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ORIGINAL ARTICLE

EVALUATION OF PREOPERATIVE GABAPENTIN ON CARDIOPULMONARY PARAMETERS AND POSTOPERATIVE PAIN IN DOGS UNDERGOING ELECTIVE OVARIOHYSTERECTOMY

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Ethical considerations: When reporting experiments on animals Observation of the ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, published on July 14, 2020 (DOI: 10.1371/journal.pbio.3000410), is applied. The authors ensure that all procedures were performed in compliance with the guidelines for animal care of their institutions or with national/international guidelines.

ABSTRACT

This study evaluated the efficacy and safety of oral gabapentin for perioperative pain control in dogs undergoing ovariohysterectomy (OVH). Ten female dogs were randomly assigned into two groups, and standard OVH was performed following anaesthesia with propofol injection (4 mg/kg). The treatment group was premedicated with 20 mg/kg oral gabapentin 8 hours before anaesthesia induction, while control dogs were administered a placebo. Adverse events associated with gabapentin were noted as they occurred. Changes in physiological and cardiopulmonary parameters were determined at 10-minutes intervals until recovery from anaesthesia. Pain severity was assessed using GCMPS-SF pain scales upon recovery from anaesthesia (time = 0) and at 12-hours intervals over 48 hours by independent observers. Physiological parameters and GCMPS-SF scores were compared using ANOVA. Diarrhoea (1/5) and swollen salivary glands (1/5) were the only adverse events associated with gabapentin administration. The rectal temperature, heart rate and pulse rate were not significantly ($p = 0.47$) different between the two groups. The postoperative pain score as well as respiratory rate and mean arterial pressure were significantly ($p < 0.05$) lower in gabapentin group. Premedication with gabapentin is safe and decreased postoperative pain scores in dogs presented for elective neutering.

Keywords: dogs; gabapentin; ovariohysterectomy; preoperative; pain

INTRODUCTION

Management of pain in animals is an essential welfare and ethical aspect of veterinary medicine. Perioperative pain can impact the well-being of the veterinary patient, while untreated acute pain can result in the development of maladaptive pain states [1]. Postoperative pain is associated with tissue damage and occurs as a result of activation of peripheral nociceptors or inflammation. Acute pain is traditionally managed using opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and local anaesthetics [2]. In spite of the effectiveness of opioid analgesic drugs in the treatment of acute pain, usage is limited because of attendant adverse effects [3]. The recent opioid epidemics in the USA and some other countries have also contributed to the poor availability of opioid analgesics for veterinary use. On the other hand, NSAID administrations are associated with gastrointestinal, hepatic, and renal toxicities in spite of their effectiveness in the control of mild to moderate nociceptive pain [2].

Xylazine is an alpha-2-adrenoreceptor agonist with analgesic and muscle relaxation properties commonly used as pre-anaesthetic and also for the control of acute pain in veterinary practice [4]. Incidence of xylazine involvement in drug-related human deaths in the US and other parts of the world has been on the increase in the last five years [5, 6]. This abuse might probably be responsible for the scarcity of xylazine, with concern that the drug may not be readily available for veterinary use, thus necessitating the need for alternative safe and effective drugs that can be used in the control of perioperative pain.

Gabapentin is a structural analogue of gamma-aminobutyric acid, formulated for treatment of convulsion and neuropathic pain [7]. The mechanism of action of gabapentin has been postulated to involve voltage-gated calcium channels binding to the alpha-2-delta subunit [8, 9]. Several clinical trials and meta-analyses showed that administration of gabapentin improves postoperative pain associated with abdominal hysterectomy and mastectomy in humans [10]. These findings led to the growing interest in the use of gabapentin for control of perioperative pain in veterinary medicine.

In veterinary medicine, gabapentin has gained popularity not only for control of acute and chronic pain but also to provide patient comfort by reducing fear and stress during transport and/or hospitalization [11]. Two recent surveys have shown widespread use of gabapentin for acute and chronic pain in veterinary medicine [7, 12] despite insufficient evidence available to support efficacy. In dogs, gabapentin has been used for postoperative pain control in dogs undergoing mastectomy with a significant reduction in the incidence of rescue medication [13]. Furthermore, the drug has been shown to decrease the isoflurane Minimum Alveolar Concentration (MAC) [14]. Pre-anesthetic oral administration of gabapentin has also been reported to prevent a rise in intraocular pressure following intubation in dogs [15].

