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Original Research Article

Post-market monitoring of efficacies and determination of acid-neutralizing capacity of some antacid formulations in Nigeria

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Abstract

Purpose: *To investigate post-market monitoring of the efficacy of antacids in different dosage forms available in Nigeria by evaluating the acid-neutralizing capacities (ANCs) of 28 antacid brands.*
Methods: *The active pharmaceutical ingredients (APIs) were collected and the ANC was determined following the US Pharmacopeia monograph which involved reacting a minimum labeled dose (MLD) of the antacid with hydrochloric acid (HCl) and the excess was neutralized with sodium hydroxide (NaOH). All determinations were made using a pH meter at 37 ± 1 °C.*
Results: *The ANC values of all brands ranged from 2.50 ± 0.23 to 28.10 ± 0.16 mEq/MLD. All the brands except one suspension contained simethicone alone and recorded ANC values above the acceptable limit (5 mEq/MLD). Antacids with aluminium hydroxide and magnesium hydroxide at amounts of ≥ 250 mg per 5 mL or tablet were associated with high ANC values. Antacids containing high amounts of single API such as sodium bicarbonate or calcium carbonate also had high ANC values.*
Conclusion: *The ANC values of all the brands except one suspension (containing simethicone alone) are above the acceptable limit (5 mEq/MLD) and as such should be included on the drug labels.*

Keywords: *Antacids, Post-market monitoring, In vitro efficacy, Acid-neutralizing capacity*

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INTRODUCTION

Post-market monitoring or surveillance of medicines is a requirement aimed at ensuring the quality sustainability of approved medicines once they are available in the market after clinical trials [1]. Seven years ago, the World Health Organization (WHO) approximated that almost 10.5 % of available medicines worldwide are either fake or substandard, and developing and low-income countries have disproportionately higher incidences of these counterfeiting activities [2]. In addition to quality monitoring, post-market surveillance also includes safety monitoring of medicines in circulation, as well as adverse drug reactions [1]. Antacids are bases and over-the-counter drugs that are frequently used for alleviating gastric hyperacidity which causes stomach upset, peptic ulcers, heartburn or gastroesophageal reflux disease (GERD) [3]. The pH of gastric juice (close to 1.5) is stimulated by food ingestion, and this acidic solution is

required for normal function of digestive enzymes as well as the digestion process [4]. Meta-analysis of studies has shown that GERD is one of the most common gastric hyperacidity-related disorders with a significant burden on the quality of life, a prevalence of up to 20 %, and substantial regional and national variations [5]. Antacids are mostly basic compounds which react with excess hydrochloric acid in gastric juice (acid-base reaction) leading to the production of salt and water raising gastric pH above 3.5. They also act by inhibiting pepsin, which is a proteolytic enzyme. Thus, antacids are distinguishable from other formulations through the Preliminary Antacid Test (PAT) procedure in which a given formulation is categorized as an antacid when the pH of the antacid-acid (HCl) solution is higher than 3.5 [6]. Antacids are usually manufactured as combinations of two or three components [7]. Effectiveness of an antacid depends on its acid-neutralizing capacity and duration of action in the stomach. Acid neutralizing capacity (ANC) is an *in vitro* test defined as the ability of an antacid to neutralize gastric acid at a temperature of 37 ± 2 °C and it is measured in milli-equivalents (mEq) per minimum dose of the antacid. Related to ANC is acid neutralization potential (ANP) in which gastric condition is simulated and the pH profile of acid neutralization of the antacid under test is recorded until the pH of the reaction mixture falls below 3.0. [6].The ANP determination provides information on the time duration during which a given sample of antacid maintains a pH above 3.5 [8]. The ANC is one of the most common *in vitro* parameters that reflect the *in vivo* efficacy of antacids and several clinical studies indicate that there is a correlation between the ANCs of antacid formulations and their *in vivo* efficacies [9]. A previous study had indicated that ANC differs significantly among competing antacid brands and it is unfortunately not stated on product labels [10].

