptake Inhibitors (SSRI), atypical antipsychotics and psychotherapy. Treatment choice and dosage were determined by the severity of depression and the presence of psychotic symptoms. Forty-seven subjects with MDE received SSRI only while 28 subjects with MDE received a combination of SSRI and atypical antipsychotics. Following the administration of study instruments, venous blood was taken at baseline for the analysis of BDNF from both cases and controls. Recruitment of participants into the study took 20 months as against an estimated 6 months due to the presence of industrial actions (within the health sector) and the unwillingness of patients and controls to be recruited into the study on the realization that biological samples would be required. Cases only were followed up for 8 weeks after which, a repeat blood sample was obtained for the analysis of serum BDNF. Study participants received phone calls a week to their 8th-week appointment and text messages were sent out a day before their follow up appointment to remind them of their appointments. However, we encountered a high dropout rate despite rigorous methods used in following up participants.

Ethical clearance to carry out the study was given by the ethical and research committee of the University of Port Harcourt Teaching Hospital (UPTH).

2.2. Measurement of Serum BDNF

Venous blood was taken from the antecubital fossa during a fasting state (before 9 a.m.) from both cases and controls, blood was centrifuged and 2mls of serum was extracted and stored at −25°C. The cases were followed up after 8 weeks of treatment and a second venous sample was taken and serum stored. At the collection site, a freezer for biological samples was used to store serum prior to transportation to the analyzing site. Regular power supply (at least 20 h a day) was provided for the storage of the samples at −25 °C and the storage freezer was filled with packed ice to keep samples frozen during the periods of lack of power supply. Biochemical analysis for BDNF was carried out at the safety molecular pathology laboratory located at the Faculty of Health Sciences and Technology, University of Nigeria, Enugu Campus, Enugu, Enugu State. Transportation of biological samples was done using a cold chain system developed by the

researcher. Samples were transported over 4 h in a cooler with packed ice. On arrival at the analysing laboratory, they were tested for viability prior to being stored at −85 °C until testing was carried out.

BDNF was analyzed using the abcam® ELISA kit. All materials and reagents were equilibrated to room temperature (18 −25°C) prior to use. One hundred microliters (100 µL) of each standard and sample were added into appropriate wells, covered and allowed to incubate at room temperature for about 2 ½ hours. After incubation, the solution was discarded and washed 4 times using the 1X wash solution. One hundred microliters (100 µL) of the 1X Biotinylated anti-Human BDNF detector was added to each well and incubated for an hour at room temperature. The solution was discarded, and the wells washed. 100 µL of 1X HRP-Streptavidin solution was added to each well and incubated at room temperature for 45 min with gentle shaking. The solution was discarded, and the washing step repeated. One hundred microliters (100 µL) of the TMB One-Step Substrate Reagent was added to each well and incubated for 30 min at room temperature in the dark shaking gently. Fifty microliters (50 µL) of Stop Solution was added to each well and read at 450 nm immediately. The mean absorbance of each duplicate standard, control and sample was calculated.

2.3. Statistical Analysis

The mean and standard deviation of serum BDNF were calculated for the cases and controls. Independent *t*-test was used to determine the significance in the difference between the serum BDNF in the cases as compared with controls. A paired *t*-test was used to determine the difference between the mean serum BDNF before and 8 weeks after treatment as usual. A Pearson moment correlation coefficient was used to determine the level of correlation between serum BDNF and depression severity using Hamilton depression rating scale and Patient Health Questionnaire – 9. All statistical analyses were done using Statistical Programme for Social Sciences (SPSS), version 20.

3. Results

Table 1 shows the distribution of socio-demographic variables in the study participants. A total of one hundred and fifty (150) participants were enrolled in the study. Seventy-five (75) of the study participants were diagnosed with MDE using the SCID and 75 were age and sex-matched controls who scored < 3 on the GHQ 12.

Using a normality test plot, serum BDNF concentration in both groups (MDE and controls) were shown to follow a normal distribution. The Shapiro-Wilk test of normality was applied to this data to determine if the normal distribution seen was similar to that which is expected in the general population. We found no significant difference (P = 0.102 (MDE) and P = 0.200 (controls)) between the serum BDNF distribution in this study from that of the expected normal distribution.

Age distribution of the study participants with MDE was normally distributed and did not differ significantly from the expected normal distribution. There was no significant relationship between serum BDNF, age and sex.

Table 2 shows the independent sample *t*-test of serum BDNF of the participants with MDE and control groups. There was a statistically significant difference between the mean serum BDNF in cases and controls (P < 0.01) and a large effect size (d = −1.17; 95% C.I. 082 – 1.52).

