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Influence of Hydrocortisone, Dexamethasone and Methylprednisolone on Wound Healing Parameters on Nigerian Indigenous Dogs

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Abstract

Wound healing is a complex activity of several cells with their products leading to tissue regeneration and repair. Twelve indigenous breeds of dogs were randomly grouped into groups I, II, III and IV of 3 dogs each. Excisional and incisional wounds were surgically created on the left and right sides respectively. The dogs in Group I were administered normal saline while Groups II, III and IV were given hydrocortisone, dexamethasone and methylprednisolone respectively at 1.0, 0.5 and 1.0 mg/kg intramuscularly post-wounding. The wounds were cleaned and assessed for epthelialisation, contraction and pus formation. RESULT: The wound dimensions from insult of excisional wound, increased steadily to peak (10.34 cm^2) at 10th day in the control, (12.21 cm^2) 17th day; (11.97 cm^2) 12th day and (13.87 cm^2) 17th day post-wounding in the hydrocortisone, dexamethasone and methylprednisolone treated groups respectively. Maximum contraction was recorded at 33rd day (3.52 cm^2) in the control, 40th days (3.55 cm^2), 30th (3.86 cm^2) and 42nd (3.98 cm^2) in the hydrocortisone, dexamethasone and methylprednisolone groups respectively with insignificant statistical difference.

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The wound dimensions from the insult in the incisional wounds increases steadily to peak (6.31 cm^2) at 7^{th} day in the control; (7.51 cm^2) 10^{th} day; (6.81 cm^2) 12^{th} day and (8.38 cm^2) 10^{th} day post-wounding in the hydrocortisone, dexamethasone, and methylprednisolone treated groups respectively. Maximum contraction was recorded after complete epithelialisation at 24^{th} day (2.32 cm^2) in the control, 21^{st} days (3.58 cm^2), and 26^{th} (2.39 cm^2) and 31^{st} (3.32 cm^2) in the hydrocortisone, dexamethasone, and methylprednisolone groups respectively with insignificant statistical difference ($p<0.05$). The administration of steroids (anti-inflamatory) does not prevent wound retraction especially with the use of methylprednisolone, however, the dexamethasone treated group had the least scar size post healing.

Keywords: Dexamethasone; hydrocortisone; methylpredisolone; steroids; wound healing

INTRODUCTION

The skin offers a defensive barrier between an individual with its external environment to counter physical damage, pathogens, fluid loss, and provide immuno-neuro-endocrine roles that is essential in the sustenance of the body homeostasis (Nejati *et al*., 2013; Canedo-Dorantes and Canedo-Agala, 2019). In order to uphold its physiological role, skin integrity must be promptly re-established in the event of an injury (Gouin *et al*., 2017; Shedoeva *et al*., 2019). Wound healing is essentially a complex physiological response which culminates in tissue regeneration and repair (Gemzell *et al*., 2010; Gonzalez *et al*., 2016; Juneja *et al*., 2020). Most surgical process involves wound creation, hence, to be surgically successful, optimal wound management to obtain minimal scar tissue, preserve and return of function within the minimal healing time is the key (Milne, 2008; Kalang et al., 2022). At the insult of injury, inflammatory signaling increases DNA availability, hence, promoting phenotypic fluidity at the injured site (Gouin *et al*., 2017; Bajpai *et al*., 2019; Canedo-Dorantes and Canedo-Agala, 2019). Hence, the cells in the wounded environment undertake conspicuous phenotypic deviations from an inactive basal state of specialized function, to a proliferating, migrating cell, establishing novel intercellular links, and executing new functions in the presence of superoxide anion (Bajpai *et al*., 2019; Canedo-Dorantes and Canedo-Agala, 2019; Zhoua *et al*., 2019; Zhou *et al*., 2020).

