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The Analgesic Effects of Metamizole-Sodium in Castrated Nigeria Indigenous Dogs

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ABSTRACT

Nociceptive pain due to surgery is associated with discomfort and suffering. Metamizole sodium, though a potent analgesic, has been banned in many countries. The study is aimed at evaluating the analgesic efficacy of metamizole-sodium in castrated indigenous Nigerian dogs using electrocardiography (ECG). Twelve indigenous Nigerian male dogs aged between 6 months and 1 year with a mean body weight of 11.66 ± 1.26 kg undergoing castration were divided into three groups of four (4) animals each (n = 4). Groups A and B were treated with metamizole sodium via intramuscular (I/M) and transdermal routes at 50 mg/kg and 150 mg/kg, respectively. Group C was treated with normal saline 5 mg/kg i.m.Patients were monitored using standard methods for neutrophil count, vital parameters (rectal temperature, respiratory rate, heart rate and blood pressure), and ECG at 10 minutes before, during and at every 6-hour interval of 48 hours post-surgery. The neutrophil count in the intramuscular group (2.91 ± 0.55 × 109 L-1) was relatively lower than in the transdermal (3.54 ± 0.61 × 109 L-1) and control groups (4.41 ± 1.25 × 109 L-1) at 48 h post-surgery. There was no significant difference in the values of vital parameters obtained between the groups. The QRS interval was lower for intramuscular (0.10 ± 0.06 s) and transdermal (0.04 ± 0.00 s) than the control group (0.20 ± 0.16 s) at 18 h post-surgery. The P and T amplitudes were significantly ($P < 0.001$) higher for the tested groups than the control group during surgery and at 12 h post-surgery, respectively. In conclusion, the administration of metamizole sodium via the transdermal route prevented the side effect of agranulocytosis, evident by the decrease in neutrophil count of the intramuscular group compared to the transdermal group. Metamizole sodium transdermal patch induced analgesia, evident by the increase in QRS interval and decrease in P and T amplitudes of the ECG reading. This may be beneficial in alleviating pain due to castration in Nigerian indigenous dogs.

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INTRODUCTION

Postoperative pain is one of the main causes of morbidity and mortality related to surgery. Nociceptive pain is associated with skin incisions **(Brennan *et al*., 2005)** and deep surgery **(Xu and Brennan, 2009).** Methods of pain assessment in dogs are not extensively standardized **(Reid *et al*., 2007).** Inadequate pain assessment decreases the validity of canine pain models and hinders the comparison of pain studies. Behavioral-like reactions to palpation, guarding and interaction with the owner; physiological, as in cardiovascular indices and stress responses; and neuroendocrine responses **(Coetzee, 2011)** are common indicators used to assess pain in non-verbal patients **(Ignacio *et al*., 2015).** Composite pain scales and multi-dimensional questionnaires have been developed for use in canine post-operative pain conditions **(Reid *et al*., 2007; Cohen *et al*., 2008).**

In previous investigations, pain has been evaluated in animals **exposed to noxious stimuli** based on changes in behavioural, physiological and neuroendocrine responses **(McMeekan *et al*., 1999; Coetzee, 2011).** Changes in animal behaviour have been evaluated using pain assessment methods based on exit speed measurement and accelerometers **(White *et al*., 2008)**, chutes **(Baldridge *et al*., 2011),** videography **(Pascale *et al*., 2012)** and vocalization **(Landa, 2015).** Physiological changes occurring due to pain response have been assessed using serum cortisol level **(Steven,**

2016; Musk *et al*., 2017), heart rate **(Williams, 2010)** and feed intake and average daily weight gain **(Musk *et al*., 2017).** Neuroendocrine responses to pain are evaluated through the measurement of neuropeptide substance P (Coetzee *et al*., 2008), skin electrical impedance (electrodermal activity) **(Pascale *et al*., 2012),** electroencephalography (EEG) **(Bergamason *et al*., 2011)** and rescue analgesia **(Pascale *et al*., 2012)**.

Topical or transdermal drug delivery is the application of a formulation to the skin to directly treat local and/or systemic disorders with the aim of containing the pharmacological or another effect of the drug **(Nimesh and Paresh, 2016).** This system of drug delivery provides constant and controlled drug administration. It allows the continuous input of drugs with short half-lives and eliminates fast entry into the systemic circulation **(Ritesh and Reni, 2015).** Transdermal delivery system (TDDS) is one of the three main types of drug delivery systems via the skin. The others are local delivery, in which the drug-containing formulation is applied to the skin directly to treat cutaneous manifestations of the disease. Regional delivery involves the application of a drug to the skin to treat diseases or alleviate disease symptoms in deep tissues beneath the skin **(Prausnitz and Langer, 2011).** The TDDS has many advantages when compared to other routes of drug administration. It reduces the load placed on the digestive tract and liver by the oral route. It minimizes harmful side effects of a drug caused by temporary overdose and also enhances patient compliance **(Singh *et al*., 2013).** It is convenient, especially in patches, which require only once-weekly application **(Gaur *et al*., 2009).**