After 8 weeks of treatment, 36 (48%) of the 75 participants with MDE returned for a repeat blood sample collection (48% follow up rate), 1 participant (1.3%) died (participant and caregivers signed against medical advice, defaulting from treatment and dropped out of the study to return 8 weeks later at the accident and emergency following refusal to eat and was certified dead the following day), 24 (32%) were lost to follow up, 9 (12%) had poor treatment compliance and 5 (6.7%) did not keep their follow up appointment.

Of the study participants who defaulted from the study protocol, about 2/3rd were females, 1/4th had financial constraints, about half identified having a recent stressful life event and 1/3rd lived alone. Of these variables, living alone was significantly associated with defaulting from the study. Table 2 also shows the mean serum BDNF concentration in the study defaulters as compared with the non-defaulters. There was a statistical difference in mean serum BDNF of both groups with moderate effect size.

Table 2 shows a paired *t*-test of mean serum BDNF before and after treatment in participants with MDE. There was a statistically significant difference between the mean serum BDNF before and after treatment (P < 0.001) with a large effect size (d = 1.24; 95% C.I. 0.73–1.74). Mean serum BDNF after treatment did not differ in a statistically significant manner from those of control at baseline.

Depression severity was rated using HAM-D and PHQ-9. Depression severity was categorized into mild, moderate, severe and very severe depression. Table 3 shows the frequency distribution of depression severity categories using HAM-D and their mean serum BDNF concentration. There was no statistically significant difference between the

Table 1
Sociodemographic Characteristics of Study Participants.

Variable		Major Depression present (Cases)	Major Depression absent (Controls)	Fishers Exact test/ Continuity correction*	ρ
Age	19–28	18	18	0.477	0.985
	29–38	25	22		
	39–48	21	23		
	49–58	8	9		
	> 58	3	3		
	Total	75	75		
Gender	Male	25	25	0.000*	1.0
	Female	50	50		
	Total	75	75		
Marital Status	single	27	31	3.544	0.481
	married	42	42		
	separated	3	–		
	divorced	1	1		
	widowed	2	1		
	Total	75	75		
Level of Education	No formal education	2	–	10.169	0.008
	primary education	2	4		
	secondary education	33	17		
	tertiary education	38	54		
	Total	75	75		

* Yates Continuity correction used.

Table 2
Independent *t*-test of Serum BDNF Concentration in Cases and Controls.

	Number	BDNF concentration (ng/ml)		t	ρ	Effect size (d)	95% C. I
		Mean	Std. Deviation				
Cases	75	26·089	1·963	−7·211	< 0·001*	1.17	0.82 – 1.52
Controls	75	28·129	1·466				
Defaulter	39	26.60	1.63	2.40	0.019*	0.55	0.09 – 1.01
Non- defaulter	36	25.54	2.16				
Before Treatment	36	25.5392	2.158	−7.215	0.000*	1.24	0.73 – 1.74
After Treatment	36	27.8025	1.385				

Table 3
Relationship Between Serum BDNF and Depression Severity (HAM-D).

Depression Severity	Frequency	Percent	Serum BDNF ng/ml	F	P
Mild Depression	10	13.3	26.5	1.445	0.228
Moderate Depression	17	22.7	26.12		
Severe Depression	15	20	26.94		
Very Severe Depression	33	44	25.61		
Total	75	100			

mean serum BDNF in the different categories (P = 0.228). Serum BDNF concentration has a weak negative correlation with depression severity using both depression rating scales (HAMD P-value = 0.412 and PHQ-9 P-value = 0.335).

4. Discussion

The neurotrophin hypothesis of depression proposes that major depression is associated with decreased levels and activity of BDNF in the brain, which is reflected as a decrease in serum BDNF. Major depression has also been linked with impaired neuronal plasticity, neurogenesis, synaptogenesis and neuronal maturation (Calabrese et al., 2014; Cowansage, LeDoux, & Monfils, 2010; Soulé, Messaoudi, & Bramham, 2006).

The mean serum BDNF concentration in study participants with MDE (cases) was significantly lower than that of the socio-demographically matched control (P < 0.01). The difference between the means of serum BDNF in cases and control had a large effect size (d = 1.17, 95% C.I. of 0.82–1.52). This converse relationship between the presence of depression and level of BDNF is a strong pointer that it could serve as a biomarker for MDE. These findings were similar to those of Karege et al., who found significantly lower serum BDNF level in depressed patients than in healthy control P < 0.01 in a Swedish population. The mean serum BDNF levels in their 30 cases (22.6 +/- 3 ng/ml) and 30 sex-matched controls (26 +/− 7 ng/ml) were lower than those found in this study despite having similar study designs. Reasons for these could be due to the population sampled (Swedish compared to Nigerian) or the collection and storage process of the blood samples. These findings of lower serum BDNF concentration in patients with MDE as compared with controls have been replicated by other studies (Aydemir, Deveci, & Taneli, 2005; Diniz et al., 2010; Karege et al., 2002).