Several studies carried out in different countries and diverse regions of the world that examined the *in vitro* efficacies of antacid formulations showed significant efficacy variations [8,10-14]. *In vitro* evaluations of the neutralizing capacities of different brands of antacids marketed in Nigeria have been carried out by different authors. However, most of these studies were on antacid tablets [15,16] while the only study that examined antacid liquid dosage form was carried out over 16 years ago [7]. Routine monitoring of medicines efficacy is important, especially in countries with high prevalence of substandard and counterfeit drugs [2]. This study investigated the effectiveness of different antacid dosage forms (tablets, suspension, effervescent granules) and extra-strength antacids containing single or multiple active ingredients, to update information on post-market monitoring.

EXPERIMENTAL

Drug sample collection

Various brands of different antacid dosage formulations used in this study were purchased from different reputable Pharmacies in different major cities in South-East, Nigeria. The brands were registered in Nigeria by the National Agency for Food Drug Administration and Control (NAFDAC). The brands of the products were substituted with codes and details of drug samples profiles are shown in Table 1, Table 2 and Table 3.

Preparation and standardization of solutions

Preparation and standardization of 1 M HCl solution

To prepare 1 M HCl solution, 84 mL of concentrated HCl (37 % w/v) was transferred into a volumetric flask (1 L) that was half-filled with distilled water. The volume was made up to 1 L with distilled water and the flask was stoppered and shaken. Standardization of the prepared 1 M HCl was performed by using analytical grade Tromethamine (Tris (hydroxymethyl)-amino methane ($HOCH_2)_3CNH_2$). Dried and crushed tromethamine (5 g) was dissolved in 50 mL of distilled water, 2 drops of bromocresol green indicator was added to the tromethamine solution, and titrated with 1 M HCl solution to endpoint which gives a pale yellow colour. Given that the molar mass of tromethamine is 121.14 g/mol, the molarity factor (F) was calculated as ratio of the weight of primary standard used in preparing the solution to the theoretical value of the weight determined from the reaction stoichiometric relationship [17]. Each 121.14 mg of tromethamine is equivalent to 1 mL of 1 M HCl as described in United States Pharmacopeia [18].

Preparation and standardization of 0.5 M NaOH solution

Sodium hydroxide (NaOH) pellets (98 %w/w) weighing 20.40 g were transferred into a beaker and dissolved in 100 mL distilled water. The solution was transferred into a 1 L volumetric flask and allowed to cool.

After making the volume up to 1 L with distilled water, the flask was stoppered and shaken. For standardization of the prepared approximate 0.5

M NaOH, analytical grade benzoic acid (200 mg) was weighed and dissolved in 15 mL of distilled water. Two drops of phenolphthalein (indicator) were added to the solution and titrated with 0.5 M NaOH to the endpoint (permanent pale pink colour). The titration procedure was done in triplicate. Sodium hydroxide reacts with benzoic acid in a 1:1 molar ratio and with the molar mass of benzoic acid as 122.12 g/mole, the molarity factor of NaOH was calculated as described in United States Pharmacopeia. Each 122.12 mg of benzoic acid is equivalent to 1 mL of 1 M NaOH [19].

Table 1: Brands of antacid suspension dosage forms

Brand	Country of origin	Batch No.	Date of manufacture	Expiry date	Listed API (mg/5mL)
SA	Nigeria	AF67204	March 2022	Feb 2025	Aluminium hydroxide (250mg), Magnesium hydroxide (250mg), Simethicone (50mg)
SB	Nigeria	GCS308	May 2022	April 2024	Magnesium trisilicate (250mg), Light Magnesium carbonate (250mg), Sodium Bicarbonate (250mg)
SC	India	2130200	Feb 2022	Jan 2025	Aluminium hydroxide (250mg), Magnesium hydroxide (250mg), Simethicone (50mg)
SD	Nigeria	R12260	June 2022	May 2025	Magnesium Hydroxide (200mg), Aluminium hydroxide (200mg), Simethicone (20mg).
SE	Nigeria	AC99156	Feb 2023	Jan 2025	Magnesium Hydroxide (400mg), Simethicone (40mg)
SF	Nigeria	23104	March 2023	Feb 2026	Magnesium hydroxide (200mg), Aluminium hydroxide 225mg, Simethicone (50mg)
SG	Nigeria	CL007	June 2022	May 2025	Aluminium hydroxide (400mg), Magnesium hydroxide (400mg, Simethicone (40mg)
SH	Nigeria	L3023009	Jan 2023	Dec 2025	Magnesium trisilicate (250mg), Light Magnesium carbonate (250mg), Sodium bicarbonate (250mg)
SI	India	ULS4031	July 2022	June 2024	Alginic acid (200mg), Magnesium trisilicate (200mg), Aluminium hydroxide (25mg), Dimethicone (125mg)
SJ	India	10221937	Aug 2022	July 2025	Aluminium hydroxide (365mg), Magnesium hydroxide (80mg), Simethicone (100 mg), deglycyrrhizinated liquorice 400mg)
SK	Nigeria	TM1100MT	May 2022	April 2024	Magnesium trisilicate (250mg)
SL	Nigeria	NAA8242	April 2023	Mar 2025	Magnesium hydroxide (400mg)
SM	Nigeria	G52201	July 2022	June 2025	Simethicone (200 mg)
SN	Nigeria	22116	May 2022	April 2024	Magnesium trisilicate (250mg)