Castration in dogs is one of the most commonly performed veterinary procedures **(Freeman *et al*., 2017).** It is carried out to control the overpopulation problem, prevent diseases of the reproductive system, and modify undesirable behaviours, including mounting of other dogs and aggression **(Kaufmann *et al*., 2017).** Methods of castration in dogs include surgical (pre-scrotal and scrotal), immunological, and sonographic alterations and the use of chemical agents **(Baba *et al*., 2016; DiGangi *et al*., 2017).**

The ECG is an electrophysiological signal that gives information on the electrical activity of the sinoatrial node and the cardiovascular activity **(Rezazadeh and Seno, 2013).** One cardiac cycle of the ECG signal is a reflection of the P wave (depolarization), QRS complex (ventricular depolarization), and T (rapid repolarization of the ventricles) waves (**Subramanian, 2017**). During the measurement of ECG, there is a chance of various artifacts being recorded along with the signal that can result in a wrong diagnosis **(Harikumar and Shivappriy, 2011; Subramanian, 2017).** The normal values for P amplitude, T amplitude, P interval, Q interval, R interval, PR, QT and ST waves are 0.2 mV, 0.1-0.5 mV, 0.11 sec, 25% of R, 1.6 mV, 0.12-0.2 sec, 0.35-0.44 and 0.05-0.15 sec, respectively **(Subramanian, 2017).** The QRS complex, also used in R peak detection to find the heart rate of an individual, is the most significant part in the ECG compared to P and T waves. The ECG has been shown to respond to pain and stress, thus producing a physiological signal **(Chu *et al*., 2017).**

Assessments of the autonomic heart rate changes during acute pain have been evaluated in different studies, though no tool for detecting objective pain has been successfully developed. Biological signals like the ECG are non-uniform and non-stationary, incorporating static background frequencies and dynamic acute changes **(Tejman-Yarden et *al*., 2016).** The signal obtained is analyzed using Fourier transform, and the wavelet transform is best for analyzing piecewise smooth functions with discrete singular points **(Gamero *et al*., 2002; Krstacic *et al*., 2012).** Studies carried out reported that the heart rate signal is the most common ECG parameter used to assess pain. The heart rate has been reported to have a relationship with the R-R interval **(Zigel *et al*., 2011).** This variable is not specific and may react to different stimuli and stressors. For example, anxiety or seizures and medications like the beta-blockers may prevent normal heart rate response and blunt pain detection.

The aim of this study was to evaluate the analgesic efficacy of metamizole-sodium transdermal patches on castrated Nigerian indigenous dogs (NIDs).

MATERIALS AND METHODS

Study area

The experiment was carried out in the Department of Veterinary Surgery and Radiology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, **Nigeria (11°10′ N, 07°38′ E)**, located in the Northern Guinea Savannah zone of Nigeria.

Experimental animals

Twelve (12) Nigeria indigenous dogs (NIDs) with an average weight of 11.66 ± 1.26 kg and aged 6 month – 12 months were used in present study. Dogs were profiled under signalment and history. Thorough systematic physical examination was conducted; including the measurement of the vital parameters of the patients. The patient's blood and faecal samples were examined and screened in clinical pathology, helminthology and parasitology laboratories of the Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria.

Study design

A case-control study on how to reduce frequent dosing and the adverse effect of metamizole-sodium as an analgesic for post-operative pain management was carried out in cases presented to Small Animal Unit of Ahmadu Bello University Veterinary Teaching Hospital, Zaria. Patients were grouped into three groups: A, B and C **(Table 1),** each comprising of four (4) dogs. For each group, rectal temperature, blood pressure, respiratory rate, pulse rate, electroencephalography and blood samples were monitored at 10 minutes before castration, during castration, 1 h post-castration and at six-hour interval spanning to 48 h post-castration.

Table 1: Patient Grouping and Post- surgical Treatment:

Drugs	Groups	Number of dogs
Metamizole sodium I.M (50 mg/kg tds) MIM	A	4
Metamizole TD (150 mg/kg) MTD	B	4
Placebo – PLA (5mg/kg)	C	4

I.M – Intramuscular. TD – Trans-dermal. PLA – Placebo. MIM – Metamizole sodium via the intramuscular route. MTD – Metamizole sodium via the trans-dermal route.