There is a dearth of reports on the effectiveness of gabapentin for perioperative pain control in dogs undergoing reproductive surgery. A study in cats subjected to ovariohysterectomy (OVH) reported that preoperative administration of oral gabapentin significantly improved analgesia and mechanical nociception threshold [16]. With this promising efficacy result, there is the need for more clinical trials to validate the analgesic potentials of gabapentin in dogs undergoing reproductive surgery. This study evaluated the safety and efficacy of gabapentin in dogs subjected to elective OVH.

MATERIALS AND METHODS

Animals

Ten intact mongrel dogs between 4 and 6 months of age with a mean weight of 7.63 ± 0.63 kg were used. They were sourced from households around the university and housed at the Veterinary Teaching Hospital throughout the duration of the experiment. The dogs were fed on dog rations twice daily, while water was provided ad libitum. Prior to the commencement of the study, the dogs were acclimatized to their environment and the handlers for a minimum period of four weeks to get the dogs used to the new environment. During this period, they were dewormed with a broad-spectrum dewormer (Prazi-wormer, Barry Vet Animal Health, Nigeria). Ethical approval (FUNAAB/COLVET/CREC/2024/03/05) was received from COLVET Research and Ethics Committee (CREC), Federal University of Agriculture, Abeokuta.

Study Design

The study involved simple randomized design. Ten dogs were assigned randomly to two groups. The first

group (Gabapentin group) consisted of five dogs premedicated with oral gabapentin (Gabapentin-Teva^{R}, Teva Pharmaceuticals CR, Praha, Czech Republic) at 20 mg/kg eight hours before the start of OVH. The second group (Control group) consisted of five dogs administered a placebo as premedication eight hours before the start of OVH. The observers were unaware of the type of premedication received by each dog.

Anaesthetic Procedure

One hour prior to the start of OVH, each dog was treated with tramadol hydrochloride (Tramadol^{R}, Gland Pharmaceuticals, India) intravenously at the rate of 3 mg/kg body weight. After aseptic preparation of the surgical site, venous access was secured using the cephalic vein. Anaesthesia was induced using 1% propofol (Hyprovan 200®, Celon Laboratories PVT LTD, Telangana, India), administered intravenously at 4 mg/kg body weight. Venous access was maintained using normal saline infusion at the rate of 5 ml/kg/hr. Anaesthesia was maintained using a continuous rate infusion of tramadol (2.6 mg/kg/hr.) and propofol (1 mg/kg/hr.).

Once, the dogs were anaesthetized, they were positioned in dorsal recumbency and draped appropriately. Thereafter, a 2% lignocaine injection (Lignovit 20-AH^{R}, Vital Healthcare PVT LTD, Nashik, India) was infiltrated on the *linea alba* at the rate of 2mg/kg and laparotomy incision was made. This stage was followed by OVH using standard technique. Before closure of the laparotomy incision, 2% lignocaine was administered intraperitoneally, and the incision was closed routinely. The dogs were monitored until recovery and kept in individual cages within the recovery room for commencement of pain assessment.

Outcome Measurement

Rectal temperatures (RT), respiratory rates (RR), heart rates (HR), pulse rates (PR), and blood pressure of the dogs were determined following loss of righting reflex and every ten-minute interval until the end of OVH. RT was measured using a digital thermometer, while RR was counted manually from abdominal excursion. The HR was measured in beats per minute by auscultation of the heart with a stethoscope, while PR was counted in beats/min by applying digital pressure on the femoral artery. The blood pressures parameters including Sytolic Arterial Pressure (SAP), Mean Arterial Pressure (MAP), and Diastolic Arterial Pressure (DAP) were obtained through a non-invasive oscillometric blood pressure device.

