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Research Article

Hormonal and Histological Changes in the Ovaries of Wistar Rats Treated with Oxycodone Hydrochloride

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Abstract

Introduction: Oxycodone hydrochloride can affect the nervous system, as well as other systems such as the endocrine and reproductive systems. Exposure to oxycodone hydrochloride is not without adverse effects. These adverse effects can lead to infertility. **Objective:** The aim of the study was to evaluate the effects of oxycodone hydrochloride on reproductive functions in adult female Wistar rats. **Materials and methods:** Fifteen adult female Wistar rats, weighing between 100 and 300 g, were used. Treatment was administered orally for thirty days. Three batches, each containing five adult female Wistar rats, were formed and treated as follows: (1) a control batch given distilled water at 10 ml/kg; (2) and (3) batches treated with oxycodone hydrochloride at doses of 5 and 10 mg/kg respectively. The variables studied included physiological measurements, hormone assays and histological analysis of the ovaries. **Results:** Exposure of adult female Wistar rats to oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg induced severe morphological alterations such as palpable adnexal masses plus a significant ($p<0.05$) increase in ovarian weight. A significant decrease ($p<0.05$) in FSH, LH and progesterone was also observed. Microscopic alterations such as cortical granuloma nodules were observed. **Conclusion:** Prolonged administration of oxycodone hydrochloride led to a significant increase in ovarian weight, associated with severe morphological alterations, hormone depletion and the appearance of microscopic ovarian alterations. All these disturbances are potentially linked to infertility.

Keywords: oxycodone hydrochloride, infertility, hormone, ovary, histology, rats

INTRODUCTION

Oxycodone hydrochloride is a semi-synthetic opioid derived from thebaine, an alkaloid naturally present in opium [1,2,3]. It exerts a pharmacological effect on the nervous system [4,5]. The therapeutic effect is essentially analgesic and sedative, focusing on the management of moderate to severe or chronic pain [4]. Oxycodone hydrochloride is prescribed for psychiatric disorders [6,7], as well as for cancer, post-operative use and as a cough suppressant [8,9,10]. It acts via μ-opioid receptors (MOR) located in the hypothalamus, inhibiting the pulsatile secretion of gonadotropin-releasing hormone (GnRH) [11,12,13]. The main mechanism is based on the suppressive effect of opioids on the hypothalamic-pituitary-gonadal axis [13,14,15]. In recent years, the drastic worldwide increase in prescriptions [16], misuse of oxycodone hydrochloride [17,18], addictions [17,19], and overdoses [20,21], have transformed what was initially a therapeutic solution into a major public health problem [16,18,22]. There is growing concern that oxycodone hydrochloride may induce adverse and harmful effects beyond the analgesic sphere [17,23]. Oxycodone hydrochloride can affect the central nervous system, and other systems such as the endocrine and reproductive systems may also be affected [4,13,17,24]. Infertility is a public health problem, and around 30% of infertilities can be attributed to factors such as drug treatments, toxins, inadequate nutrient intake and pollution [25,26]. These factors can have adverse effects on reproductive function and/or fertility [25,26]. The hypothalamic-pituitary-gonadal axis is a key system

regulating hormone secretion and fertility in women [27,28,29]. Disruption of this axis by oxycodone hydrochloride can affect fertility and, with reservations, induce infertility [4,30,31]. From its neuropsychic [32,33], and addictive [17,19] effects, oxycodone hydrochloride has raised concerns about its potential deleterious effects on female reproductive functions. The aim of this study was to evaluate the effects of oxycodone hydrochloride on reproductive function in adult female Wistar rats.

MATERIALS AND METHODS

Animals and treatments

Fifteen adult female Wistar rats, weighing between 100 and 300 g, from the animal house of the Faculty of Health Sciences, were used. They were kept in their natural habitat, with free access to food and water. The various products were administered orally at different doses for thirty days. Three batches, each containing five adult female Wistar rats, were set up and treated as follows:

- the first batch served as a control and received distilled water at 5 ml/kg ;
- the second batch was treated with oxycodone hydrochloride at a dose of 5 mg/kg ;
- the third batch was treated with oxycodone hydrochloride at 10 mg/kg.

The doses used corresponded to therapeutic doses in clinical practice [4,34,35].

