

# The Clinicopathological Evaluations of the Efficacy of Incorporation of Amantadine Hydrochloride in the Treatment of West African Dwarf Goats Experimentally Infected with Peste des Petits Ruminants Virus

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## Abstract

Peste des petits ruminants poses a major threat to the development of small ruminant production. The objective of this study was to determine the comparative efficacy of amantadine hydrochloride (HCl), oxytetracycline long acting (LA) and levamisole in West African dwarf (WAD) goats experimentally infected with PPR. In addition to the presence of the characteristic clinical signs, complement ELISA and haem agglutination inhibition (HI) tests were used to confirm PPR infection in the West African dwarf goats, then treatment was instituted in the different groups namely, group 1 which was treated with amantadine HCl orally, oxytetracycline LA intramuscularly (IM) and levamisole per os. Group 2 was treated with oxytetracycline LA IM and levamisole. Group 3 was treated with levamisole while group 4 served as untreated control. The physiological parameters namely rectal temperature, pulse rate and respiratory rates of the different groups were recorded. The mortality rates in the different treatment groups were also recorded. The respiratory rates of the WAD goats increased as the infection progressed, but the increase was not significant ( $P>0.05$ ). The treatment helped reduce the respiratory rates in the treated WAD. The rectal temperatures of all the animals in the different treatment groups increased only slightly as the infection progressed and was not significant ( $P>0.05$ ). The percentage mortalities were 0% in Group 1, 25% in the Group 2, 50% in the treated group 3 and highest (75%) in the untreated group respectively. In conclusion, incorporation of specific antiviral agents like amantadine hydrochloride in the treatment regimen with oxytetracycline and levamisole particularly during the early stages of the infection can reduce morbidity and mortality of the disease to the barest minimum.

**Keywords:** amantadine HCl; levamisole; mortality; oxytetracycline; peste des petits ruminants

## Introduction

There are limitations of the contribution of small ruminants to household economies and livelihood in 3<sup>rd</sup> world countries due to factors such as infectious diseases, such as peste des petits ruminants (PPR), poor nutrition and marketing systems (Mbyuzi *et al.*, 2014). This disease

PPR is a disease of economic and veterinary importance leading to considerable economic losses (Ugochukwu *et al.*, 2019).

PPR is an increasingly alarming contagious, viral disease (Balamurugan *et al.*, 2014; Khaskheli *et al.*, 2017). It is also a transboundary disease causing important economic losses due high morbidity and mortality, and has therefore been classified among diseases that must be reported to the World Organisation for Animal Health (OIE) (Abubakar

*et al.*, 2011; Odombi *et al.*, 2011; Libeau *et al.*, 2014). It poses a major threat to the development of small ruminant production in all areas where it has been reported, namely Africa, the Middle East and Asia (Diallo, 2006; Chauhan *et al.*, 2009; Baron *et al.*, 2011; Odombi *et al.*, 2011).

PPR mortality rates in affected small ruminant populations may reach 100% whereas rates may be 20% or less in endemic areas (Abu Elzein *et al.*, 1990; Roeder and Obi, 1999). Clinically, PPR is characterized by pyrexia, ulcerative stomatitis; catarrhal inflammation of the ocular and nasal mucosae, bronchopneumonia, and diarrhoea and in many cases could lead to death (Brown *et al.*, 1991; Odombi *et al.*, 2011; Balamurugan *et al.*, 2014; Ugochukwu *et al.*, 2019).

As poor people in developing countries rely on small ruminants, particularly goats, for their livelihoods, it has been suggested that the control of PPR in endemic regions should be reflected in developing poverty alleviation policies (Perry *et al.*, 2002).