Its important to note that, improper management increase duration of hospitalisation, expenditure, stress (discomfort), deterioration of condition and death of patients. Wounds with excessive tissue loss are allowed to heal by secondary intention, while patients receiving immunosuppressive drugs or are immunosuppressed will have suppressed inflammatory response and in the aged, hormone replacement therapy reverses age-linked conditions (Mir *et al*., 2018; Alemu *et al*., 2020). This positive response is generally enhanced with occlusive or semi-occlusive dressing (Can and Thao, 2020; Mehmet *et al*., 2020). Wound management is of great concern in both human and animal health and requires frequent dressing and management reviews (Mir *et al*., 2018; O'Brien *et al*., 2018). Wound repair usually ends with a scar, which is absent during fetal growth, suggestive of the immune system interference (Hosseinkhani *et al*., 2017; Barnes *et al*., 2018; Moore *et al*., 2018).

Steroids exert both metabolic and hormonal effects by influencing gluconeogenesis, increasing blood flow to the skin, reduce sebaceous gland secretion, as well as the function, and formation of connective tissue, thus depressing scarring (Hassan and Egege, 2004; Brown *et al*., 2008). They limit oedema formation, control excessive inflammatory response, thereby enhancing drug penetration. The major physiological role for steroids, is that of increasing the ability of the body to resist stress. Hence, the use of steroids for days is rarely troublesome but dosing for more than a week at inflammatory-suppressing dosage carries the possibility of suppressing pituitary-adrenal responsiveness (Rashmi *et al*., 2005; Albano *et al*., 2021). The role of cyokines and immune cells in enhancing surgical wound healing is only visible via

inflammatory reaction, of which steroids may be used to modulate the inflammatory response in favour of wound healing as they enhance cellular stability and membrane receptor response. Cortisone retards the development of granulation tissue. Dexamethasone increases the phagocytic activity of monocytes/ macrophages (Carolina *et al*., 2018; Desgeorges *et al*., 2019). Cellular events in wound healing are depressed by steroid and also reduces circulating endothelial progenitor cells (Barcha and Ranzer, 2018). Patients with conditions that require prolong administration of steroid and are being operated upon are at high risk of delayed wound healing (Carolina *et al*., 2018). However, conflicting reports occur on the effect of steroids on wound healing; like steroids may delay wound healing (Poungvarin, 2004; Milne, 2008), while Nasser *et al*. (2008) reported that steroids have no negative effect on wound but speed-up wound healing. The conflicting reports may be as a result of different steroids been used; hence, this work compares the effects of the commonly used and available steroids on wound healing

MATERIALS AND METHODS

Acclimatisation of Experimental Animals and Pre-Surgical Management

Twelve Nigerian indigenous breeds of dogs were acquired and transported to the Veterinary Teaching Hospital, Ahmadu Bello University, Zaria and were accommodated in the Small Animal Kennel of the hospital. The twelve dogs weighing between 10-18 kg, were allowed to acclimatise in the kennel for two weeks. The dogs were physically examined, blood and faecal samples were also taken for laboratory screening at the Protozoology, Clinical Pathology and Helminthology Laboratories for haemoparasite, haemogram and helminthes respectively. The samples taken to Protozoology Laboratory were negative for all haemoparasites and the haemogram from the Clinical Pathology Laboratory were all within normal range. However, samples sent to Helminthology Laboratory were positive for tape worm and hook worms, the animals were treated with Praziquantel (7 mg/kg) and Oxytetracycline (20 mg/kg) for secondary bacterial infection.

Surgical Procedure (Wounding)

Food and water were provided *ad li-bitum* throughout the period of the experiment; except six hours prior to surgery, feed and water were not given to the dogs. Following aseptic procedures, the dogs were pre-aneasthetised with Atropine sulphate (0.02 mg/kg) and Chlorpromazine hydrochloride (0.5mg/kg) intravascularly (IV), they were anaesthetised with Thiopentone sodium (25mg/kg IV), and rectangularly draped. Using the sterilised wound template on the cranio-dorsal part of the animal, a 2 X 3 cm area was marked. Five centimeter away from the scapular and 3 cm from the vertebrae for the excisional wound on the left side; 15 cm from the excisional point, a 5 cm mark was made 3 cm away from the vertebrae on the left side of each dog, these were reversed on the right side. The wounds were surgically created, haemorrhages were controlled through the application of sterilised gauze under digital pressure or haemostatic forceps.