Adverse Effects of Gabapentin

Each dog was monitored for adverse effects associated with gabapentin usage before, during, and after OVH. An adverse effect was defined as any undesirable change that occurred following gabapentin usage, whether considered or not considered to its use. Reported adverse reactions of gabapentin, such as sedation, depression, lethargy, incoordination, vomition and diarrhoea were looked out for. Sedation was considered as adverse effect if it became prolonged after OVH.

Postoperative Pain Assessment

The Glasgow Composite Pain Scale short form (GCMPS-SF) was used for pain assessment post OVH. Rescue analgesia (tramadol injection administered through the intramuscular route) was provided if GCMPS-SF scores were $\geq 6/20$. For postoperative pain assessment, the dogs were evaluated inside their cages without being disturbed. Assessment was done after recovery from anaesthesia and every 12 hours up to 48 hours post OVH.

Statistical Analysis

Data were tested for normality using a Shapiro-Wilk test. Physiological parameters and GCMPS-SF scores were compared using analysis of variance (ANOVA) for repeated measures at $p \leq 0.05$. Data analysis was performed using SPSS Statistics (V25, IBM, Armonk, NY, USA).

RESULTS

The adverse events reported in this study include vomition, diarrhoea and swollen salivary glands (Table 1). Vomition was observed in one (1) of the dogs in the control group, while diarrhoea was observed in one (1) of the dogs in the gabapentin group. The vomition was observed once and occurred before induction of anaesthesia, while the

diarrhoea occurred once after recovery from anaesthesia. In addition, one dog each from the gabapentin and control groups had swollen salivary glands. The swollen salivary glands were observed 12 hours post-surgery. All the adverse events observed resolved spontaneously without any medical intervention.

Table 1. Adverse events associated with oral administration of gabapentin in dogs undergoing elective OVH

Adverse Effects	Control Group	Gabapentin Group
Sedation	+(0/5)	+(0/5)
Depression	+(0/5)	+(0/5)
Lethargy	+(0/5)	+(0/5)
Incoordination	+(0/5)	+(0/5)
Vomition	+(1/5)	+(0/5)
Diarrhoea	+(0/5)	+(1/5)
Swollen salivary gland	+(1/5)	+(1/5)

Number of dogs in parentheses + = Present

The rectal temperature of the dogs decreased progressively throughout the surgery (Fig. 1). The rectal temperature did not differ significantly ($p > 0.05$) between gabapentin premedicated dogs and the control except at 70 minutes from commencement of anaesthesia when the rectal temperature was significantly ($p < 0.05$) higher in the gabapentin premedicated dogs than the control dogs (Fig. 1).

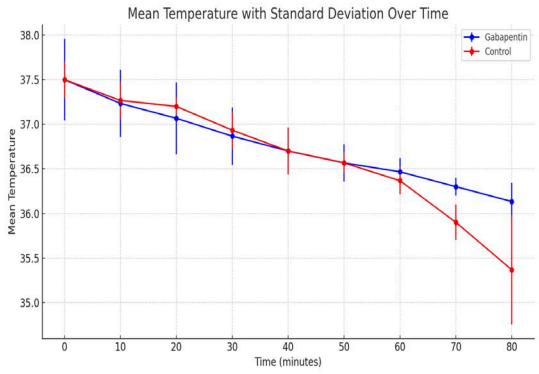

Fig. 1. Rectal temperature of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

Changes in respiratory rates of dogs undergoing elective OVH following premedication with oral gabapentin or placebo is shown in Fig. 2. The respiratory rates in gabapentin premedicated dogs increased progressively throughout the duration of the surgery, while the respiratory rates of control dogs decreased progressively through the duration of the surgery. The respiratory rates were significantly ($p < 0.05$) lower in the gabapentin premedicated dogs up to 60 minutes of the surgery compared with the control dogs (Fig. 2). The heart rates of the dogs increased progressively throughout the surgery (Fig. 3). The heart rates did not differ significantly ($p > 0.05$) between gabapentin premedicated dogs and the control dogs throughout duration of the surgery. The pulse rates of the dogs increased progressively throughout the surgery (Fig. 4). The pulse rates did not differ significantly ($p > 0.05$) between gabapentin premedicated dogs and the control dogs throughout the duration of the surgery.

