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# The Effect of Lidocaine with/without Epinephrine on Healing of Cutaneous Incised Wounds in Donkeys: An Experimental Study

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## Abstract

**Objective:** To study the effect of lidocaine with / without epinephrine on the wound healing.

**Study Design:** An experimental study.

**Animals:** 18 clinically healthy donkeys of both sexes.

**Methods:** Animals were divided into 3 equal main groups, lidocaine group in which plain lidocaine 2% was used for local infiltration, epinephrine group in which lidocaine 2% with epinephrine 0.00227% was used and the control group, in which wounds were induced under effect of intravenous (IV) thiopental aesthesia 10% (6 mg/kg) without any local infiltration. Wound samples were taken for histopathological examination on the 7$^{th}$ and the 14$^{th}$ days post wound induction.

**Results:** There was no distinct difference in bleeding after wound inductions between the experimental groups. Grossly, lidocaine group had delayed healing process on the 7$^{th}$ day post wound induction, manifested by dehiscence between wound edges especially in the mid-way of the wounds. Lidocaine with epinephrine group had good healing process with complete closure between wound edges within the same period. Rate of infection was of high incidence in lidocaine group. In histopathological examination, skin sections of lidocaine group showed extensive hemorrhage on the 7$^{th}$ day post wound induction and there was incomplete epithelization in the epidermis by the 14th day post wound induction. Lidocaine with epinephrine group showed partial epithelization of the epidermis on the 7$^{th}$ day while on the 14$^{th}$ day post wound induction; skin section had completed epithelization in the epidermis with presence of mature collagen bundles at the dermis.

**Conclusions:** The present study showed that addition of epinephrine to lidocaine enhances and accelerates the healing process more bitter than plain lidocaine.

**Keywords:** Lidocaine; Epinephrine; Healing; Donkeys

## Introduction

Uncomplicated wound healing is one of the major goals of every surgical procedure [1]. Food animal practitioners commonly perform local anesthetic techniques due to the dangers associated with general anesthesia [2].

Surgical wound infiltration with local anesthetic agents is widely used to provide a cost effective and relatively low risk method of localized analgesia; the technique is not difficult and has relatively few side effects [3]. In addition, local anesthetics provide a reversible regional loss of sensation and could be used to delay nociceptive input in postoperative pain management [4].

Lidocaine is the most widely used local anesthetic in the veterinary field. It possesses a reasonably rapid onset of action, with good spreading properties [5]. Local infiltration anesthesia is usually accompanied with some problems. Infection, irritation, distortion of the wound, swelling and some delay in wound healing are the most ones [2].

The addition of adrenaline to a local anesthetic prolongs its duration as well as reduces bleeding during operations at the site of injection [6].

Due to the contrary and conflicting results of many researchers on the effects of lidocaine with and without epinephrine on wound healing process in many literatures, the purpose of the present study was to clarify the effect of lidocaine with and without epinephrine on the wound healing process in experimental cutaneous incised wounds in donkeys.

## Materials and Methods

### Animal model

18 clinically healthy donkeys of both sexes, weighing between 90 to 200 kg body weights were used in this study. The animals were housed

in a well-ventilated and temperature controlled room with water and food available.

## Experimental design

This study has been proved by the national ethical committee (faculty of Veterinary Medicine, Assuit University, Egypt).

Animals were given wounds of a 5 cm length in the skin at the mid neck regions under complete aseptic condition using a changeable scalpel no. 24. Bleeding was controlled using pressure with sterile gauze.

According to the local analgesic used for wound induction, animals were divided randomly into three main equal groups, lidocaine group (L group=6 animals) in which wounds were made under the effect of linear local infiltration using 10 ml Lidocaine 2%, lidocaine/epinephrine group (P group=6 animals) in which a Lidocaine 2% with adrenaline 0.00227% was used and the control group (C group=6 animals) in which wounds were made under the effect of intravenous (IV) thiopental anaesthesia 10% solution (6 mg/kg) without use of any local analgesic infiltration at the site of incision (repeated doses were used when needed).