Blood and organ sampling and histology

Blood and ovaries were gently collected after ethyl ether inhalation anaesthesia. Serum was decanted after centrifugation and used for biomedical analysis. Ovaries were weighed, fixed by immersion in 10% formalin and oriented for analysis (macroscopic and microscopic). Specimens were systematically identified, recorded and processed, then embedded in kerosene. Sections 4 µm thick were cut, stained with hematoxylin and eosin for light microscopic evaluation [36].

Hormone levels

Analysis of FSH, LH and progesterone levels was performed by enzyme-linked immunosorbent assay (ELISA) using the Cypress ® kit [36].

Statistical analysis

Results were expressed as mean ± standard error. Batches of treated animals were compared with the control group for each variable. Comparisons of non-evolving parameters were made using Student's t-test and one-factor ANOVA, followed by a Tukey test for comparison between several experimental batches. Data were entered into Excel 2019. Tests were performed using Statistical Package for Social Science, version 20. The significance level corresponded to a risk of error $p<0.05$.

Ethics

The study was conducted in compliance with Directive 2010/6106/EU on the protection of laboratory animals [37].

RESULTS

Organ weights

Oxycodone hydrochloride was administered orally for 30 days at doses of 5 and 10 mg/Kg to adult female Wistar rats in batches 2 and 3 respectively. The control lot received 5 ml/kg of distilled water. Organ weights were recorded after dissection.

Table I. Organ weight index

Organ	ED 5 ml/kg	Oxy 5 mg/kg	Oxy 10 mg/kg
Right ovary	0.01±0.001	0.67±0.20 ***	0.28±0.03 *
Left ovary	0.01±0.001	0.28±0.03 *	0.28±0.03 *

Results were expressed as mean ± standard error. (*): p<0.05; (**): p<0.001; (***): p<0.0001; NS (not significant) by student's t-test. ED: Distilled water; Oxy: Oxycodone hydrochloride.

Ovarian macroscopy

Animals exposed to oxycodone hydrochloride showed morphological changes, the effect of which may be dose-dependent. Figure (1) shows the condition of the ovaries in batches treated with oxycodone hydrochloride at doses of 5 and 10 mg/kg.