There is no specific treatment for peste des petits ruminants; however, drugs that control bacterial and parasitic complications may decrease mortality (Ugochukwu, 1983). Specifically, oxytetracycline and chlortetracycline are recommended to prevent secondary pulmonary infections (Islam *et al.*, 2012). Anene *et al.* (1987) working on the treatment of goats with natural clinical infection with PPR found that despite using three different therapeutic regimens, the response of WAD goats to these treatment formulations was poor. This was attributed in part to failure to institute anti-diarrhoeic drugs (Anene *et al.*, 1987) as recommended and shown by Wosu (1989) and Abubakar and Irfan (2014). However, Adu and Joannis (1985) reported that the use of PPR hyper immune serum in the treatment of animals in the early stages of the infection before the onset of diarrhoea resulted in the protection and recovery of the affected goats. Nevertheless, once diarrhoea has set in, treating with hyper immune serum becomes useless (Taylor, 1979). Levamisole apart from its anthelmintic activity, has been demonstrated to stimulate host defensive mechanism against some infections (Hardman and Limbird, 2001; Undiandeye *et al.*, 2014). It is said to also promote vaccine-therapy particularly in low producing animals. Its immune-potentiating ability is said to be apparently due to its ability to stimulate cell mediated immunity and macrophage function by stimulating T and B cells proliferation and antibodies production (Chukwu, 1987; Hardman and Limbird, 2001). Levamisole is recognized as an immune-potentiator (Taki and Schwartz, 1994).

Since the time of Edward Jenner and Louis Pasteur, vaccines have contributed to prevention, control and even eradication of human and animal diseases more than any other tool available to human or veterinary medicine (Riedel, 2005; Lombard *et al.*, 2007). Classical vaccine technologies, including inactivated and attenuated vaccines, have been used for decades with significant success against a number of viral and bacterial diseases of livestock (FAO, 2011; Meeusen *et al.*, 2007). The use of vaccines in the effective control of PPR has been demonstrated (Ademosun, 1994). However, despite of the strict vaccination programs and other preventive and clinical

measures the PPR outbreaks are frequent (Abubakar *et al.*, 2015a), hence, the need to conduct this study, to determine the comparative efficacy of amantadine hydrochloride, oxytetracycline long acting and levamisole in West African dwarf (WAD) goats suffering from experimental infection with PPR.

## Materials and Methods

### Study area

Nsukka, a town in Nsukka Local Government Area of Enugu State, Nigeria was our study area. Nsukka is situated at latitude 6°51'24"N and longitude 7° 23'45"E. The climate here is tropical. The average temperature in Nsukka is 24.9 °C. The average annual rainfall is 1579 mm (Ugochukwu *et al.*, 2017b).

### Experimental animals

Sixteen WAD goats identified by neck tags consisting of eight males and eight females, whose ages ranged from 6 months to one year and weighing between 4 kg and 6 kg were purchased from Ibagwa-Aka Livestock Market, Igbo Eze South Local Government Area Enugu State, Nigeria and which by clinical and serological examination were confirmed to be negative for natural infection of PPR. They were allowed to stabilize for 7 days in the animal section of the Department of Veterinary Medicine, University of Nigeria, Nsukka. During the period of stabilization, the goats in the treated groups were administered with levamisole at the dose of 10 mg/kg given as a drench stat and oxytetracycline LA 20 mg/kg of body weight intramuscularly as cover against helminth and bacterial infections respectively.

### Experimental infection

The WAD goats after a period of stabilization and acclimatization were experimentally infected by the application of mucopurulent nasal and ocular discharges using cotton wool swabs from goats adjudged and confirmed by haem agglutination inhibition test and complement-ELISA to be suffering from PPR infection; this was done according to standard procedures as described by Nduaka and Ihemelandu (1973). Three to five days after experimental infection, the goats were kept in a common pen and began to show classical clinical signs of PPR.

### Serological diagnosis

Confirmation of PPR serologically in this study was mainly by c-ELISA in which about 5ml of blood was collected from the jugular vein of each animal and emptied into a sterile universal bottle, then placed in a slanting position for the blood to clot at room temperature for 1 hour. The expressed serum was centrifuged at 3000 rpm for 15 minutes at 4 °C and a clear straw coloured serum was collected. PPR c-ELISA kit designed to detect antibodies directed against the nucleoprotein of peste des petits ruminants (PPR) virus, developed by FAO reference laboratory (CIRAD-EMVT, Montpellier, France) was used. Procedure for monoclonal antibody based competitive-ELISA was done according to Singh *et al.* (2004) and haem agglutination inhibition test done

following the standard procedures as described by Ezeibe *et al.* (2003) and Manoharan *et al.* (2005).