Metamizole sodium transdermal patch MSTDP preparations

The drug-loaded matrix-type patch of metamizole sodium was prepared using solvent casting method. A Petri dish with a total area of 44.15 cm^2 **(Fig. 1).** Polymers were weighed and dissolved in 10 mL of water, methanol (1: 1) solution to form a clear solution. Metamizole sodium (150 mg/kg) was added to the solution. Polyethene glycol 400 (30 % w/w of total polymer) served as a plasticiser and propylene glycol (15 % w/w of total polymer) was used as a permeation enhancer. The obtained uniform solution was cast on the glycerine lubricated Petri dish and dried at room temperature (25-26 $^{\circ}C$) for 24 h. An inverted funnel was placed over the Petri dish to prevent fast evaporation of the solvent (Cherukuri *et al*., 2017). Then MSTDP separated from the foil paper **(Fig. 2).**

Fig. 1: Mixture of all the reagents in a Petri dish (white arrow).

Fig. 2: Prepared MSTDP. Note its separation from the foil paper (white arrow).

Castration

Presurgical procedure

Normal saline was given intravenously to maintain patent catheterization for the administration of the pre-anaesthetic and anaesthetic agent (midazolam 0.02 mg/kg i.v. and propofol 6 mg/kg i.v., respectively). Metamizole sodium (50 mg/kg) was administered to group A via the intramuscular route at the thigh muscle (5 minutes after the pre-anaesthetic administration), and in group B a metamizole sodium transdermal patch (150 mg/kg) was placed 2 cm away from the proposed incision site (5 minutes after the pre-anaesthetic administration). The multi-parameter and the EEG monitoring machine were connected to the patient. The anaesthetic agent was administered 10 minutes afterwards. **(Fig. 3**) The pre-scrotal region, which had already been clipped a day before surgery, was prepared for the surgery with chlorhexidine scrub and covered with a chlorhexidine-soaked surgical sponge.

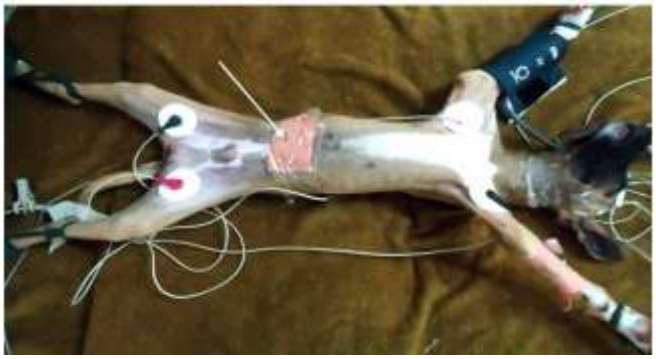

Fig. 3: Reveals eexperimental dog on the surgical table with placement of MSTDP in the group B and EEG monitoring machine pre surgery.

Surgical procedure

The dog was placed in dorsal recumbency on a surgical table at the theater. The sponge was removed, and the surgical site was draped aseptically **(Fig. 4).**

Fig. 4: Reveals dog on dorsal recumbency aseptically draped for castration. E= sterile gauze bandage, F = Sterile drape.

An incision was made just cranial to the scrotum and continued cranially 2 to 5 cm, based on the dog's size, until it was sufficient to allow testicular exteriorization **(Fig. 5).** The spermatic cord was identified and exteriorized, then two curved haemostats were used to crush the spermatic cord tissues proximal to the testicle and the spermatic cord was transected distal to the second haemostat with a scalpel blade **(Fig. 6).** The most proximal haemostat was removed, and the spermatic cord was ligated using size 2-0 chromic catgut. The other haemostat was removed subsequently. This procedure was repeated for the second testicle. The incision was closed with size 2-0 nylon suture material in a horizontal interrupted suture pattern **(Snell *et al*., 2015) (Fig. 7).**

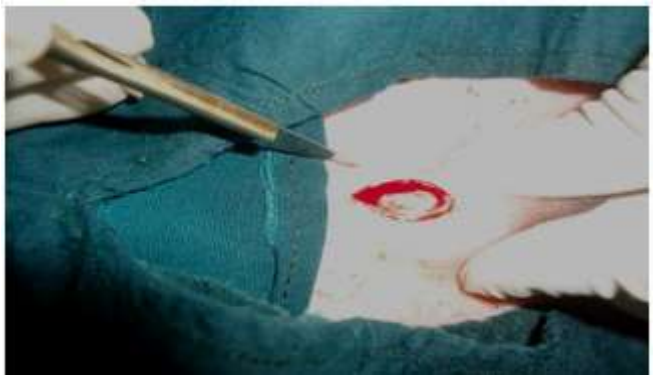

Fig. 5: A 2 cm pre-scrotal incision to access the testicle and spermatic cord.