Table 2: Brands of antacid tablet dosage forms

Brand	Country of origin	Batch number	Date of manufacture	Expiry date	Listed API (mg/tablet)
TA	India	2370863	Feb 2022	Jan 2025	Aluminium hydroxide gel (300 mg), Magnesium aluminium silicate hydrate (50mg), Magnesium hydroxide (25mg), Simethicone (25mg).
TB	Nigeria	L221066	April 2022	Mar 2025	Aluminium hydroxide gel (400mg), Magnesium hydroxide (200mg), Simethicone (25mg).
TC	Nigeria	4504A	Aug 2022	July 2025	Aluminium hydroxide (400mg), Magnesium hydroxide (25mg), Activated simethicone (10mg)
TD	Nigeria	4501	Sept 2021	Aug 2024	Magnesium trisilicate (250mg), Magnesium carbonate (250mg), Sodium carbonate (250mg)
TE	Nigeria	MT5853	Feb 2023	Jan 2026	Magnesium trisilicate (250mg), Dried aluminium hydroxide (120mg).
TF	Nigeria	AD05105	May 2023	April 2026	Aluminium hydroxide (300mg), Magnesium trisilicate (50mg), Magnesium hydroxide (25mg), Simethicone (10mg).
TG	Nigeria	AO334	Feb 23	Jan 2026	Magnesium trisilicate (250mg), Calcium carbonate (200mg)
TH	Nigeria	2E06B2	June 2022	May 2024	Simethicone (200mg)
TI	Nigeria	5504B	Aug 2022	July 2024	Sodium bicarbonate (500mg)
TJ	Nigeria	3502	April 2023	Mar 2026	Calcium carbonate (2500mg)

Table 3: Brands of antacid effervescent (TE) and extra strength (TX) tablet dosage forms

Brand	Country of origin	Batch number	Date of Manufacture	Expiry date	Listed API (mg/tablet)
TEA	Germany	X24KKH	June 2021	Feb 2024	Anhydrous citric acid (1000mg), Aspirin (225mg), Sodium bicarbonate (1916mg)
TEB	Mexico	3F018	Aug 2022	May 2025	Anhydrous citric acid (1000mg), Aspirin (325 mg), Sodium bicarbonate (1916mg)
TXC	Nigeria	A2014	Feb 2021	Dec 2023	Aluminium hydroxide (200mg), Magnesium hydroxide (200mg), Simethicone (25mg)
TXD	UK	ADT630	May 2022	May 2024	Sodium alginate (250 mg), Sodium bicarbonate (106.5 mg), Calcium carbonate (187.5mg)

TEA and TEB are effervescent tablets; TXC and TXD are tablets labeled as extra strength

Evaluation of the ANC of antacid formulations

Liquid samples (Suspensions)

The antacid product equivalent to its minimum labeled dose (10 mL in most cases) was transferred into a 250 mL beaker and distilled water was added to bring the volume to 70 mL. Standardized 1 M (30 mL) HCl was added to the preparation and stirred for 15 min followed by the addition of 2 drops of bromophenol blue indicator. Excess HCl was titrated with 0.5 M NaOH solution until a purple colour was formed and a stable pH of 3.5 was reached. The pH meter (Ocean Star Technologies, Hong Kong) was used to calibrate the pH to 4.0 and 6.86 using the respective buffer powders. Operation of the pH meter at pH 1.0 was checked using 0.1 M HCl. The back titration procedure was done in triplicate [19].