#### Study design

After experimental PPR infection in these goats, PPR was confirmed by monoclonal antibody based competitive-ELISA (c-ELISA) and haem agglutination inhibition (HI) tests. The 16 experimentally infected WAD goats were divided into three different chemotherapeutic groups as follows, goats in group 1, consisted of 4 WAD goats suffering from experimental infection of PPR and were treated with amantadine HCl 100 mg bid 5/7 per os by drenching, oxytetracycline LA 20 mg/kg of body weight Intramuscularly (IM) and levamisole 10 mg/kg body weight given as a drench. Group 2 consisted of 4 WAD goats suffering from experimental infection of PPR and were treated with oxytetracycline LA 20 mg/kg of body weight Intramuscularly (IM) and levamisole 10 mg/kg body weight given as a drench stat. Group 3 consisted of 4 WAD goats suffering from experimental infection of PPR and were treated with levamisole 10 mg/kg body weight given as a drench while group 4 consisted of 4 WAD goats suffering from experimental infection of PPR which served as untreated control. The physiological parameters namely rectal temperature, pulse rate and respiratory rates of the different groups were recorded. The mortality rates in the different treatment groups were also recorded.

#### Treatment

Amantadine hydrochloride produced by Auden Mckenzie (Pharma Division) Ltd UK, administered at the dose of 100 mg/kg orally. Oxtetracycline hydrochloride long acting (Pfizer Inc. US (Primamycin/LA) was administered at the dose of 20 mg of the drug per kg of body weight intramuscularly. Levamisole produced by Kahira Pharmaceuticals and Chemical industries Cairo, Egypt and administered at the dose of 10 mg/kg body weight per os.

#### Tissue sample collection, preservation and processing

Samples of the lung and intestines were collected from the experimental animals at post mortem. These samples were fixed in 10% neutral buffered formaldehyde for histopathology tissue processing. These samples were all processed following standard procedures as described by Drury and Wallington (1980).

#### Statistical analysis

Mean values and standard deviation were calculated from the physiological parameters. Data and the results were compared statistically using students' T-test assessing the mutual statistical differences and analysed using Analysis of variance (ANOVA). Significance was accepted at  $P \leq 0.05$ .

#### Results

Clinical signs appeared 5 days post infection affecting respiratory and gastrointestinal systems and the following were observed clinically ante mortem, pyrexia, anorexia, cachexia, starry hair coat, respiratory distress evidenced by coughing, sneezing and mucous to muco-purulent nasooocular discharges as shown in Fig. 1 and diarrhoea (Fig. 2).

Post-mortem findings of the WAD goats that died post infection revealed starry hair coats, ulcerative cheilitis and ulcerative stomatitis as seen in Fig. 3. Predominantly seen were linear discontinuous haemorrhage (zebra stripes) on the mucosa of colon and rectum as shown in Fig. 4, frothy exudates in the respiratory pathways and pneumocongestion, this is shown in Fig. 5. The Histopathological findings include thickening of inter lobular spaces, pneumocongestion in interlobular spaces, infiltration of mononuclear cells into inter-alveolar and interlobular spaces in the lungs (Fig. 6). Fig. 7 shows ulceration of mucosal surface, focal areas of ulceration on the intestinal villi, haemorrhage on the lamina propria of the intestines. The result of the findings in these experiments involving the incorporation of Amantadine hydrochloride in the treatment regimen of PPR is presented in Tables 1 and 2.

The respiratory rates of the WAD goats as shown in Table 1 increased as the infection progressed, but the increase was not significant ( $P > 0.05$ ). However, it would appear that the treatment helped reduce the respiratory rates in the treated WAD to a physiological normal level. The rectal temperatures of all the animals in the different treatment groups increased only slightly as the infection progressed and was not significant ( $P > 0.05$ ). These are shown in Table 1.

The total percentage survival was 68.75% of all the animals in the 4 groups after day 27 of the experiment. The total percentage mortality in all the treatment groups was 31.25% indicating a reduced mortality pattern (Table 2). It is interesting to note that the percentage mortalities were 0% in group 1 and 25% in the group 2, 50% in the group 3 and highest (75%) in the untreated group. Goats in group 1 as shown in Fig. 8 showed recovery from some of the typical clinical manifestations of peste des petits ruminants.