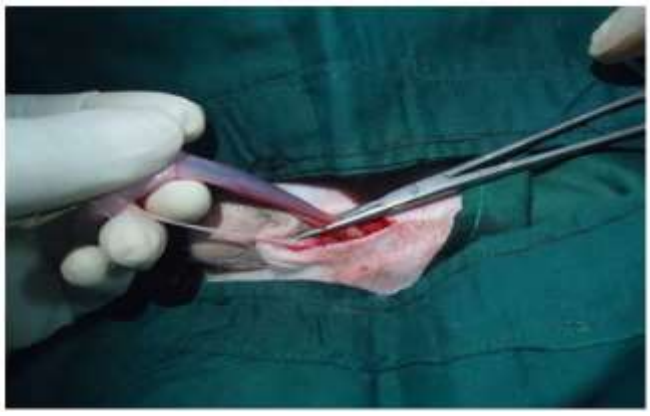

Fig. 6: Showing exteriorization of one of the testicles and Ligation of the spermatic cord with a forceps

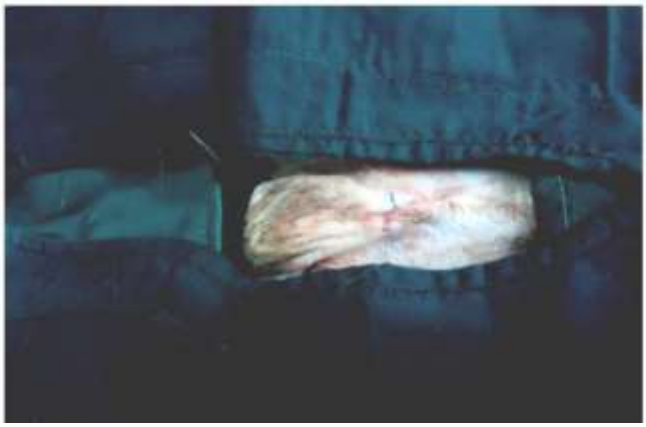

Fig. 7: Showed Closure of the surgical site using size 2-0 nylon suture material in a horizontal interrupted suture pattern.

Parameters monitoring

Body Temperature (^{O}C), Respiratory rate (breath/min), blood pressure (mmHg) and pulse rate were monitored at 5 minutes interval all through surgery and at 1, 6, 12, 18, 24 and 48 h post-surgery using the multi-parameter monitoring machine connected to the body of the dogs.

Electrocardiographic monitoring

Electrodes were placed directly on the skin of each dog; one on each of the fore-limbs close to the distal region of the olecranon, and on each hind-limb close to the cranial region of the patella and the thoracic region **(Fig. 8)**. Alcohol (96%) was applied to the skin, where the electrode was placed in order to obtain better electric conductivity. On each dog, a base-line ECG reading was obtained for 10 minutes before commencing castration. The recording continued all through the procedure and at 6 h interval spanning for 48-h post-castration. Data were collected and stored in a personal computer for off-line analysis.

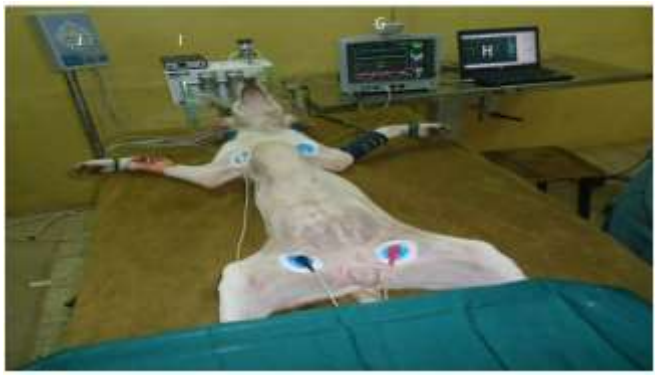

Fig. 8: showed experimental dog on the surgical table with positioning of the electrode for ECG recording (arrowhead). G = Veterinary multi-parameter monitoring machine, H = Computer for collecting and analysing ECG mappings, I = Suction machine, J = ECG sensor.

Haematological evaluation

Blood samples (2 mL) were collected from the cephalic vein 10 minutes before surgery, and at 1, 6, 12, 18, 24 and 48 h post-surgery. The blood samples were taken to clinical pathology laboratory in ethylenediaminetetraacetic-sodium ($EDTA\text{-}Na^{+}$) bottles, for total and differential white blood cell count.

Ethical clearance

Ethical clearance was sought and approval was given by the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC/2018/039) for the use of dogs, and permission was sought from clients for the use of their dogs for the study.

Data analyses

Data obtained from EEG and haematology were expressed using mean ± standard error of mean (Mean ± SEM). The EEG and haematological data were subjected to repeated-measures two-way analysis of variance (ANOVA) (mixed model), followed by Bonferroni *post- hoc* test to compare the difference between the mean of the control and treated groups. GraphPad Prism version 20.0 for Windows (GraphPad Software, San Diego, California, USA) was used for the analyses. Values of $P < 0.05$ were considered significant.