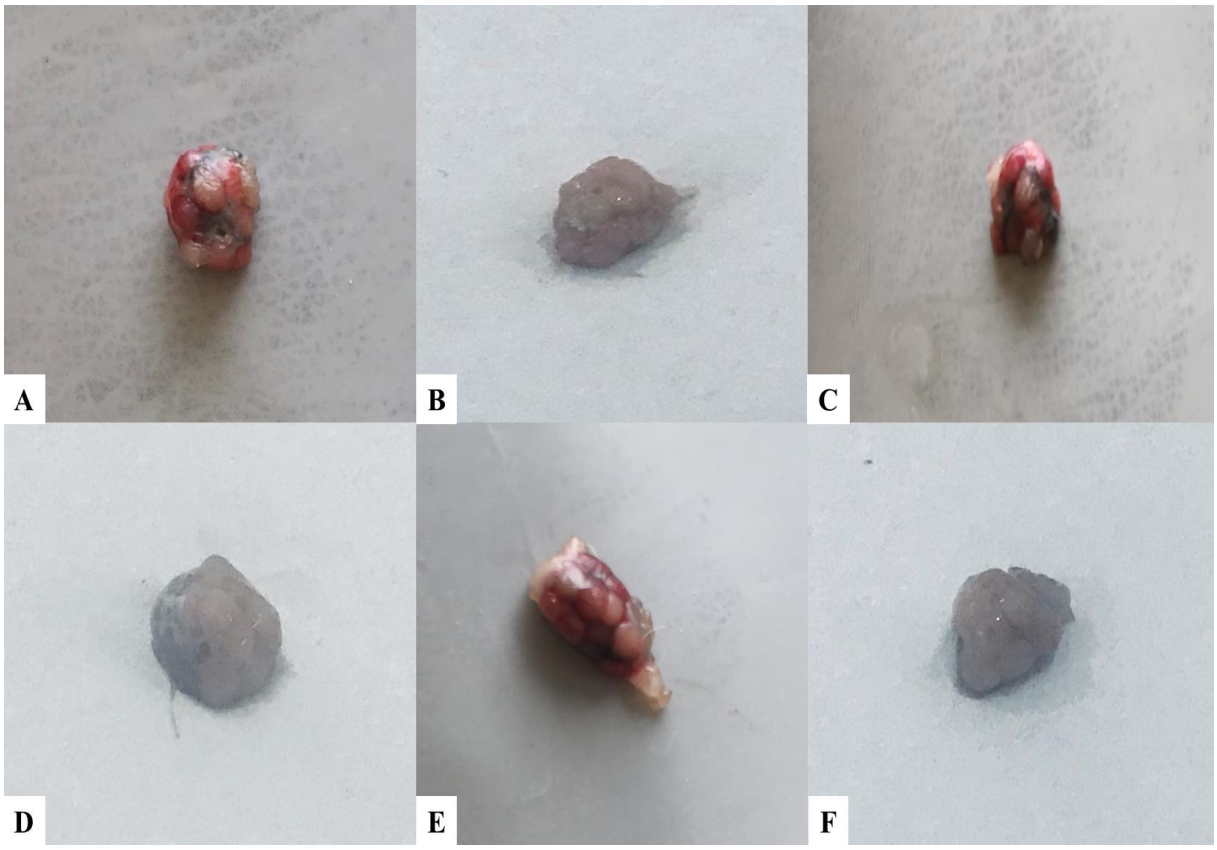

Figure 1. Photographs of the ovaries of adult female Wistar rats from batches treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg.

Hormone levels

Oxycodone hydrochloride was administered orally for 30 days at doses of 5 and 10 mg/Kg in adult female Wistar rats. The effects observed on hormonal parameters are presented in Table II.

Table II. Effects of oxycodone hydrochloride on hormonal parameters

Parameters	ED 5 ml/kg	Oxy 5 mg/kg	Oxy 10 mg/kg
FSH	11.82 ± 1.96	3.16 ± 0.15 *	2.91 ± 0.11 *
LH	14.33 ± 1.94	1.26 ± 0.22 *	1.16±1.08 *
Progesterone	45.21 ± 1.29	18.87 ± 7.86 **	10.27 ± 0.48 ***

Results were expressed as mean ± standard error. (*): p<0.05; (**): p<0.001; (***): p<0.0001; NS (not significant) by student's t-test. ED: Distilled water; Oxy: Oxycodone hydrochloride.

Ovarian microscopy

Animals exposed to oxycodone hydrochloride showed alterations whose effect may be dose-dependent. Figures 2, 3 and 4 illustrate the microscopic status of the ovaries in batches treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg.