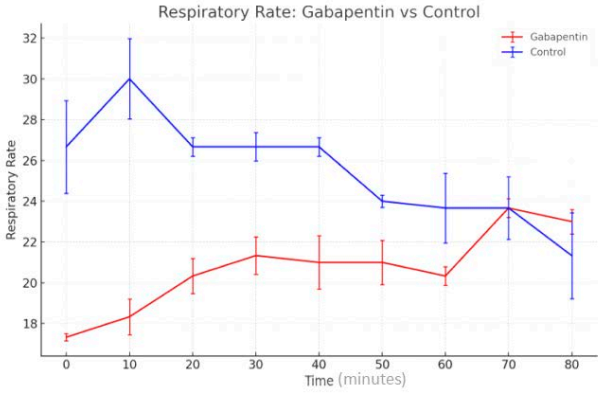

Fig. 2. Respiratory rates of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

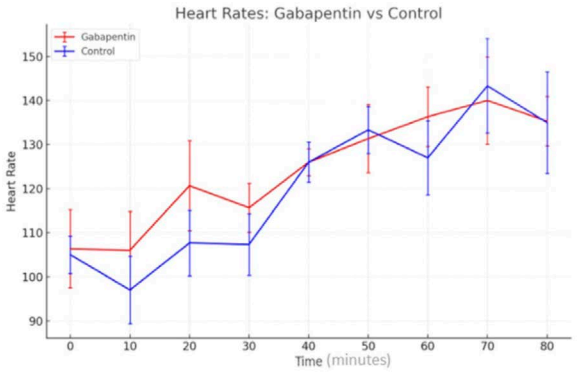

Fig. 3. Heart rates of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

The systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) of dogs undergoing OVH and premedicated with either gabapentin or placebo are shown in figure 5a–c. The SAP, DAP, and MAP were significantly ($p < 0.05$) lower at 50- and

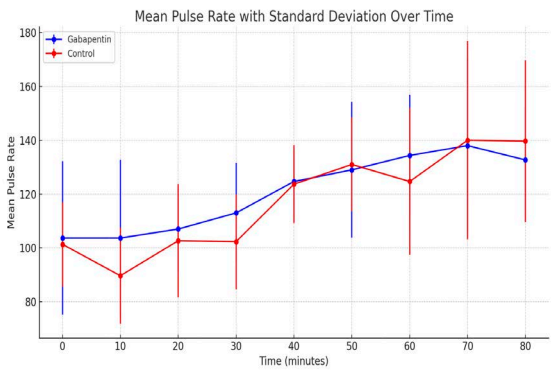

Fig. 4. Pulse rates of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

60-minutes period of the OVH in gabapentin premedicated dogs than in the control dogs.

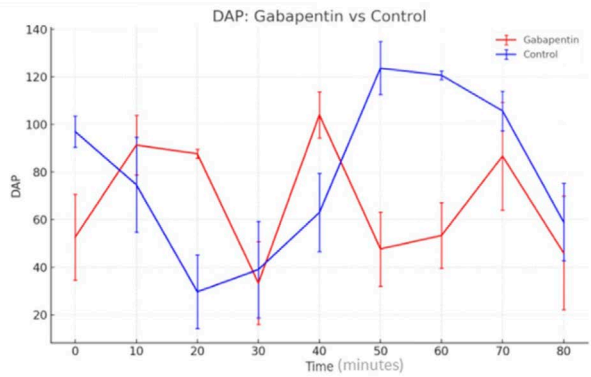

Fig. 5a. Diastolic blood pressure of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

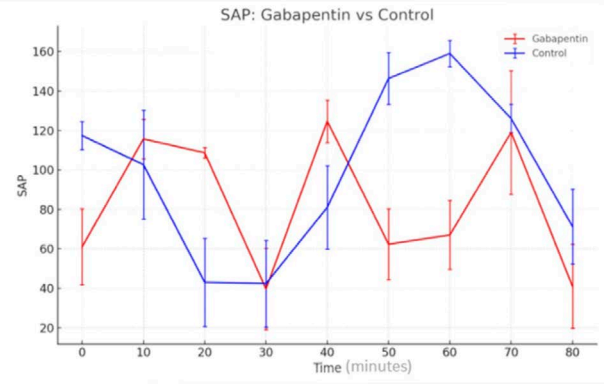

Fig. 5b. Systolic blood pressure of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