Fig. 1. A WAD goat suffering from PPR showing mucopurulent ocular discharges



Fig. 2 Perineal region of a WAD goat suffering from PPR showing profuse watery diarrhoea



Fig. 3. Arrow pointing at the ulceration on the upper hard palate of a WAD goat suffering from PPR

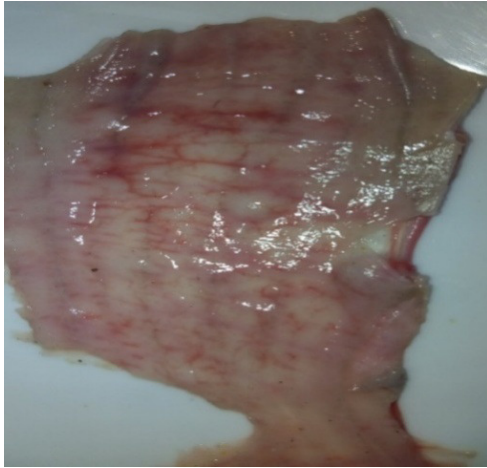


Fig. 4. Intestinal section showing linear discontinuous areas of haemorrhage (Zebra stripes)

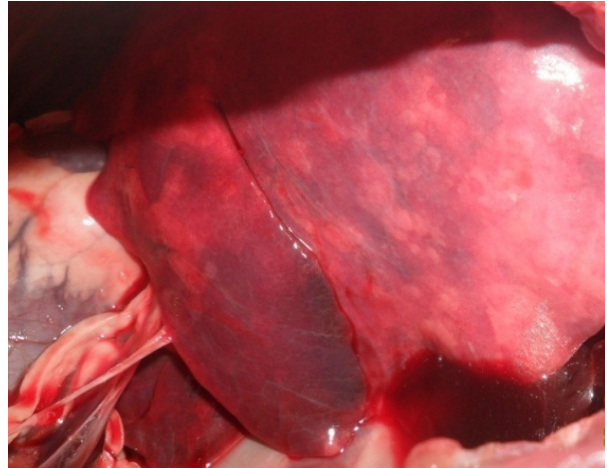


Fig. 5. Left lung showing congestion in a WAD goat suffering from PPR

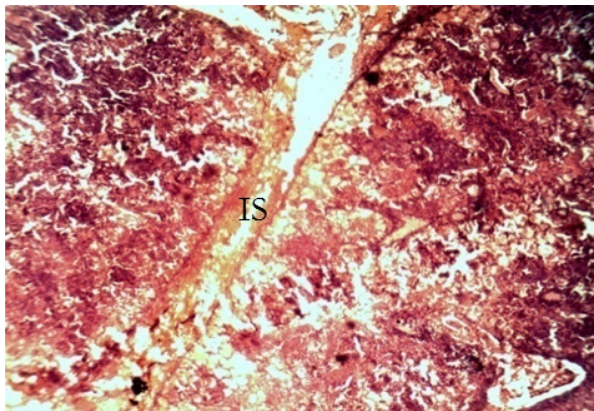


Fig. 6. Thickening of inter lobular spaces (IS) of the lungs, arrow pointing at pulmonary congestion in interlobular spaces, infiltration of mononuclear cells into inter-alveolar and interlobular spaces X 100 H&E

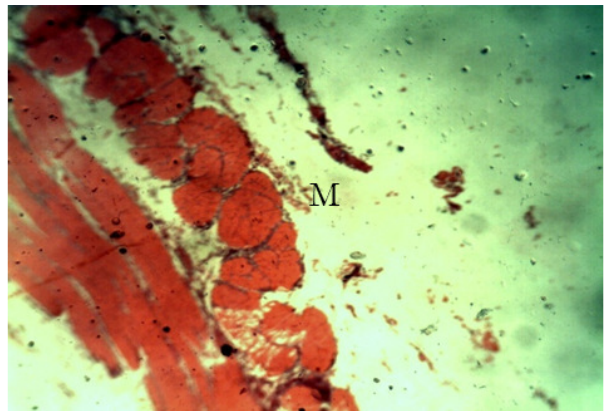


Fig. 7. Ulceration of mucosal (M) surface of the intestines X 100 H&E

Table 1. Physiological parameters of West African dwarf goats under different treatment combinations