(Brunoni et al., 2008) in their systematic review and meta-analysis on clinical cases of Major Depressive Disorder and BDNF (n = 1504 excluding all studies with bipolar depression) also found significantly lower serum BDNF in patients with MDD than controls. However, the mean serum BDNF was lower (cases = 19.59 ng/ml and controls = 27.75 ng/ml) when compared with this study.

A community-based study in the United States of America with 2099 healthy respondents, determined that serum BDNF level of healthy individuals ranged from 1 to 27 ng/ml with a median of 14 ng/ml which is also lower than what was observed in this study. Serum BDNF was found to be normally distributed in this study which is consistent with the findings in other studies (Terracciano et al., 2011).

The findings from this study suggest that MDE is characterized by decreased serum BDNF level, and as such, indicates that a reduction in level and activity of BDNF in the brain is integral in the pathophysiology of depression. It can, therefore, be inferred that Major Depression is characterized by decreased neuronal plasticity. This is in support of the neurotrophic hypothesis of depression (Lee & Kim, 2010).

Serum BDNF in the study participants were found to be higher than those in the reviewed literature. These differences were statistically significant with large effect sizes. One can speculate that the higher serum BDNF level observed in this study compared to reviewed literature might be a factor of the population studied. Reviewed studies were carried out in Western countries amongst a mainly Caucasian population with paucity of studies from African countries. This raises a strong focus on the influence environmental, genetic and racial factors have on BDNF. It has been noted that exposure to sunlight has an effect on BDNF. The number of sunshine hours has been shown to correlate positively with serum BDNF concentration probably due to its effect on non-neuronal sources of BDNF of which the skin is an important source (Erpolat, Celik, & Bozkurt, 2017; Molendijk et al., 2012).

Serum BDNF concentration has been shown to be significantly lower in patients with MDE as compared with age and sex-matched controls. However, we were unable to find any significant correlation between serum BDNF and depression severity using two validated depression rating scales (HAM-D P-value = 0.412 and PHQ-9 P-value = 0.335). There was also no significant difference in the mean serum BDNF concentration in the different depression severity categories using HAM-D (mild, moderate, severe and very severe) P = 0.228. This lack of significance might reflect the spread of depression severity scores as the majority of the study participants had moderate and severe depression and the minority had mild depression.

The lack of significance in the association between serum BDNF and depression severity was also shown by Jevtovic et al. (Jevtović et al., 2011). They studied 139 patients (64females and 75males) with MDD using DSM-IV criteria and rated depression severity with HAM-D. The study participants were free of psychoactive medications for 2 weeks before recruitment into the study. They were unable to find any statistical difference in the mean serum BDNF concentration and the different categories of depression severity (mild, moderately severe and severe) F = 1.896; ρ = 0.168.

Despite finding a negative correlation between serum BDNF and depression severity score in this study, It was not shown to be statistically significant r = −0.096, P = 0.412. This finding is also consistent with the study by Kreinin et al., who had a similar study design (case-control study design, with 51 depressed patients (female to male ratio 2:1), who were physically stable and had been free of psychotropic medication 1 month prior to initiation of therapy). They rated depression severity with HAM-D and measured serum BDNF on the 8th week of antidepressant therapy. They found a weak negative correlation between baseline BDNF concentration and HAM-D scores (Kreinin et al., 2015).

Other studies have been able to show a significant relationship between serum BDNF and depression severity scores. (Shimizu et al., 2003), studied 3 different groups (16 antidepressant naive patients with MDD, 17 antidepressant treated patients with MDD and 50 controls) in a Japanese population. Using HAM-D, they found a significant negative correlation between serum BDNF (using sandwich ELISA method) and depression severity score ($r = -0.35$; ρ value = 0.045). (Karege et al., 2002) using the Montgomery Asberg Rating Scale (MADRS), also found a similar statistically significant negative correlation ($r = -0.55$; ρ value < 0.02). These studies, however, had relatively smaller sample sizes as compared to this present study.

It is, therefore, still debatable if serum BDNF concentration correlates significantly with depression severity at baseline (patients free from all forms of treatment). Despite the similarities in the study design in the different literature reviewed, findings have not been consistent. Further studies are required as well as a systematic review and meta-analysis of available data so as to enable one to take an evidence-based decision on the relationship between serum BDNF and depression severity.