For histopathological sampling purposes, each main group was subdivided into 2 subgroups, each of three animals (L7 and L14), (P7 and P14) and (C7 and C14) for the lidocaine (L), lidocaine/epinephrine (P) and control (C) groups respectively (Table 1).

| Groups | Subgroups | No. of Animals | Type of local analgesia |
|---|---|---|---|
| C | C7 | 3 | Tiopental (6 mg/kg) 10% (intravenous) |
| | C14 | 3 | |
| L | L7 | 3 | Lidocaine 2% |
| | L14 | 3 | |
| P | P7 | 3 | Lidocaine 2%/Epinephrine 0.00227% |
| | P14 | 3 | |
| Total | 18 | | |

**Table 1:** Showing experimental animals groups.

All incisional skin wounds were closed by simple interrupted suture pattern using non-absorbable suture material, silk no. 2. Antibiotics and anti-inflammatory were not administered postoperatively.

All wounds were kept under clinical observation from the 1st day up to the 14$^{th}$ day post wound induction. Bleeding after incisions, gross changes during the healing period, as well as incidence of infection if found were recorded during the observation time (14 days). Vital signs (temperature, heart rate and respiratory rate) were assessed daily during the time of the experiment.

## Sampling for histopathological examination

Samples for histopathological examination were collected on the 7$^{th}$ day post wound induction from subgroups L7, P7 and C7 and on the 14$^{th}$ day from subgroups L14, P14 and C14.

On the day of sampling the animals were euthanized using a chloral hydrate intravenous 10% (9 gm/50 Kg BW). An excision 2 × 2 cm wound samples including the line of wound healing were obtained from the middle of the wound for histopathological examination.

## Sample preparation

Samples were dissected at 1 × 1 × 0.05 cm and were immediately fixed in 10% neutral buffer. The fixed materials were dehydrated in an ascending series of ethanol, cleared in methyl benzoate and then embedded in paraffin wax. Transverse and longitudinal paraffin sections at 5-8 µm in thickness were done and stained with Harris haematoxylin and Eosin [7], and were examined microscopically.

## Results

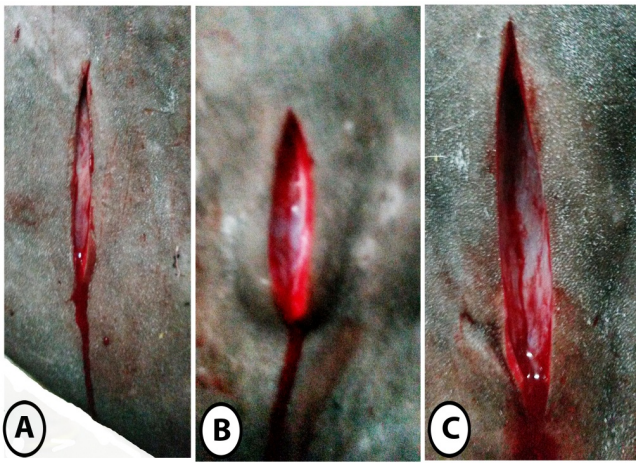


**Figure 1:** Bleeding at site of incision. **1A:** control group, **1B:** lidocaine group, **1C:** lidocaine with epinephrine group.

## Clinical observations

Gross examination of the wounds in group (L) showed delayed healing process and wound dehiscence especially in the midway of the wound on the 7$^{th}$ day post wound induction. In comparison, wounds in groups (P and C) showed complete closure with good adhesions between the wound edges within the same period. Grossly, the wound healing was analogous in all groups at the 14$^{th}$ day post wound induction (Figures 2A, 2B and 2C). Vital signs measurements (body temperature, heart rate and respiratory rate) showed non-significant changes.