RESULTS

Echocardiographic Results

The result of echocardiographic were the P amplitude in the transdermal group P wave (0.50 ± 0.50 mV) was higher ($P<0.05$) than that of the intramuscular and control group during surgery **Table 2.**

Table 2: P-wave Amplitudes (mV) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.00 ± 0.03	0.25 ± 0.05	0.25 ± 0.25
Intra surgery	0.00 ± 0.00	0.25 ± 0.05^{a}	0.50 ± 0.50^{b}
Closure	0.00 ± 0.00	0.25 ± 0.05	0.25 ± 0.25
1 hour	0.25 ± 0.05	0.25± 0.05	0.08 ± 0.03
6 hour	0.25 ± 0.75	0.00 ± 0.08	0.25 ± 0.03
12 hour	0.25 ± 0.75	0.00 ± 0.15	0.10 ± 0.00
18 hour	0.00 ± 0.03	0.25 ± 0.05	0.10 ± 0.03
24 hour	0.25 ± 0.03	0.25 ± 0.05	0.03 ± 0.00
48 hour	0.00 ± 0.05	0.00 ± 0.03	0.03 ± 0.00

P- wave amplitude for the control, intramuscular and transdermal group before, during and after castration. ^{a,b} = Mean with the different superscript letter within row are significantly different ($^{a,b}P < 0.05$).

While, there was no significant ($P < 0.05$) difference in the P duration, R duration and R-R interval between all the groups **(Table 3, 4 and 5, respectively).**

Table 3: P Durations (s) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.0 4± 0.00	0.06 ± 0.01	0.06 ± 0.02
Intra surgery	0.0 4± 0.00	0.05 ± 0.01	0.04 ± 0.00
Closure	0.03 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
1 hour	0.03 ± 0.01	0.04 ± 0.00	0.05 ± 0.02
6 hour	0.04 ± 0.00	0.03 ± 0.01	0.04 ± 0.00
12 hour	0.04 ± 0.00	0.05 ± 0.01	0.03 ± 0.00
18 hour	0.04 ± 0.02	0.05 ± 0.01	0.05± 0.01
24 hour	0.04 ± 0.00	0.06 ± 0.01	0.04 ± 0.00
48 hour	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00

Mean values of the P duration for the control, intramuscular and transdermal group before, during and after castration with no significant different ($P > 0.05$).

Table 4: R Durations (s) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.20 ± 0.00	0.40 ± 0.11	0.40 ± 0.08
Intra surgery	0.20 ± 0.04	0.30 ± 0.13	0.30 ± 0.11
Closure	0.20 ± 0.01	0.30 ± 0.07	0.30 ± 0.1
1 hour	0.40 ± 0.014	0.50 ± 0.08	0.30 ± 0.04
6 hour	0.50 ± 0.16	0.30 ± 0.05	0.30 ± 0.05
12 hour	0.20 ± 0.06	0.20 ± 0.06	0.30 ± 0.07
18 hour	0.20 ± 0.04	0.30 ± 0.07	0.30 ± 0.06
24 hour	0.20 ± 0.09	0.30 ± 0.05	0.20 ± 0.05
48 hour	0.10 ± 0.08	0.30 ± 0.08	0.02 ± 0.03

Table 5: R-R interval (s) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.40 ±0.11	0.42 ± 0.08	0.35 ± 0.17
Intra surgery	0.42 ± 0.10	0.43 ± 0.09	0.47 ± 0.08
Closure	0.41 ± 0.10	0.59 ± 0.04	0.51 ± 0.05
1 hour	0.40 ± 0.04	0.70 ± 0.07	0.47 ± 0.15
6 hour	0.52 ± 0.14	0.33 ± 0.01	0.29 ± 0.03
12 hour	0.39 ± 0.05	0.37 ± 0.03	0.29 ± 0.03
18 hour	0.41 ± 0.05	0.58 ± 0.09	0.36 ± 0.04
24 hour	0.35 ± 0.08	0.67 ± 0.17	0.49 ± 0.17
48 hour	0.42 ± 0.10	0.64 ± 0.26	0.48 ± 0.06

Mean values of the R-R interval for the control, intramuscular and transdermal group before, during and after castration with no significant different ($P > 0.05$).

The QRS duration for the control group was higher ($P < 0.001$, $P < 0.01$ respectively) than the transdermal and intramuscular group at 18-h post-surgery **(Table 6).**

Table 6: QRS Durations (s) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
Intra surgery	0.03 ± 0.01	0.04 ± 0.00	0.04 ± 0.00
Closure	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
1 hour	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
6 hour	0.04 ± 0.00	0.05 ± 0.01	0.04 ± 0.01
12 hour	0.04 ± 0.00	0.05 ± 0.01	0.04± 0.00
18 hour	0.20 ± 0.16	0.10 ± 0.06[b]	0.04 ± 0.00[c]
24 hour	0.02 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
48 hour	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00

Mean values of the QRS duration for the control, intramuscular and transdermal group before, during and after castration. [b,c] = Mean with the different superscript letter within row are significantly different ($P < 0.01$,$P < 0.001$) respectively.