Post-Surgical (Wounding) Management

Daily wound dressing was observed until absence of visible wound discharges, subsequently, an alternate day of dressings were employed. The dogs were grouped randomly into groups I, II, III and IV of 3 dogs each (Table 1). The dogs in the control group (group I) was not given any medication (steroids) but normal saline, Group II was given hydrocortisone at 1 mg/kg body weight intramuscularly, Group III was given dexamethasone at 0.5mg/kg intramuscularly and Group IV was given methylprednisolone at 1mg/kg intramuscularly. The steroids were administered as a single dose post-wounding.

Table 1. Experimental design (grouping, treatment and sampling days).
Key: No.= Number; IM= Intramuscular; WE= Wound evaluation

Group	Treatment	No. of dogs	Days for WE
I	No steroid given	3	0, 3, 7, 14, 21
II	Hydrocortisone 1mg/kg IM. 1/7	3	0, 3, 7, 14, 21
III	Dexamethasone 0.5mg/kg IM. 1/7	3	0, 3, 7, 14, 21
IV	Methylprednisolone 1mg/kg IM. 5/7	3	0, 3, 7, 14, 21

Aseptical procedures were adhered to during post-operative wound dressing and data collection. The wounds were cleaned four times at each dressing using sterilised guaze and dilute Chlorhexidine (Purit®) by gentle dabbing. Charmil® gel was applied, subsequently covered with a sterile gauze, stabilized with an adhesive plaster and held in place using crêpe bandage.

Data Collection/ Statistical Analysis
Wound dimensions were taken using flexible measuring tape. The mean values of excisional wound area, incisional wound area, rate of epithelisation of excisional and incisional wounds were subjected to statistical analysis using One way Analysis of Variance (ANOVA) SPSS version 23 to determine the significance of the result at probability value of less than 95% which was considered as significant.

RESULTS
Wound area was measured using a flexible meter rule, while the mean excisional wound area for the control, hydrocortisone, dexamethasone, and methylprednisolone treated group were documented respectively. Excision wound and epithelialisation dimensions were also detailed in Figures 1 and 2 respectively, while the mean incisional wound dimensions and epithelization in Figures 3 and 4 accordingly.