## Infection rate

Wound infection was recorded in three animals in subgroup (L7), these animals were excluded from the experiment.

## Histopathological examination

### Group C (control)

**Subgroup (C7):** Skin sections showed hematoma formation with inflammatory cell infiltrating the tissue at the site of the wound (Figure 3A).

**Subgroup (C14):** There was complete epithelisation of the epidermis with granulation tissue formation at the dermal layer (immature granulation tissue) (Figure 3B).

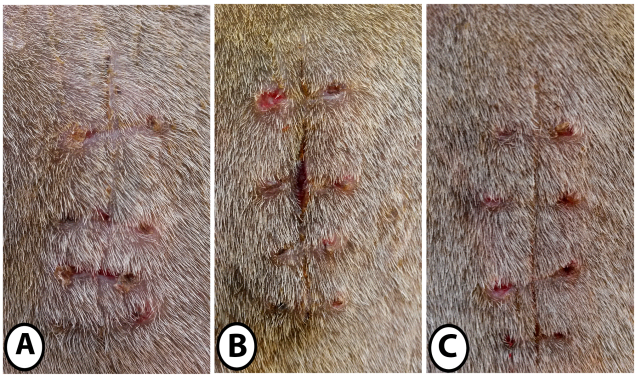


**Figure 2:** Healing process grossly. **2A**: control group, **2B:** lidocaine group, **2C:** lidocaine with epinephrine group.

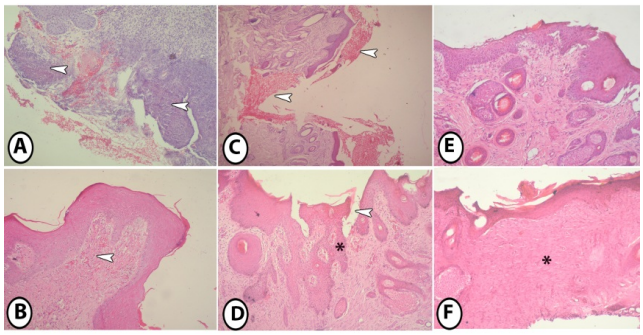


**Figure 3:** Histopathological examination. **3A:** Control group at 7 days post-wound induction showing infiltration of many inflammatory cells at site of the wound (arrowheads), **3B:** Control group at 14 days post-wound induction showing immature granulation tissue (arrowhead), **3C:** Lidocaine group at 7 days post-wound induction showing extensive hemorrhage (arrowheads), **3D:** lidocaine group at 14 days post-wound induction showing incomplete epithelization of epidermis (arrowhead). Note formation of granulation tissue at subepithelial layer (asterisk). **3E:** Lidocaine with epinephrine group at 7 days post-wound induction showing partial epithelization of epidermis, **3F:** Lidocaine with epinephrine group at 14 days post-wound induction showing presence of mature collagen bundles at the dermis (asterisk).

**Group L (lidocaine group)**

**Subgroup (L7):** Skin sections showed extensive hemorrhage (Figure 3C).

**Subgroup (L14):** On the 14$^{th}$ day post wound induction; there was incomplete epithelization of the epidermis with presence of granulation tissue formation at the subepithelial layer (Figure 3D).

**Group P (Lidocaine with epinephrine)**

**Subgroup (P7):** On the 7$^{th}$ day post wound induction there was partial epithelization of the epidermis with presence of inflammatory cell infiltrating the dermis (Figure 3E).

**Subgroup (P14):** On the 14$^{th}$ day post wound induction, skin sections showed complete epithelization of the epidermis with presence of mature collagen bundles at the dermis with absence of skin adenexia (Figure 3F).

According to the results of the histopathological examinations of our study, it was clear that lidocaine/epinephrine group was the best group regarding to the healing process (complete epithelization +mature granulation formation) while during the same period the control group has been showed complete epithelization with immature granulation tissue formation at the dermal layer. However, lidocaine group failed to achieve the same results within the same time

## Discussion

Lidocaine is the most local analgesic used in most of surgical interferences in large animals that can be done under local analgesia as it is effective, has a rapid onset, considerable long duration and inexpensive.