Depression has been shown to be associated with poor medication and treatment plan compliance (DiMatteo, Lepper, & Croghan, 2000; Piccinni et al., 2008). Thirty-six of the 75 study participants met the treatment compliance criteria for a repeat BDNF assay after 8 weeks of treatment. Treatment adherence was assessed through medication counting and review of patients' case files.

Living alone was associated with dropping out of this study (P-value 0.03). Participants who defaulted from the study were observed to have significantly higher serum BDNF levels than participants who were compliant with the study protocol (P-value 0.02), with medium effect size and large confidence interval. This infers that the study defaulters had milder depression severity based on the negative correlation between serum BDNF and depression severity. It is, therefore, possible that the relatively low follow up rate might be due to the diagnosis of MDE being associated with poor drug and treatment follow up, lack of social support seen in people who live alone and milder forms of depression severity. However, the role insight, cultural and religious influences have on follow up rate needs to be ruled out. This was not within the scope of this present study to pursue.

Following 8 weeks of treatment, there was an increase in the mean serum BDNF of the MDE group. The difference in mean serum BDNF pre and post-treatment (Table 2) was found to be statistically significant (P value < 0.01) and had a large effect size (d = 1.24). The mean serum BDNF concentration after 8 weeks of treatment was found to not be significantly different from the mean serum BDNF concentration of the control group at baseline (P = 0.38). This rise in serum BDNF following treatment of depression clearly strengthens the relationship between serum BDNF and presence of MDE as it reflects remission of illness and evidence of recovery. All study participants received a form of treatment however, treatment was not standardized. Despite the varying types of treatment used in this study, there was an associated increase in serum BDNF following 8 weeks of treatment.

Findings from this study are consistent with other clinical studies reviewed. (Gonul et al., 2005) found a significant increase of mean serum BDNF P < 0.001 in patients with MDD after 8 weeks of antidepressant treatment, which no longer differed from the control group. (Aydemir et al., 2005) found a significant increase in mean serum BDNF following 12 weeks of Venlafaxine treatment.

In contradiction, (Piccinni et al., 2008) did not find any significant increase in serum BDNF following 1 year of antidepressant treatment. This study however only followed up 15 drug-free depressed patients for 1 year of antidepressant treatment and had a high dropout rate. A larger sample size might have shown significance.

A meta-analysis of clinical studies has also confirmed the increase in serum BDNF following antidepressant treatment (p = 0.03) (Sen, Duman, & Sanacora, 2008). These studies reviewed sought to find the difference after antidepressant treatment and none looked at the effect of psychological therapy on serum BDNF.

It is evident from this study that SSRI treatment increases serum BDNF (to levels similar to non-depressed population) and it can thus be extrapolated that this increase in serum BDNF reflects increased central nervous system BDNF activity and thus increase in neuronal plasticity, neurogenesis and synaptogenesis. Administration of antidepressants is known to increase extracellular serotonin leading to positive regulation of BDNF transcription with increased pro-BDNF (BDNF precursor) and ultimately to increased central and peripheral BDNF (Martinowich & Lu, 2008). This mechanism of action accounts for the increase in serum BDNF following treatment with SSRI as has been demonstrated in this study.

The findings from this study support the neurotrophin hypothesis of depression and agree with the view that an increase in extracellular serotonin (as would occur upon administration of SSRI) may increase serum BDNF levels.

4.1. Limitations

1 Study design: This study is a single centre hospital-based study and as such, the results cannot be extrapolated to the specified or the general population.
2 Lack of prior research studies on the topic in Nigeria had limitations on the scope of literature reviewed and peculiar problems that could be encountered in our environment. An example is the relatively low follow up rate of this study. Prior research studies might have highlighted this and suggested ways of tackling the problem.
3 Standardized rating scale for medication adherence was not used.

Contributors

Dr. Frances Adiukwu developed the concept for this research, recruited the study participants and wrote up the paper.

Professor Princewill Stanley supervised the research from concept to completion and reviewed the final draft for publication

Professor Jude Ohaeri developed the methods and supervised the research. He worked with Dr. Frances Adiukwu on the statistical analysis of the results and as well as writing up the paper for publication.

Role of funding source

This study was funded by Dr. Adiukwu Frances who is the principle author. No external funding was gotten and thus all aspects of the study in terms of the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication were decided by the authors of this study.

Conflict of interest statement

Adiukwu Frances N. declares no Conflict of interest.
Stanley Princewill C. declares no conflict of interest.
Ohaeri Jude declares no conflict of interest.

Ethical statement

Ethical clearance was given for this study from the ethical and research committee of the University of Port Harcourt Teaching Hospital.

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