Chewable and non-chewable tablet sample

The sample (not less than 20 tablets) of each antacid tablet was weighed separately for each product and crushed in a mortar. Several crushed tablets equivalent to the minimum labeled dose (mostly 2 tablets) of the antacid were transferred into a 250 mL beaker. This was followed by the addition of 70 mL water and 30 mL standardized 1 M HCl solution and stirred until the crushed tablet completely dissolved. Bromophenol blue indicator (2 drops) was added and excess HCl was titrated with standardized 0.5 M NaOH to a purple colour and a stable pH of 3.5 was reached. The titration procedure was done in triplicate [6,19].

Effervescent products

The minimum labeled dose of each dosage form was transferred to a 250 mL beaker and 10 mL distilled water was added. The solution was stirred until the reaction stopped and 60 mL of water was added. Subsequent steps were as described for the antacid suspension products [6,19].

Calculation of acid neutralization capacity

The ANC is a measure of the amount of acid that is neutralized by an antacid. The United States Pharmacopoeia [19] expresses the acid neutralization capacity test as a back-titration technique using 0.5 N NaOH as titrant to pH 3.5. The number of milliequivalents of acid (HCl 1 N) neutralized by the minimum labeled dosage (MLD) of an antacid was determined. For each of the antacid products, the ANC, measured as the number of mEq of the acid consumed by the antacid, was calculated using Eq 1.

$$\text{Total mEq} = (30 \times N_{HCl}) - (V_{NaOH} \times N_{NaOH}) \quad \ldots (1)$$

Where N_{HCl} = normality of HCl; N_{NaOH} = normality of NaOH; V_{NaOH} = volume of NaOH used for the titration. The results were expressed in terms of mEq of acid consumed per MLD of the tested antacid [19].

Correlation of ANC and total moles of API

The total number of moles was determined by converting the weight of each of the active ingredients in a product into moles (weight in g divided by molecular weight) and summing the moles. The correlation was obtained by plotting the ANC versus total moles of active ingredient in a product.

Statistical analysis

Data on ANC values were analyzed using Microsoft Excel (version 2010). Measurement data were expressed as mean ± standard deviation (SD) and compared using t-test. $P < 0.05$ was considered statistically significant.

RESULTS

Drug sample collection

In this study, a total of fourteen (14) antacid suspensions, ten (10) chewable and non-chewable tablets, two (2) effervescent and two (2) extra-strength tablet dosage forms were analyzed (Table 1, Table 2 and Table 3). These antacids in liquid dosage forms had different organoleptic properties as the colours of the suspensions ranged from white to light pink or pink with a peppermint taste. The tablets also had varied colours such as yellow, green, white or pink and mostly of mint taste.

Acid neutralizing capacity of the formulations

All antacid formulations except SM contain simethicone alone and meet the acceptable ANC limit of 5 mEq per Minimum labeled Dose (Table 4, Table 5 and Table 6).

Correlation of acid neutralizing capacity and total moles of API

To predict the ANC of the brands with known API or combinations, a correlation of the various ANC and the actual content of API was plotted.

Table 4: Acid-neutralizing capacity of various brands of antacid suspension dosage forms

Brand	V_{HCl} (mL)	V_{NaOH} (ml)	ANC/MLD (mEq ± SD)	ANC Status
SA	30	14.87	22.57±0.16	High ANC
SB	30	22.00	19.00±0.22	Intermediate ANC
SC	30	12.50	23.75±0.16	High ANC
SD	30	23.00	18.50±0.23	Intermediate ANC
SE	30	20.00	20.00±0.22	Intermediate ANC
SF	30	16.00	22.00±0.24	Intermediate –High ANC
SG	30	15.50	22.25±0.15	High ANC
SH	30	18.25	20.87±0.24	Intermediate-High ANC
SI	30	24.00	18.00±0.13	Intermediate ANC
SJ	30	18.70	20.64±0.23	Intermediate-High ANC
SK	30	20.50	19.75±0.15	Intermediate ANC
SL	30	5.97	27.02±0.21	High ANC
SM	30	55.00	2.50±0.23	Low ANC
SN	30	20.30	19.85±0.20	Intermediate ANC

Standard deviation of triplicate (SD); the volume of 1 M HCl added (V_{HCl}); the average volume of 0.5 M NaOH that reacted (V_{NaOH})