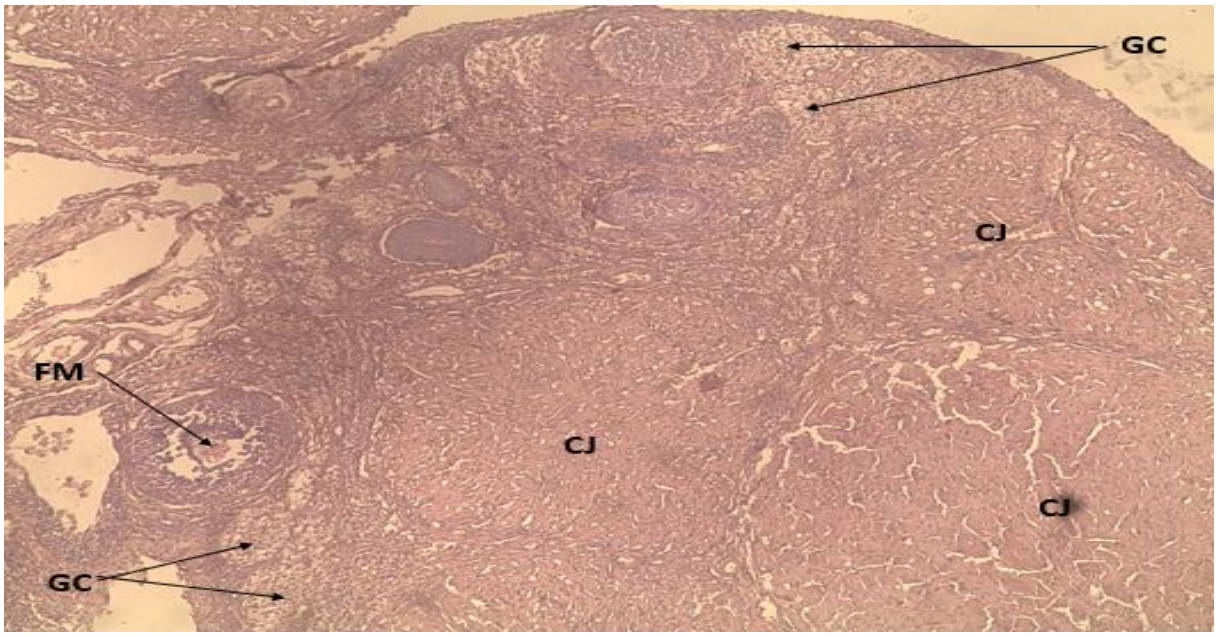

Figure 2. Microphotograph of the ovary of an adult female Wistar rat, treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg. The cross-section shows ovarian parenchyma with several corpora lutea (CJ) and mature follicles (FM). Several cortical granuloma nodules (GC) are also visible. HE × 10.

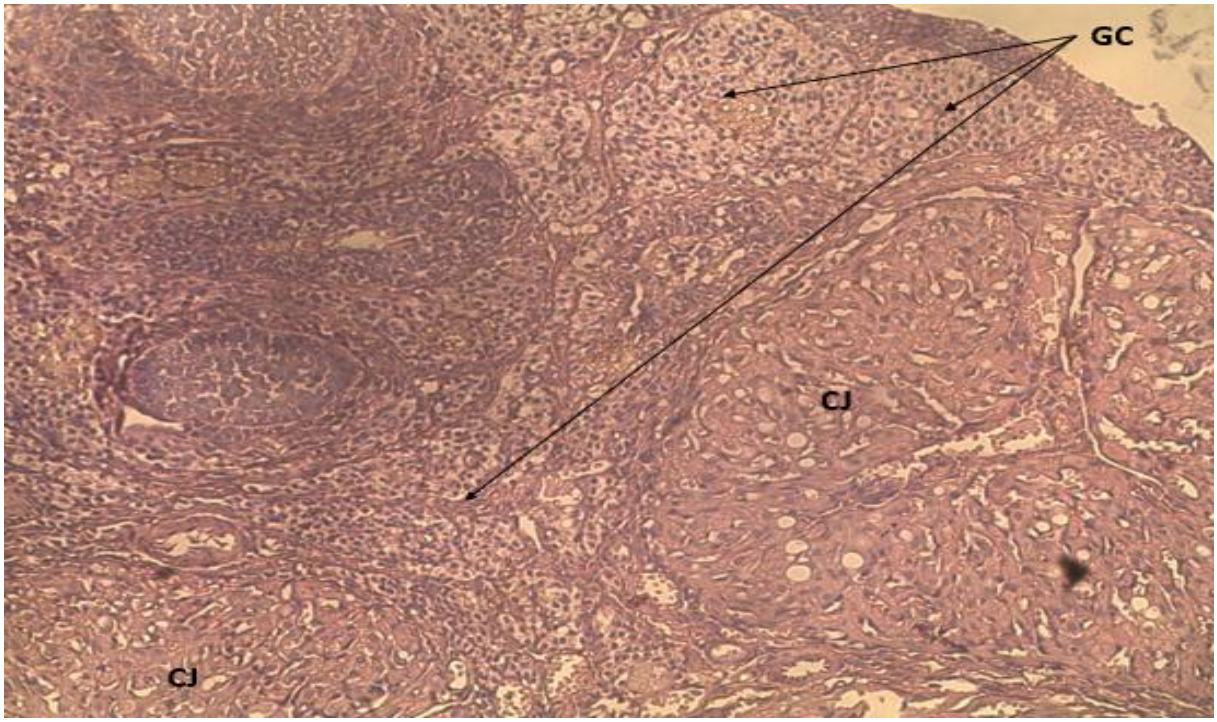

Figure 3. Microphotograph of the ovary of an adult female Wistar rat, treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg. The magnification was HE × 20, allowing better appreciation of the corpora lutea (CJ) made up of granulosa cells and the cortical granulomas (CG) composed of histiocytes.