Despite the known advantages of adding the epinephrine as a vasoconstrictor agent to local analgesic agents; many surgeons do not prefer such combination thinking that it may be caused delaying in the healing process of wounds.

Few studies were done on the effect of adding of epinephrine to lidocaine on wound healing after surgery [1,8-12].

Most of these studies were performed on small animal models, as rats [1,8,9,12], mice [13], guinea pigs [10,14], and rabbits [15]. The concordance rate between rodents and human is only 53% which suggests that results from rodent models are not likely to translate into improved clinical outcomes [16].

This is the first study done on a large animal model, the donkey, which is a very important animal for many farmers and commonly admitted to the veterinary clinics with different surgical affections and it is very important to obtain a rapid healing process without any surgical complications.

In the present study, the amount of bleeding following surgical incisions was little and controllable by routine pressure tampon. There was no distinct difference between studied groups. This may be attributed to the sharpness of the surgical scalpel used for wound induction which causes a very localized tissue damage but no injury to the surrounding cells rather than the transient vasoconstriction that occurs as an initial response to the injury that lasting 5-10 min. The effect of the epinephrine as a vasoconstricting agent to control oozing of blood and decrease the haematoma formation in the wound may be more distinct in highly vascular areas such as scalp [17].

Lidocaine exerts a biphasic effect on peripheral vascular smooth muscle, so at low doses it causes vasoconstriction and at high doses vasodilatation [18]. This was matched with findings of this study by using small doses of lidocaine 2% in group (L).

The histopathological results in our study showed that the period of healing in lidocaine/epinephrine group was shorter and the epithelization was rapid and complete in comparison to the healing process in plain lidocaine group where there was incomplete epithelization till the 14$^{th}$ day post wound induction.

This was an explanation to our gross findings of wound dehiscence in lodocaine group and hence the increased incidence of infection in this group.

However our findings were not in agreement with [10] who reported that infiltration of the wounds with lidocaine 2% had antibacterial effect and decreased the bacterial count (Staphylocoocus aureus) in such wounds whereas the addition of epinephrine (1:100000) to lidocaine increased the bacterial count by 20 fold comparable with the control values. They attributed this to the hypoxia secondary to the vasoconstricting effect of epinephrine that may interfere with the host defense mechanisms accessing the wound site.

In another study, [18] has been recorded that lignocaine has been associated with poor wound healing and increased risk of wound infection especially when combined with adrenaline.

Also, healing process in lidocaine/epinephrine group also characterized by mature collagen fibers in contrast to immature ones in the control group.

Similar findings to our results were recorded and [1] who stated that addition of epinephrine to lidocaine did not impair wound healing, on contrarily it accelerates wound healing in the early phase by stimulating fibrosis.

On the other hand our results were with disagreement with [13-15] who recorded that lidocaine did not alter substantially wound healing [8] have been found that lignocaine at various concentrations (0.5-2%) had an adverse effect on wound healing and adrenaline (1:100000) potentiated this effect.

Impairment of wound healing in lidocaine groups may be attributed to that lidocaine affects collagenization, reduces the level of collagen as well as increases the activity of the collagen-degrading enzyme MMP-2 and decreased the initial quantity of mast cells at the wound site [12,13].

*In vitro* studies on human skin, [19] suggested that lignocaine depressed the synthesis of mucopolysaccharides and hence possibly that of collagen, tending to impair wound healing.

Drucker et al. have been found that lidocaine 1% decreased collagen fibers number by morphometry as well as vascularity was significantly lower in lidocaine treated animals [14].

## Conclusion

The present study cleared that addition of epinephrine to lidocaine enhances as well as accelerates the healing process in wounds more better than plain lidocaine.

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