The T amplitude was significantly ($P < 0.001$) lower for the control group (0.18 ± 0.05 mV) than the intramuscular (1.03 ± 0.00 mV) and transdermal groups (0.20 ± 0.00 mV) at 12-h post-surgery **(Table 7).**

Table 7: T Amplitudes (mV) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
Pre surgery	0.10 ± 0.00	0.18 ± 0.08	0.28 ± 0.08
Intra surgery	0.10 ± 0.00	0.08 ± 0.00	0.10 ± 0.03
Closure	0.08 ± 0.00	0.18 ± 0.08	0.20 ± 0.10
1 hour	0.10 ± 0.03	0.05 ± 0.03	0.18 ± 0.15
6 hour	0.10 ± 0.03	0.10 ± 0.00	0.13 ± 0.10
12 hour	0.18 ± 0.05	1.03 ± 0.00[c]	0.20 ± 0.00[b]
18 hour	0.10 ± 0.00	0. 25 ± 0.05	0.08 ± 0.05
24 hour	0.08 ± 0.05	0.15 ± 0.05	0.20 ± 0.10
48 hour	0.10 ± 0.00	0.33 ± 0.20	0.13 ± 0.03

Mean values of the T amplitude for the control, intramuscular and transdermal group before, during and after castration. [b,c] = Mean with different superscript letter within row is significantly different ([b,c]$P < 0.001$) .

Haemogramme result

There was no significant ($P > 0.05$) difference in the neutrophil count between the control and the intramuscular group. However, the neutrophil count for the control group ($7.79 \pm 3.21 \times 10^9\ L^{-1}$) was higher ($P > 0.05$) compare to the transdermal group ($3.97 \pm 0.60 \times 10^9\ L^{-1}$) pre-surgery. Similarly, there was no significant difference in the values obtained for the intramuscular and transdermal group. Although, a relative decrease in the neutrophil count was observed for the intramuscular group ($2.19 \pm 0.55 \times 10^9\ L^{-1}$) when compare to the transdermal group ($3.45 \pm 0.61 \times 10^9\ L^{-1}$) during the study period **(Fig. 9)**.

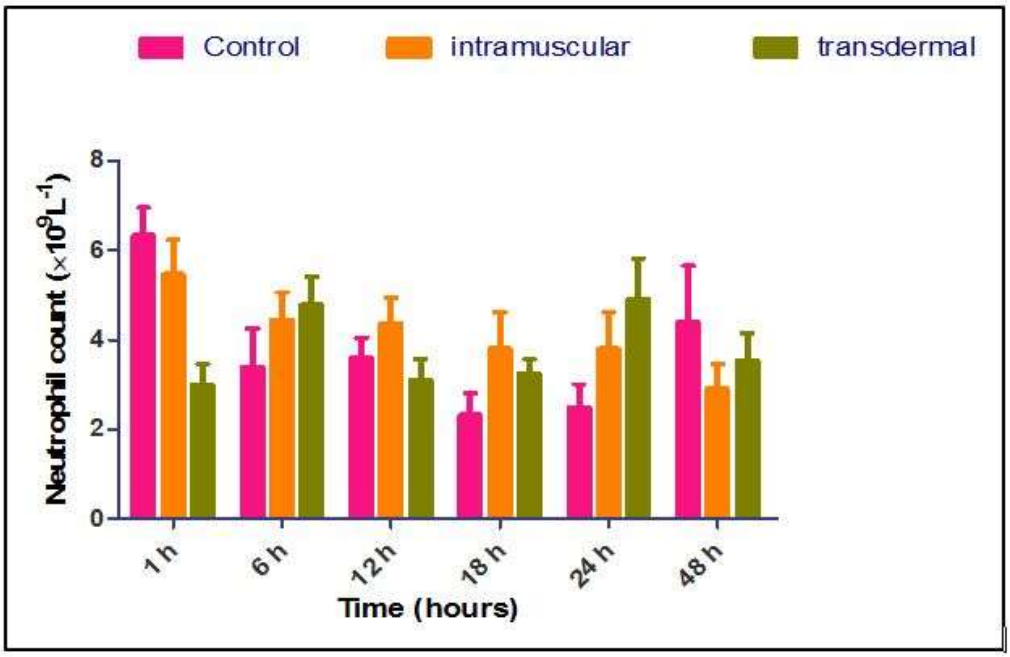

Fig.9: Blood neutrophil count for the control, intramuscular and transdermal groups after castration. No significant difference was observed at the end of the experiment. But a relative decrease for the neutrophil count of the intramuscular route group was observed when compared to the transdermal route group at 48 h post castration.