Group ID Tag	Temperature °C (respiratory rate/min)										Mean±SD
	1 (PI)	3 (PI)	5 (PI)	7 (PI)	9 (PI)	11 (PI)	13 (PI)	15 (PI)	17 (PI)	20 (PI)	
Gr. 1 IDT 4 (Male)	37.9 (32)	38.2 (32)	37.8 (36)	38.8 (28)	37.4 (28)	38.8 (30)	38.8 (30)	39 (30)	39 (30)	39 (32)	38.57±0.18 (30.80±0.74)
Gr. 1 IDT 5 (Male)	38.9 (30)	37.7 (24)	37.7 (24)	37.7 (28)	36.2 (24)	38.4 (30)	38.5 (30)	39 (32)	38.5 (30)	39 (30)	38.14±0.28 (30.00±0.99)
Gr. 1 IDT 6 (Female)	39.3 (36)	39.3 (36)	38.8 (32)	38.6 (36)	37.5 (24)	39.5 (30)	39.5 (30)	40 (30)	39 (32)	39.5 (32)	39.10±0.22 (31.80±1.17)
Gr. 1 IDT 11 (Female)	38.1 (28)	37.8 (34)	38.8 (32)	39 (36)	36 (28)	38.3 (32)	38.5 (30)	39 (30)	39.5 (32)	40 (30)	38.50±0.35 (31.20±0.80)
Gr. 2 IDT 3 (Male)	37.7 (28)	37.7 (34)	38.4 (24)	37 (40)	38.1 (32)	38.5 (30)	39 (30)	39 (30)	39 (30)	39.5 (32)	38.37±0.24 (31.00±1.31)
Gr. 2 IDT 8 (Female)	38.5 (38)	37.5 (28)	38.7 (28)	39 (32)	37.2 (28)	28 (30)	38.5 (30)	39 (30)	39 (30)	39.5 (32)	38.49±0.23 (29.40±0.60)
Gr. 2 IDT 12 (Male)	38.7 (36)	28 (32)	37 (28)	38 (34)	37 (40)	37.5 (34)	38 (32)	38.5 (32)	dead (0)	0 (0)	30.27±5.05 (33.25±1.25)
Gr. 2 IDT 14 (Female)	38.8 (28)	37.8 (40)	40 (36)	40.4 (34)	38 (28)	39 (34)	39 (28)	39 (30)	39 (30)	39 (30)	38.85±0.25 (33.40±1.37)
Gr. 3 IDT 2 (Female)	38.6 (32)	38.2 (32)	38.3 (28)	39.4 (36)	38.1 (32)	38 (26)	38.5 (28)	39 (30)	39 (32)	39 (32)	38.61±0.15 (30.80±0.90)
Gr. 3 IDT 9 (Male)	38 (28)	38.9 (48)	38.4 (40)	40.6 (40)	39 (24)	dead (0)	0 (0)	0 (0)	0 (0)	0 (0)	19.46±6.50 (36±4.38)
Gr. 3 IDT 15 (Female)	38.1 (32)	37.2 (36)	38.9 (28)	39.5 (32)	38.2 (28)	38 (34)	39 (30)	39 (28)	39.5 (30)	39 (32)	38.56±0.24 (30.60±0.97)
Gr. 3 IDT 16 (Male)	38.7 (32)	38.8 (36)	38.8 (32)	39.4 (40)	38.4 (28)	38.4 (30)	39 (30)	39.5 (28)	39 (30)	39.5 (30)	38.95±0.13 (31.60±1.19)
Gr. 4 IDT 1 (Male)	37.1 (28)	38.4 (36)	38.5 (28)	38.8 (32)	39.7 (37)	37.8 (40)	38 (38)	38 (36)	39 (36)	39.5 (34)	38.48±0.25 (34.50±1.28)
Gr. 4 IDT 7 (Female)	37.9 (36)	37.6 (36)	37.8 (38)	dead (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11.33±5.77 (35.33±0.67)
Gr. 4 IDT 8 (Female)	38.5 (38)	37.5 (28)	38.7 (28)	39 (32)	37.2 (28)	28 (30)	38.5 (30)	39 (30)	39 (30)	39.5 (32)	38.49±0.23 (29.40±0.60)
Gr. 4 IDT 13 (Male)	38.1 (32)	37.3 (28)	39.5 (40.4)	37.6 (28)	36.2 (36)	37 (32)	38 (32)	39 (30)	39 (30)	39 (30)	38.07±0.34 (31.80±1.17)
Mean±SD °C (min)	38.33±0.14 (31.13±0.88)	38.05±0.15 (34.50±1.40)	38.31±0.15 (31.88±1.24)	38.86±0.26 (33.33±1.15)	37.59±0.27 (31±1.22)	38.13±0.19 (31.14±0.83)	38.59±0.13 (30.57±0.71)	39.00±0.12 (30.43±0.52)	39.04±0.07 (31.38±0.47)	39.31±0.09 (31.38±0.25)	