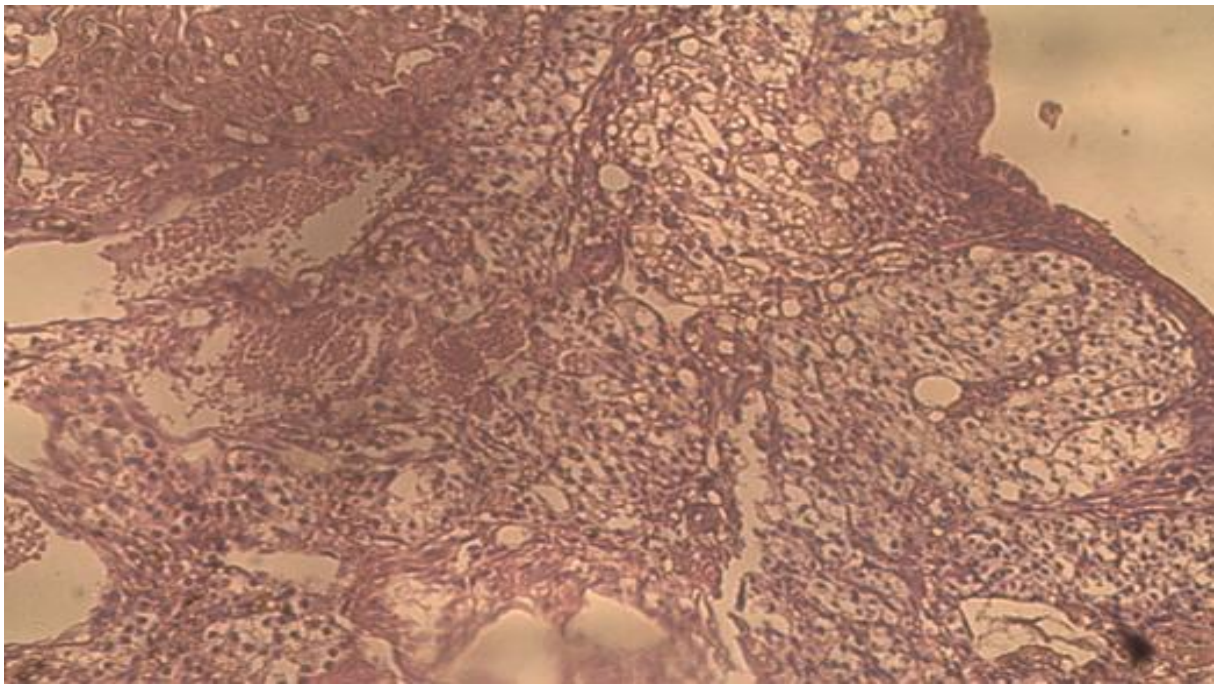

Figure 4. Microphotograph of adult female Wistar rat ovary, treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg. This was HE × 40 and show details of the histiocytic cells that make up these cortical granulomas. These cells are rounded/polygonal, with abundant foamy cytoplasm.