In Table 8, there was no significant difference in the lymphocyte count in the control when compared to the intramuscular group. The transdermal group ($7.86 \pm 2.21 \times 10^9\ L^{-1}$) was higher than the control group ($P < 0.01$, 2.71 ± 0.79) and intramuscular group ($3.64 \pm 0.96 \times 10^9\ L^{-1}$, $P < 0.05$) at 48-h post-surgery. The monocytes count of the control group was significantly ($P < 0.01$) higher than that of the transdermal and intramuscular group at 6 -h post-surgery **(Table 9).**

Table 8: Lymphocytes count ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	5.43 ± 0.36	3.47 ± 0.37	4.14 ± 1.35
6 hour	3.67 ± 1.65	3.10 ± 0.83	4.35 ± 0.36
12 hour	4.46 ± 0.94	3.09 ± 0.58	4.90 ± 0.07
18 hour	4.00 ± 0.19	3.29 ± 0.30	4.51 ± 0.330
24 hour	5.773 ± 2.55	3.29 ± 0.30	3.77 ± 0.42
48 hour	2.71 ± 0.79	3.64 ± 0.96^a	$7.86 \pm .21^c$

Mean values of the Lymphocytes count for the control, intramuscular and transdermal group after castration. [a,c =] Mean with different superscript letter within row are significantly different at ($P < 0.05$, $P < 0.001$) respectively.

Table 9: Monocytes Count ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	0.54 ± 0.26	0.32 ± 0.1	0.50 ± 0.14
6 hour	1.84 ± 0.38	1.29 ± 0.16^a	0.38 ± 0.11^b
12 hour	0.97 ± 0.49	0.89 ± 0.49	0.18 ± 0.04
18 hour	0.72 ± 0.44	0.73 ± 0.21	0.19 ± 0.05
24 hour	1.59 ± 0.31	0.70 ± 0.21	0.71 ± 0.07
48 hour	0.52 ± 0.27	1.17 ± 0.40	1.03 ± 0.28

Mean values of the Monocytes count for the control, intramuscular and transdermal group after castration. [a,b =] Mean with different superscript letter within row is significantly different at ($P < 0.05$, $P < 0.01$) respectively.

No significant difference was observed in the eosinophil count between the control and the rest of the groups **(Table 10).**

Table 10: Eosinophils Count ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	0.34 ± 0.20	0.66 ± 0.37	0.31 ± 0.11
6 hour	0.16 ± 0.08	0.1 ± 0.06	0.07 ± 0.04
12 hour	0.42 ± 0.10	0.12 ± 0.06	0.27 ± 0.14
18 hour	0.12 ± 0.12	0.26 ± 0.17	0.33 ± 0.08
24 hour	0.36 ± 0.36	0.26 ± 0.17	0.00 ± 0.00
48 hour	0.13 ± 0.07	0.07 ± 0.07	0.09 ± 0.05

Mean values of the Eosinophil count for the control, intramuscular and transdermal group after castration. No significantly difference ($P > 0.05$) between groups.

There were more band cells observed in the control ($8.45 \pm 4.40 \times 10^9 L^{-1}$) group, when compared to the intramuscular ($0.96 \pm 0.08 \times 10^9 L^{-1}$, $P<0.001$) and transdermal ($0.03 \pm 0.03 \times 10^9 L^{-1}$, $P<0.001$) group at 1-h post-surgery **(Table 11).**

Table 11: Band Cells ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	8.45 ± 4.40	0.75 ± 0.39^b	0.37 ± 0.053^c
6 hour	0.65 ± 0.37	1.09 ± 0.12	1.19 ± 0.17
12 hour	2.99 ± 2.00	1.44 ± 0.08	1.65 ± 0.09
18 hour	1.19 ± 0.59	0.51 ± 0.31	1.53 ± 0.21
24 hour	0.24 ±0.20	0.51 ± 0.32	1.47 ± 0.76
48 hour	1.01 ±0.36	1.19 ± 0.61	0.31 ± 0.31

Mean values of the Band cells count for the control, intramuscular and transdermal group after castration. ^{b,c} = Mean with different superscript letter within row are significantly different at ($^{b,c}P < 0.001$).

The total white blood cells count of the control group ($16.3 \pm 4.05 \times 10^9 L^{-1}$) was significantly ($P < 0.05$) higher compare to the transdermal and intramuscular before the surgery as shown in **Table 12.**

Table 12: Total White Blood Cells Count ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	10.67 ± 4.08	10.55 ± 1.30	8.45 ± 2.10
6 hour	9.25 ± 0.00	9.95 ± 0.20	10.77 ± 0.84
12 hour	10.4 ± 0.00	10.17 ± 1.19	10.08 ± 0.12
18 hour	8.43 ± 0.49	8.60 ±0.58	9.47 ± 0.73
24 hour	11.03 ± 2.51	8.60 ± 0.58	10.88 ± 1.69
48 hour	8.8 ± 1.35	9.00 ± 0.98	12.93 ± 1.70

Mean values of the Total white blood cell count for the control, intramuscular and transdermal group after castration. No significant difference ($P > 0.05$) between the groups.