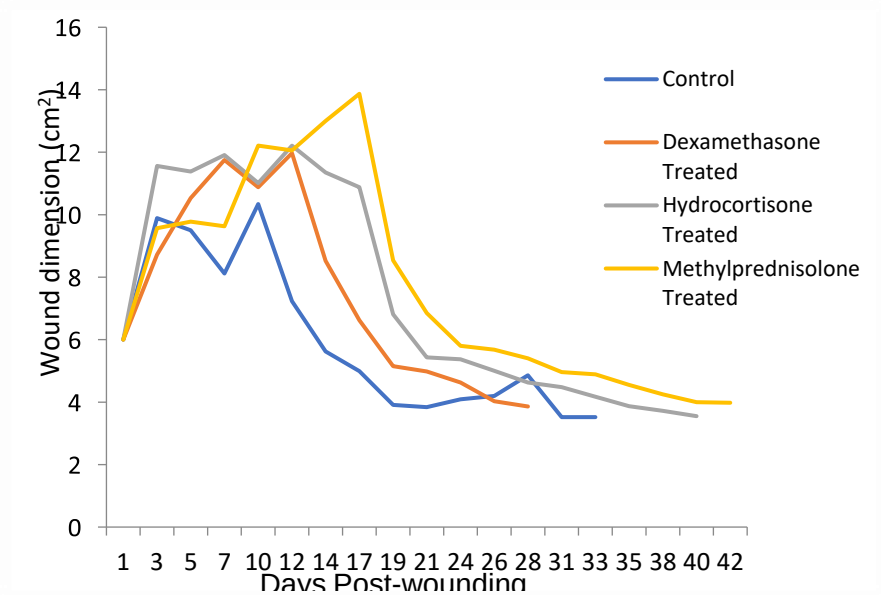

Figure I: Mean excisional wound area

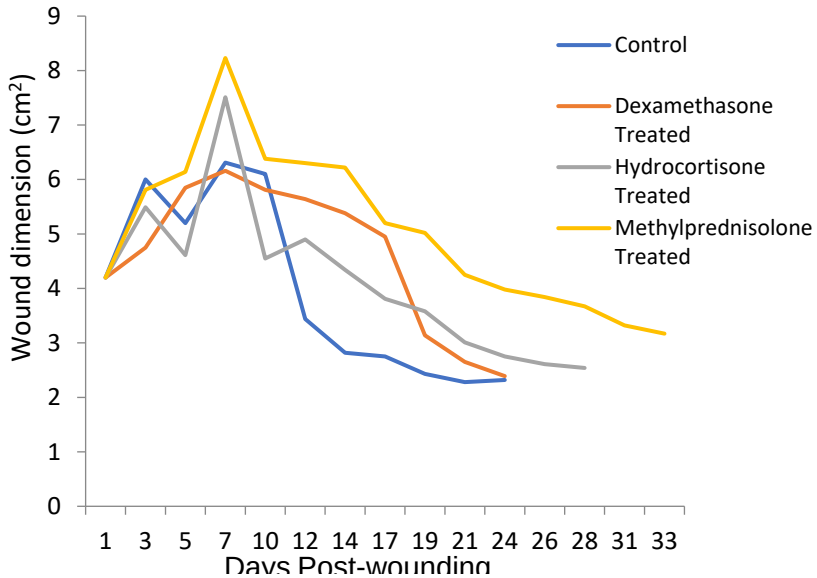

Figure II: Mean incisional wound area in centimeter square

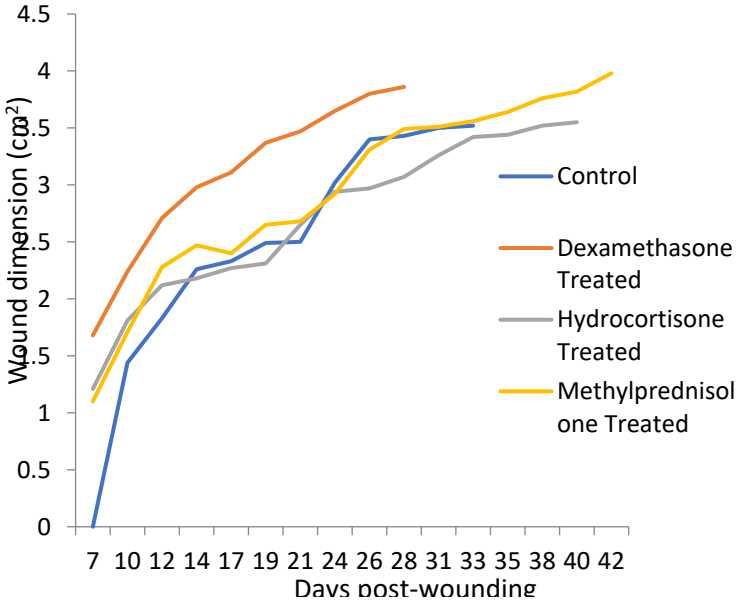

Figure III: Mean excisional wound epithelisation area

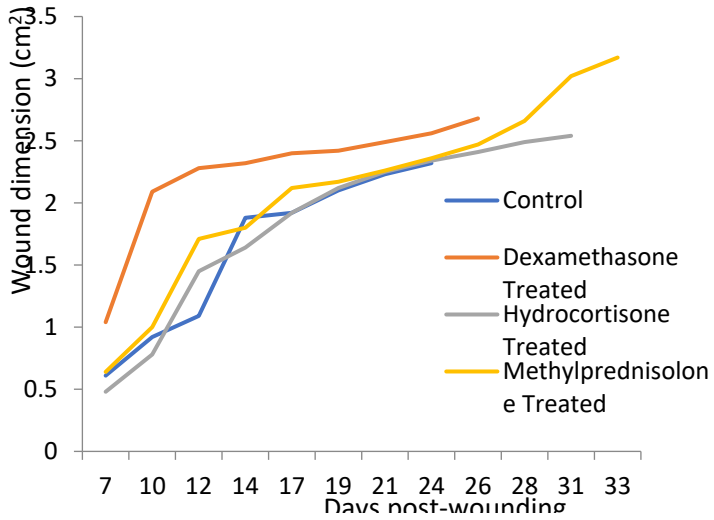

Figure 4: Mean incisional wound epithelisation area

Wounds on the first five days of dressing were stained with Charmil® gel used in the wound management. Pus was also seen in all the groups from day three post wounding and persisted till Charmil® gel was unable to stain the tissue, coinciding with the progression of granulation tissue by 10th day. However, pus persisted in hydrocortisone-treated group to 12th day post-wounding and 14th day post-wounding in the methylprednisolone-treated group. Scanty granulation tissue formation was visible in all experimental groups by 3rd day at the wound edges and completely became bright pink by 14th day post-wounding in all the groups.
Signs of itching occurred in the control and hydrocortisone treated group between 3rd and 8th days post wounding. However, this was not seen in the group treated with dexamethasone and methylprednisolone. Hair regrowth was more by day ten post-wounding in the methylprednisolone and hydrocortisone-treated groups compared to that in the control and the dexamethasone-treated groups.