DISCUSSION

Prolonged administration of oxycodone hydrochloride is not without adverse effects [4,21,22]. Oxycodone hydrochloride can affect the central nervous system, as well as other systems such as the endocrine and reproductive systems [4,15,33]. Its influence can be brought to bear on the neuroendocrine axis, which includes hypothalamic GnRH neurons and pituitary cells that secrete FSH and LH in response to GnRH [11,38,39]. μ-opioid receptors (MORs) play a crucial role in regulating GnRH secretion [17,40]. When an opioid binds to these receptors, it inhibits pulsatile GnRH secretion, with significant implications for reproductive regulation. By inhibiting adenylate cyclase, opioids also reduce the production of cAMP, leading to a decrease in the transcription of target genes related to reproduction [11]. The central nervous system has an essential role in modulating the physiological and behavioral elements associated with normal reproductive functions [4,25,36]. The use of oxycodone hydrochloride may reduce sex hormone levels and impair reproductive functions [4]. This exposure may be responsible for impaired fertility in adult female Wistar rats. The aim of our study was to evaluate the effects of oxycodone hydrochloride on reproductive functions in adult female Wistar rats. Oxycodone hydrochloride was administered orally for thirty days at doses of 5 and 10 mg/Kg to female Wistar rats in batches 2 and 3 respectively, while the control batch received 10 ml/kg of distilled water. Morphological evaluation of the organs may support the hypothesis of a mechanism of infertility [4,12,41]. Table (I), presented the effects of oxycodone hydrochloride on organ weights. Adult female Wistar rats treated with oxycodone hydrochloride showed increased ovarian weights at doses of 5 and 10 mg/Kg respectively, compared with the control lot. The significant increase in ovarian weight may reflect the morphological changes mentioned above. Ovarian macroscopy has been important in the study of female infertility [36, 42]. Figure (1), illustrated ovarian alteration in adult female Wistar rats treated with oxycodone hydrochloride at doses of 5 and 10 mg/Kg respectively. Our results showed that oxycodone hydrochloride can induce palpable adnexal masses on the ovary [43,44]. These masses may resemble a nodule or cyst, or be suggestive of ovarian cancer. These changes may be correlated with infertility [26,43,44,45,46]. Opioids have a profound effect on the endocrine system, particularly on the hypothalamic-pituitary-gonadal axis, which can lead to a drop in progesterone levels in women [13,47,48,49]. FSH and LH are gonadotropins produced by the anterior pituitary, under the control of hypothalamic GnRH [11,38]. FSH stimulates the development of ovarian follicles [50]. Synergistically, LH induces ovulation and corpora lutea formation [50,51]. Table (II) shows the effect of oxycodone hydrochloride on hormonal parameters. Our results showed a significant decrease in FSH, LH and progesterone levels in adult female Wistar rats treated with oxycodone hydrochloride at doses of 5 and 10 mg/kg compared with the control batch. Oxycodone hydrochloride may inhibit the release of GnRH (hypothalamic hormone) [13,52]. This reduces FSH and LH secretion, as well as progesterone deficiency [13,52,53]. These alterations can lead to infertility [13,41,45,52,53,54]. Animals exposed to oxycodone hydrochloride showed alterations whose effect may be dose-dependent. Figures (2), (3) and (4), illustrated microscopic alterations of the ovaries in batches treated with oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg. Figure (2) showed ovarian parenchyma with several corpora lutea (CJ) and mature follicles (FM). Several cortical granuloma nodules (GC) were also noted. The corpus luteum may be highly vascularized, making

them vulnerable to internal bleeding [47,55,56,57]. Sometimes internal hemorrhage occurs in the corpus luteum, resulting in a hemorrhagic cyst [47,55,56,58]. Nodular formations may suggest cyclic ovarian activity plus chronic inflammatory lesion [55,59,60]. Also, cysts of the organized hemorrhagic corpus luteum type [45,47,55]. Figures (2) and (3), respectively illustrated corpora lutea (CJ) made of granulosa cells and cortical granulomas (GC) are composed of histiocytes, as well as details of histiocytic cells [61,62,63,64]. These cells are rounded/polygonal, with abundant foamy cytoplasm [55,64]. All these histological changes may be associated with infertility [47,55,64,65].

CONCLUSION

Prolonged administration of oxycodone hydrochloride at doses of 5 mg/kg and 10 mg/kg induced a significant increase in ovarian weight associated with severe morphological alterations. This exposure led to ovarian hormone depletion and the appearance of microscopic alterations such as cortical granuloma nodules. Further studies are needed to confirm these findings, clarify their molecular mechanisms and reveal their clinical implications for treatment.

Conflicts of interest: All authors declare that they have no conflicts of interest in relation to this work.

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Ethical Approval: The study was conducted in compliance with Directive 2010/6106/EU on the protection of laboratory animals.

Authors' contributions:

Participation in research design: AME Mboungou Malonga, Alice Matété Mounoi.

Experiments carried out: AME Mboungou Malonga, Alice Matété Mounoi, CA Itoua Opimba.

Contribution of new reagents or analytical tools: SM Osseke, MN Zeguel, A Matété Mounoi.

Data analysis performed: AME Mboungou Malonga, LO Mozoma, LM Miguel, E G Balebou.

Authors or contributors to the manuscript: AME Mboungou Malonga, LO Mozoma, LM Miguel, H Akassa, Alice Matété Mounoi, E Mokondjimobe, D Moukassa, AA Abena.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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