PI-Post Infection; IDT-Identity Tag; SD- Standard Deviation

Table 2. Morbidity and mortality pattern in different treatment combinations

Groups	Neck tag no	Sex	%Morbidity	%Mortality
Group 1	4	Male	100%	0%
	5	Male		
	6	Female		
	11	Female		
Group 2	3	Male	100%	25%
	8	Female		
	(12)	Male		
Group 3	14	Female	100%	50%
	(2)	Female		
	(9)	Male		
	15	Female		
Group 4	16	Male	100%	75%
	1	Male		
	(7)	Female		
	(8)	Female		
	(13)	Male		

Note Numbers in circle died before day 27 of the experiment.

## Discussion

The clinical manifestations of PPR observed in this study agree with the findings in previous studies by Jalees *et al.* (2013), Pope *et al.* (2013), Balamurugan *et al.* (2014), Das *et al.* (2015).

The physiological parameters namely temperature, respiratory rates and pulse rates were higher in untreated infected WAD goats (group 4) when compared with those in group 1, 2 and 3 which were treated, this agrees with the findings of previous researchers like Tariq and Shahzad (2013); Mahmud and Galbat (2017) and Meher *et al.* (2017).

The slight increase in the respiratory rate could be due to pulmonary involvement, which is a constant feature of peste des petits ruminants, this is due to the fact that PPR virus induced immune-suppression predisposes to secondary bacterial infections, where pneumonia is the most frequently observed bacterial complication in peste des petits ruminants virus (PPRV) infected animals (Chauhan *et al.*, 2009; Abubakar *et al.*, 2015b).

Same for the mortality in the untreated group, it was higher than what was recorded for the treated groups. This finding agrees with findings of Diallo *et al.* (2006), Abubakar *et al.* (2011) and Mahajan *et al.* (2012).

The morbidity pattern in all the treatment groups was 100%, the percentage mortality was 0% in group 1. This experiment showed that the incorporation of the antiviral agent, amantadine HCL reduced the mortality to zero. Amantadine HCL also known as Symmetrel, is a recognized antiviral agent against paramyxoviruses. It acts by interfering with viral penetration, uncoating and assembly (Saliki, 1998). It has been effectively used in treating human influenza (Allen *et al.*, 2006).

Narayanan *et al.* (2008), treated clinical cases of PPR were treated with broad-spectrum antibiotics. The findings of this present study supports the argument that incorporation of oxytetracycline into the treatment regime of PPR can be effective in combating secondary bacterial infection in PPR infection (Ugochukwu *et al.*, 2017a).

Levamisole incorporated into the treatment regimen in WAD goats in group 1, 2 and 3 and as evidently shown in the findings from animals in group 3, helped reduce mortality and morbidity because of its role as an anthelmintic and immune-potentiator and should be considered in the treatment regimen in PPR infection.

## Conclusions

In conclusion, in areas that cannot be effectively covered by vaccination especially, where there is an outbreak of the deadly disease, incorporation of specific antiviral agents like amantadine hydrochloride in the treatment regimen with oxytetracycline and levamisole as observed in chemotherapeutic group 1, particularly during the early stages of the infection when they provide a good curative option that can reduce morbidity and mortality of the disease to the barest minimum. Further work is envisaged to assess fully the possible immune-potentiating ability of levamisole in the management of PPR. Based on the results of this experiment, amantadine hydrochloride, an antiviral

agent against paramyxoviruses is recommended in combination with long acting oxytetracycline and levamisole in the chemotherapy of peste des petits ruminants not only to reduce the morbidity but also the mortality in natural infections of PPR.

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## Ethical Considerations

The ethical conditions governing the use and conduct of experiments with live animals were strictly observed by Ward and Elsea (1997) and the experimental protocol was approved by the Senate committee on Medical and Research ethics, University of Nigeria, Nsukka.

## Authors' Contributions

E.I. Ugochukwu conceived the idea, E.I. Ugochukwu, I.C. Ugochukwu and C.F. Ikem carried out the research, and I.C. Ugochukwu, J.N. Omeke and I.C. Aneke wrote the manuscript while N.A. Sani, N.T. Emejuo and I.S. Idoko did the statistical analysis and also made immense intellectual contribution to this research. All authors read and approved the manuscript for submission.

## Conflict of Interest

The authors declare that there are no conflicts of interest related to this article.

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