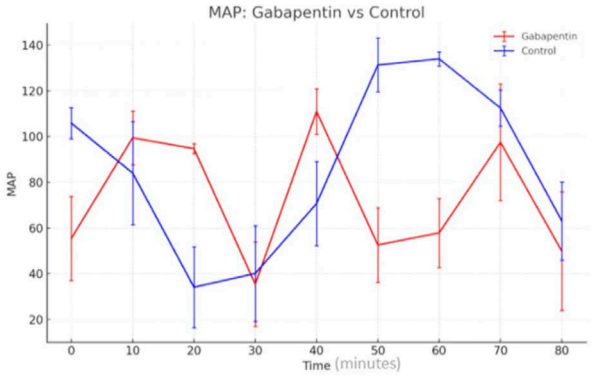

Fig. 5c. Mean arterial pressure of dogs undergoing elective OVH following premedication with either gabapentin (20 mg/kg PO) or placebo (control group) and anaesthetized with propofol (4 mg/kg IV)

The result of the postoperative pain score using the Glasgow Composite Pain Measure (GCMPS-SF) scale in dogs subjected to OVH is shown in Fig 6. The maximum pain score was 4, while the minimum pain score was 1. The pain score was significantly lower ($p < 0.05$) in dogs premedicated with gabapentin than in control dogs. Thereafter, there was no significant difference ($p > 0.05$) in the pain scores between dogs premedicated with gabapentin and the control group.

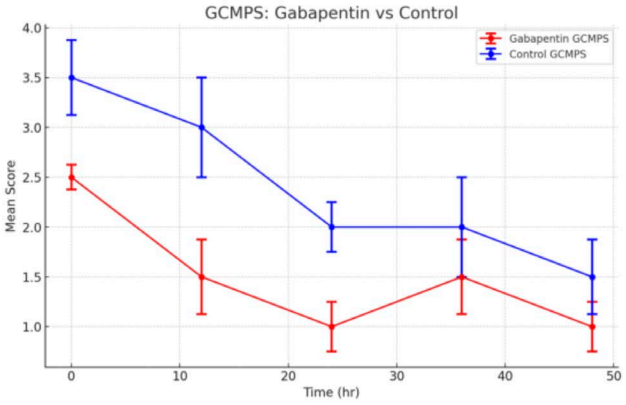

Fig. 6. Pain assessment scores of dogs subjected to elective OVH using the Glasgow Composite Pain Measure (GCMPS-SF) scale. Dogs were premedicated with either gabapentin (20 mg/kg PO) or placebo and anaesthetized with propofol (4 mg/kg IV).

DISCUSSION

The result of this study showed that preoperative administration of gabapentin in dogs undergoing elective OVH is characterized by minimal adverse events that require no medical intervention. In addition, premedication with oral tramadol did not significantly alter RT, HR, or

PR in dogs undergoing elective OVH. However, oral gabapentin significantly lowers respiratory rates and alters the blood pressures in dogs undergoing elective OVH. In addition, premedication with oral gabapentin in dogs undergoing OVH is associated with better postoperative pain scores compared with placebo.

Premedication with oral gabapentin was associated with fewer and milder adverse events that required no intervention. In a previous study involving evaluation of gabapentin and topiramate in dogs with Chiari-like malformation [17], oral gabapentin administration was reported to be associated with adverse events such as vomition, diarrhoea, sedation and polyphagia. None of the dogs in this current study were observed with prolonged sedation following recovery from anaesthesia and this may be related to the time of administration to the dog. In a similar study in healthy cats, sedation or other gabapentin-related adverse effects were not observed [18]. One dog each from the gabapentin premedicated and placebo groups was observed with a swollen salivary gland. The exact cause of this symptom is unknown and might be unrelated to the use of gabapentin since the same sign was also observed in the control groups. These findings suggested that premedication with oral gabapentin is safe in dogs.