In Table 13, there was no significant difference in the parked cell volume (PCV) between all the groups.

Table 13: Parked Cell Volume (PCV) (%) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	29.33 ± 1.20	26.33 ± 4.06	29.67 ± 1.33
6 hour	29.00 ± 1.00	22.00 ± 2.08	27.7 0 ± 3.70
12 hour	32.33 ± 0.88	31.33 ± 2.85	35.67 ± 2.33
18 hour	31.00 ± 1.53	26.33 ± 3.53	35.00 ± 3.00
24 hour	30.33 ± 0.33	26.22 ± 3.53	29.33 ± 0.67
48 hour	32.33 ± 0.88	33.00 ± 2.31	31.33 ± 1.33

Mean values of the parked cell volume for the control, intramuscular and transdermal group after castration. No significant difference ($P > 0.05$) between the groups.

Table 14: Basophils Count ($\times 10^9 L^{-1}$) (Mean ± SEM):

Time	Control (n = 4)	Intramuscular route (n = 4)	Transdermal route (n = 4)
1 hour	0.43 ± 0.29	0.16 ± 0.16^a	0.00 ± 0.00^b
6 hour	0.03 ± 0.03	0.07 ± 0.07	0.00 ± 0.00
12 hour	0.14 ±0.07	0.24 ± 0.14	0.00 ± 0.00
18 hour	0.03 ± 0.03	0.03 ± 0.03	0.00 ± 0.00
24 hour	0.00 ± 0.00	0.03 ± 0.03	0.00 ± 0.00
48 hour	0.02 ± 0.02	0.00 ± 0.00	0.09 ± 0.05

Mean values of the Basophils count for the control, intramuscular and transdermal group after castration. ^{a,b} = Mean with the superscript letter within row is significantly different at ($^{a,b}P < 0.05$) compare to the control group at 1 h post-surgery.

DISCUSSION

Stress changes autonomic balance by influencing intraventricular conduction time of the cardiovascular system. These changes cause an increase in QRS duration on ECG tracings (Omkar and Santhosh, 2018). At 18 h post-surgery, the QRS intervals for the transdermal and intramuscular groups were shorter compared to the control group; this may be due to the analgesic effect of metamizole sodium on the treated groups. We, however, observed that the QRS values recorded for the intramuscular group were relatively higher than those of the transdermal group. This may be attributed to pain at the site of injection for patients in the intramuscular group. An earlier report by Arpana *et al*., (2015) had observed an increase in QRS duration in humans when stressed. Stress has also been discovered to induce changes in ventricular repolarization by augmentation of the autonomic nervous system, discharging catecholamines and glucocorticoids (Omkar and Santhosh, 2018).

The T amplitude of the control group was higher than the intramuscular and transdermal groups in our study. Although Omkar and Santhosh, (2018) reported that there was no significant difference in the T amplitudes of ECG readings in stressed and non-stressed patients except for the variations in shape in the wave pattern due to the release of catecholamines and glucocorticoids observed in stressed patients. Chu *et al*., (2017) however, had earlier reported that T amplitude, in addition to the QRS complex, also gives useful information on pain perception.

In this study, although there was no significant difference in the neutrophil cell count between the transdermal and intramuscular groups, the value obtained for the transdermal group at the end of the experiment was relatively high compared to the value recorded for the intramuscular group.The decrease observed in the intramuscular group may be due to the effect of metamizole sodium on white blood cells, most especially the neutrophils. Metamizole sodium

possesses a life-threatening risk of agranulocytosis with an unpredictable but fatal onset. (Nikolova *et al*., 2012).

When the pre-surgical values were compared to the value obtained at 48 h post-surgery, the percentage decrease of neutrophil count for the transdermal group was 13.83%, while the intramuscular group decreased by 57.33%. This shows that there was much more decrease in the neutrophil count of the intramuscular group than the transdermal group.This is inconsistent with the report of Huber *et al*. (2015), who discovered that 30% of patients treated with metamizole sodium had a gradual drop in their neutrophil cell count leading to neutropenia, and continuous administration may lead to agranulocytosis with a count below 0.1 × 109 cells/L. We, therefore, hypothesized that the decrease in the cell count observed following the use of this drug is a gradual process, which first manifests as a gradual decrease of the neutrophil cells resulting in neutropenia, and continued administration may lead to agranulocytosis.

CONCLUSIONS

The administration of metamizole sodium via the transdermal route prevented the side effect of agranulocytosis, evident by the decrease in neutrophil count of the IM group compared to the transdermal group. Metamizole sodium transdermal patch induced analgesia, evident by the increase in QRS interval and decrease in P and T amplitudes of the ECG reading. This may be beneficial in alleviating pain due to castration in Nigerian indigenous dogs.

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