Excisional wound dimensions at insult progressively increases to peak (10.34 cm^2) at day ten in the control, (11.97 cm^2) day twelve, (12.21 cm^2) and (13.87 cm^2) day seventeen post-wounding in the dexamethasone, hydrocortisone and methylprednisolone treated groups respectively. Maximum contraction was recorded in this study immediately after complete epithelialisation as summarised in Figures 1 and 2, though, not statistically significant ($p<0.05$). The wound dimensions from the insult of the wound in the incisional wounds increases steadily to peak (6.31 cm^2) at day seven in the control, (6.81 cm^2) day twelve, (7.51 cm^2) 10th day and (8.38 cm^2) day ten post-wounding in the dexamethasone, hydrocortisone and methylprednisolone treated groups respectively. Maximum wound contractions were recorded in this study immediately after complete epithelialisation (Figures 3 and 4) though, not statistically significant from each other ($p<0.05$).

Table 2: Percentage of excisional wound contraction

Group	Initial Wound Size (cm)	Final Wound Size (cm)	Percentage contraction (%)
Control	6	3.52	41
Hydrocortisone	6	3.86	36
Dexamethasone	6	3.55	41
Methylprednisolone	6	3.98	34

Table 3: Percentage of incisional wound contraction

Group	Initial Wound Size (cm)	Final Wound Size (cm)	Percentage contraction (%)
Control	4.2	2.32	45
Hydrocortisone	4.2	2.39	43
Dexamethasone	4.2	2.54	39
Methylprednisolone	4.2	3.17	24

The incisional wounds were presented in Figures 5-12, while excisional wounds Figures 9-12 indicating wound stain, granulation tissue and epithelisation.

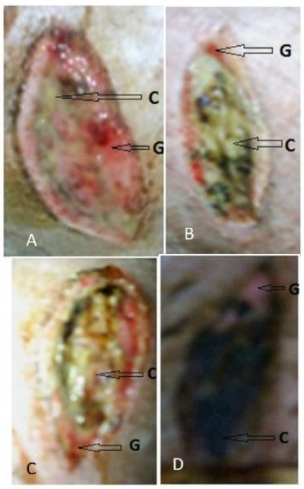

Figure 5. Day 3 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Charmil (C); Granulation tissue (G).

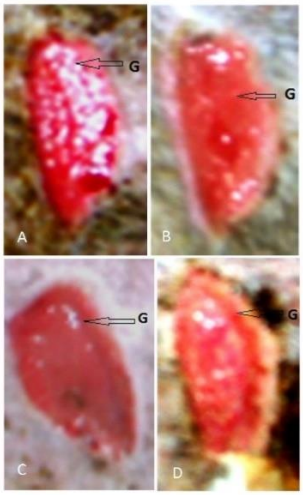

Figure 6. Day 7 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G).