Table 5: Acid-neutralizing capacity of various brands of antacid tablet dosage forms

Brand	V_{HCl} (mL)	V_{NaOH} (mL)	ANC/MLD (mEq ± SD)	ANC Status
TA	30	18.50	20.75±0.17	Intermediate ANC
TB	30	21.45	19.28±0.22	Intermediate ANC
TC	30	45.47	7.27±0.25	Low ANC
TD	30	17.73	21.14±0.15	Intermediate ANC
TE	30	22.00	19.00±0.24	Intermediate ANC
TF	30	19.60	20.20±0.16	Intermediate ANC
TG	30	31.70	14.42±0.23	Low ANC
TH	30	35.00	10.00±0.21	Low ANC
TI	30	35.00	12.50±0.20	Low ANC
TJ	30	13.50	23.25±0.21	High ANC

Standard deviation of triplicate (SD); the volume of 1 M HCl added (V_{HCl}); the average volume of 0.5 M NaOH that reacted (V_{NaOH})

Table 6: Acid neutralizing capacity of various brands of antacid effervescent (TE) and extra strength (TX) tablet dosage forms

Brand	V_{HCl} (mL)	V_{NaOH} (mL)	ANC/MLD (mEq ± SD)	ANC Status
TEA	30	3.80	28.10±0.16	High ANC
TEB	30	4.40	27.80±0.21	High ANC
TXC	30	13.00	23.50±0.20	High ANC
TXD	30	20.00	20.00±0.17	Intermediate ANC

Standard deviation of triplicate (SD); the volume of 1 M HCl added (V_{HCl}); the average volume of 0.5 M NaOH that reacted (V_{NaOH})

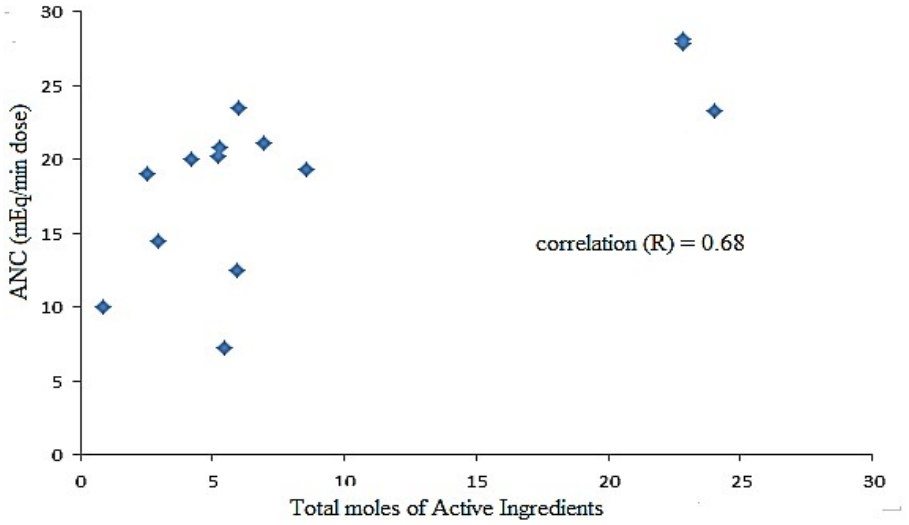

Figure 1: Correlation between total moles of active ingredients and ANC values

The result showed a correlation of 0.68 between total moles of APIs in each antacid tablet formulation with corresponding ANC values (Figure 1). However, a weak correlation of 0.44 was obtained with the liquid antacid formulations for the same parameters.

DISCUSSION

Producers of antacid formulations usually develop products that are appealing to consumers in terms of palatability and other organoleptic characteristics [12]. Majority of antacids containe multiple APIs with only a few containing single API such as SK, SL SM and SN for suspensions and TH, TI and TJ for the tablet formulations. It is known that combination of different APIs in antacids enhances antacid efficacy and reduces side effects [7]. While magnesium antacids cause diarrhea, calcium and aluminum-containing antacids are associated with constipation, but a combination of these antacids minimizes their individual side effects [4]. Some antacids contain simethicone either alone or in combination with other APIs. Unlike the typical antacids that neutralize gastric hyperacidity, simethicone is an anti-flatulent agent that utilizes its antifoaming properties to reduce the gases produced in the GIT by acid neutralization reactions, thereby reducing gastric discomfort [3].