The rectal temperatures of the dogs in this study progressively decreased throughout the duration of the surgery irrespective of the premedication type. This progressive decrease in rectal temperature might be associated with the surgery rather than the administration of gabapentin. A previous report in cats showed that gabapentin administration did not alter rectal temperature in cats [19]. Perioperative hypothermia is a common complication associated with anaesthesia and surgery and is being linked to redistribution of body heat and decreased metabolism [20]. Thus, it is logical to conclude that the progressive decrease in rectal temperature in the dogs is associated with the OVH. This explains why temperature control mechanisms such as the use of circulating hot water blankets should be used in dogs undergoing major surgeries.

Respiratory rates of dogs premedicated with oral gabapentin were significantly higher than the control dogs. This may be due to the anxiolytic effect of gabapentin. Stress, whether physiologic or surgical has been reported to increase sympathetic discharge with release of epinephrine, norepinephrine, and cortisol, resulting in elevation of respiratory rate and blood pressure [21].

In this study, the heart and pulse rates of dogs undergoing elective OVH and premedicated with either gabapentin or placebo increased progressively throughout the surgery. This progressive increase in heart and pulse rates might be associated with surgical stimulations rather than the type of premedication. Surgical stimulation has been reported to influence autonomic reflex regulation depending on the anaesthesia type [22]. Lack of changes in the heart rates between gabapentin premedicated and the control dogs suggests that oral gabapentin does not result in any significant change in haemodynamics as previously reported in cats [21].

Premedication with oral gabapentin has been reported to decrease intraocular pressure in dogs anaesthetized with propofol [15]. A similar blood pressure lowering effect was reported in cats receiving oral gabapentin [23]. The DBP, SBP, and MAP were significantly lower at 50 and 60 minutes during OVH in dogs premedicated with gabapentin. These findings may be associated with the inhibitory effect of gabapentin on membrane voltage-gated calcium channels [11].

Premedication with oral gabapentin in dogs undergoing OVH resulted in decreased postoperative pain scores compared to control dogs. This result is contrary to that reported in cats undergoing OVH, where premedication with gabapentin did not influence pain score [18]. Analgesic activities of gabapentin may be related to its anxiolytic effect, which mitigates pain experience or expression in the young dogs. The disparity in the results of this current study and the previous study might be related to the type of anaesthetic drugs used and the method of assessment of postoperative pain. In this study, the dogs were anaesthetized with propofol, an alkyl phenol hypnotic drug with an absence of analgesia [24], and tramadol, a weak mu opioid analgesic [25].

There are few limitations that should be taken into consideration when interpreting the result of this study. The sample size in this study is small when compared with similar studies. The relatively small sample size might have accounted for the large standard deviation obtained in the pain assessment score. The relatively young age of the dog might have influenced the pain correlates assessed by the pain scale. In addition, pain was assessed by final-year veterinary students who might not be experienced in recognizing the correlates for appropriate pain recognition. However, the observers were trained for two weeks before commencement of the study.

CONCLUSION

Premedication with oral gabapentin in healthy dogs undergoing elective OVH is relatively safe and did not alter the physiological parameters of the dogs. In addition, oral gabapentin decreased postoperative pain scores in dogs undergoing elective OVH. It is recommended that oral gabapentin can be used as a component of multimodal analgesic agents for surgical procedures of healthy dogs in poor resource settings where access to true opioid analgesics is difficult or in cases where non-steroidal anti-inflammatory drugs are contraindicated due to safety reasons.

Data Availability Statement

The raw data of this study will be made available by the authors upon request to the corresponding author.

Ethical Statement

Ethical approval (**FUNAAB/COLVET/CREC/2024/03/05**) was received from the COLVET Research and Ethics Committee (CREC), Federal University of Agriculture, Abeokuta, Ogun State, Nigeria.

Conflict of Interest

The authors declare no conflict of interest.

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Generative AI Statement

The authors declare that no generative AI or AI-assisted tools were used while writing the manuscript.

Authors' Contributions

Conceptualization, design, funding, supervision, and critical review of manuscript: R. A. Ajadi; Data collection, analysis, and processing; literature review and manuscript writing: I. O. Oyenekan, J. O. Osunlakin, K. Adeoyo, A. O. Makinde, and O. F. Kehinde

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