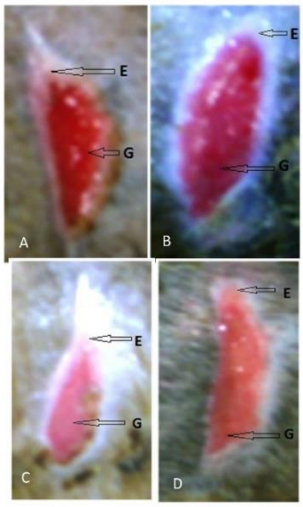

Figure 7. Day 14 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G). Epithelisation (E).

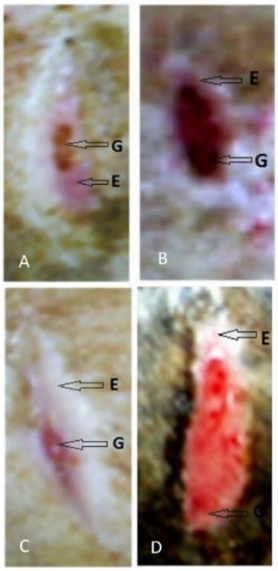

Figure 8. Day 21 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G).

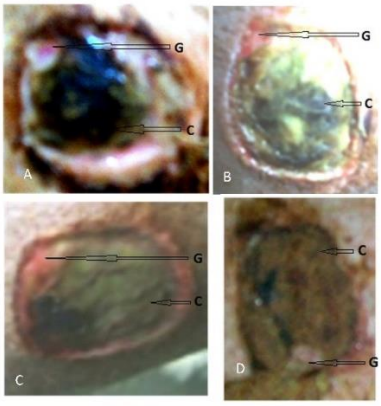

Figure 9. Day 3 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G);
Epithelisation (E).

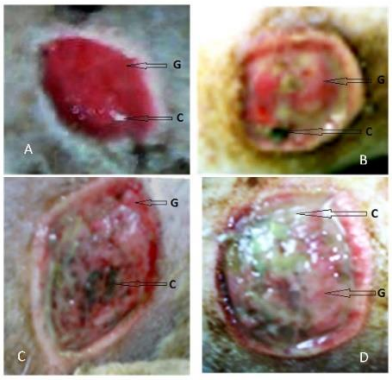

Figure 10. Day 7 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G);
Epithelisation (E).

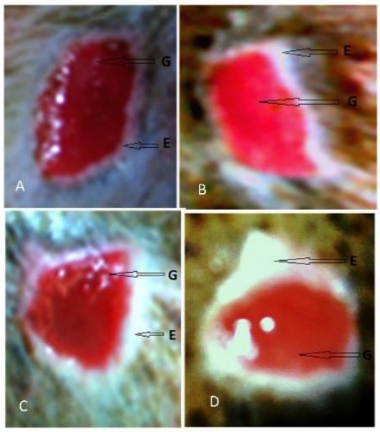

Figure 11. Day 14 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G);
Epithelisation (E).

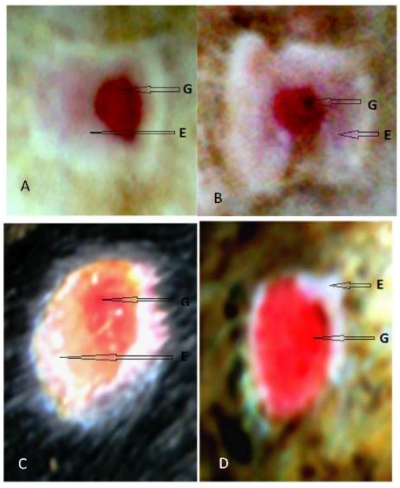

Figure 12. Day 21 post-wounding. A: Control group. B. Hydrocortisone group C. Dexamethasone group. D. Methylprednisolone group. Note:- Granulation tissue (G);
Epithelisation (E).