The ANC, which measures the ability of antacids to react with and neutralize gastric acid, is an important parameter for assessing the efficacy of antacids. An official USP monograph for ANC determination was followed in this study [19]. From the results, the antacids were classified according to their ANC values into three groups: (i) those with relatively low ANC values and these were taken as ANCs less than 50 % of the maximum achievable value (< 15 mEq/min labeled dose); (ii) those with intermediate ANC between 50 – 73 % of the maximum achievable value (15.00 - 22.00 mEq/dose); and those with high ANC ≥ 74 % of maximum (22.25 – 28.10 mEq/dose) achievable value [9,19]. Antacids classified as having low ANC values from this study contained either simethicone alone or not more than two antacids with no or low amounts of magnesium hydroxide. On the other hand, antacids with high ANCs contained both $Al(OH)_3$ (≥ 250 mg/5 mL) and $Mg(OH)_2$ (≥ 250 mg/5 mL; eg SA, SC, and SG), or high dose/amount of only $Mg(OH)_2$ (400 mg/5 mL; eg SL) or high dose of only calcium carbonate (2500 mg/tablet; e.g., TJ).

In a previous study, a correlation was observed between ANC values and doses of calcium carbonate in tested antacid products [14]. Also, effervescent antacid formulations containing high amounts of sodium bicarbonate (1916 mg/tablet) exhibited high ANCs (eg TEA and TEB). It is apparent from these results that antacid suspensions or tablet formulations that contained a single API but in high amounts do demonstrate high ANCs, while a combination of both aluminium hydroxide and magnesium hydroxide at amounts of ≥ 250 mg per 5mL or tablet also have high ANCs. Furthermore, those classified as intermediate ANC (15.00 to 22.00 mEq/dose) contained APIs that were in between the low and high ANC classifications in terms of the type and amounts. Thus, these results suggest that it might be possible to predict the range of values of ANC of an antacid by having information on the API contents and combinations. This

assertion is also supported by the modest correlation coefficient of 0.68 observed between total moles of APIs in each antacid tablet formulation and corresponding ANC values. However, a weak correlation coefficient of 0.44 was obtained with the liquid antacid formulations for the same parameters.

It is known that the same quantity of active ingredients but in different dosage forms may result in different ANC values and this is attributed to the difference in excipients used in the preparation [19]. For example, ANC of the suspension formulation containing simethicone alone was significantly different from the tablet containing the same amount of simethicone (SM compared to TH). A combination of aluminium hydroxide and magnesium hydroxide ≥ 250 mg per 5 mL or tablet is important for high ANC values. This observation conforms with reports of several *in vitro* studies that compared ANCs of different formulations containing different APIs. All of these studies reported that formulations having aluminum hydroxide and magnesium hydroxide have high ANCs, and hence are expected to have higher efficacies compared to other antacids [11,17].

Several clinical studies have demonstrated a correlation between the ANCs of antacid formulations and their *in vivo* efficacies. [6,9]. Antacids with high ANCs are the antacids of choice in treating various gastrointestinal problems caused by gastric hyperacidity. Those with low ANC values should be the least preferred antacid formulations but their efficacies are enhanced by taking larger doses of the antacids. Some studies have indicated that the cost of an antacid does not reflect in its quality or efficacy [10]. Based on this, it is recommended that the ANC value of an antacid is quoted on the product label for quality monitoring, post-market surveillance and also monitoring of pharmaceuticals for the safety of medicines in circulation and evaluation of adverse drug reactions.

CONCLUSION

All the antacid brands contain different combinations of APIs and in varying quantities, with majority containing simethicone or dimethicone as an antifoaming agent. The ANC values of all the brands except one suspension (containing simethicone alone) are above the acceptable limit (5 mEq/MLD). Antacids with aluminium hydroxide and magnesium hydroxide ≥ 250 mg per 5 mL are associated with higher ANC values and those with low amounts of magnesium hydroxide, have relatively low ANC values.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Ezeala IC collected the data from the study and wrote the original draft of the manuscript, Nnadi CO analyzed the data, wrote and edited the manuscript, and Onyeji CO conceived, conceptualized, designed the study and proofread the manuscript. All authors read and approved the manuscript for publication.

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