DISCUSSION

From this study, wound size increased steadily from the day of wounding which could be due to severe infiltration of inflammatory cells into the injured site in all the experimental groups as seen in the 3rd day post-wounding. The initial increase in wound size could likely be due to inflammatory cell infiltration and oedema. Janice (2002) reported increase in wound size during necrotic tissue debridement, and decrease as infection was controlled, Joseph and Chris (2007) also observed initial increase in wound size. We also observed in this study that, the inflammatory process of wound healing was not prevented in the steroid treated, Mahmut *et al*. (2003) also reported more inflammatory response in the steroid treated groups. The control group had least wound retraction relative to the steroid treated groups in this current studies. Carolina *et al*. (2018) reported that, steroid reduces inflammation, inflammatory cells infiltration and oedema. However, we observed that, steroids did not prevent wound retraction, perhaps it could be due to the phenotypic fluidity of the wounded area. (Gouin *et al*., 2017; Canedo-Dorantes and Canedo-Agala, 2019) similar observation has been reported. Steady reduction in wound size from its insult without wound retraction was documented (Nayak *et al*. 2011; Umeh *et al*., 2014; Alemu *et al*., 2020). The methylprednisolone-treated group had the least reduction in wound size at the end of the healing process, while the hydrocortisone-treated group among the steroid treated groups tends to be more effective in

reducing incisional wound size. This could be due to the fact that hydrocortisone have the least glucocorticoid effects after cortisone (Martin, 2003) Hence, it may be preferred in a less invasive surgical procedure or minor wounds. Dexamethasone proved to be more efficient in reducing excisional wound size, hence, it may be preferred in invasive surgical procedures or degloving wounds. Perhaps the use of the steroids prior to wounding may be efficient in controlling the infiltration of inflammatory cells and oedema, since it has been established that inflammatory process commences at the insult of the wound and that steroids block the inflammatory process (Gabriel *et al.,* 2009). Increase in wound size in the steroid treated groups may not only be due to inflammatory cells, but also, reduce in skin rigidity, increase in flaccidity of skin, reduce in bond between skin cells and increase in retraction of cells from injured site. Epithelialisation from the wound edges occurred from 5th and 3rd day post-wounding in the excisional and incisional wounds respectively. This observation is similar to the report of Gabriel *et al.* (2009). We observed that epithelialisation was not uniform, but more from one direction (unilateral), that is, caudo-cranially, the non-uniform epithelialisation could be due to skin cells arrangement, looseness of the skin from the underlying structures, slow debridement of debris and necrotic tissue, low oxygen tension or non-uniform distribution of cytokines. However, Fishman (2009) has earlier reported uniform epithelialisation from all wound edges**.** The short healing time observed in the dexamethasone for excisional wound and hydrocortisone for the incisional wound, answers the observation raised by Rasheed and Qasim, (2013), that no report carries difference in the use of these steroids. Reduction in wound size was sharp between 10th – 21st day especially in the steroid treated wounds. This was contrary to Raja and Sundar (2015) who reported maximal wound contraction between 8th – 11th day. Granulation tissue formation was observed on 3rd day post-wounding in all the groups at the wound edges. Granulation tissue formation is evident from 48 hours of post-wounding (Peacock and Kelman, 1990). Significant advance of granulation tissue was observed by 7th day in both the excisional and the incisional wound of all the experimental groups, but were relatively more in the dexamethasone and the control group. This may explain why the control and the dexamethasone had almost same time of excisional wound healing, and also it may also mean that dexamethasone had insignificant suppressive effect on fibroblast, while hydrocortisone expresses enhanced incisional wound healing. Bright pink granulation tissue colouration signifies less collagen deposits (Peacock and Kelman, 1990). This was also seen in this work as the bright red granulation tissue on 14th day in the incisional wound turns slightly deem and 21th day in the excisional wounds, most likely will coincide with high fibroblast activities/ proliferation.

CONCLUSION

The wound sizes at the end of this study were smaller in the groups that showed signs of itching (control and hydrocortisone group). Mast cells could have significant role in wound contraction and may be responsible for the itching? Steroid did not prevent wound retraction (increase in wound size), rather, more wound retraction was witness in this study with the use of steroids. Peak of collagen deposit between 12th – 21st day post wounding, coincided with high fibroblast and myofibroblast. We also conclude that the management of wounds with steroids enhanced epithelialisation especially with the use of methyleprednisolone.

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CONFLICT OF INTERESTS

The authors declared that there is no conflict of interests.

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