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Prophylactic antibiotics in augmenting Surgical wound healing

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SUMMARY

Antibiotics are widely used in treatment of bacterial and protozoan diseases in both human and animals. In production animal systems, the overuse and abuse of antibiotics have contributed to the widespread of antimicrobial resistant bacterial strains and drug residues in food chain. Oxytetracycline for example is a common antibiotic employed for treating various bacterial diseases and wound infection. This study aimed at investigating the use of prophylactic antibiotics in augmenting surgical wound healing in animals. Sixty-four adult guinea pigs were employed in this study and randomly divided into four equal groups (n=16). Animals were fully anaesthetized using Xylazine 5.0 mg/kg and Ketamine 44.0 mg/kg. Laparotomy incisions (3 cm long) were made on aseptically prepared sites on the ventral abdomen. The abdominal muscles and peritoneum were sutured by Catgut® while Silk® was used to suture the skin. Animals in group one received Oxytetracycline intramuscular injection two hours before the operation; group two were injected with OTC immediately after the operation; group three received OTC spray on the wound immediately after the procedure; and group four animals were left untreated to serve as the control group. Animals were monitored for two weeks where general appearance and wound contraction was recorded. The wounds in pre-operative group healed faster (7 days), followed by topical group (10 days). Wounds in post-operative and control groups had delayed healing and showed evidence of infection. The study showed that prophylactic antibiotics administration pre-operatively minimize post-operative wound infection and promotes healing.

Keywords: Antibiotics, Prophylaxis, Surgical wound, Pre-operative, Post-operative

INTRODUCTION

A primary function of a normal, intact skin is to control microbial populations that live on the skin surface and to prevent underlying tissues from becoming colonized and invaded by potential pathogens. Exposure of subcutaneous tissue following loss of skin integrity provides a favorable environment for microbial colonization and proliferation (Bogaard *et al.*, 2002). A wound is a bodily injury causing disruption of normal continuity of structures either accidentally or planned (Bowler *et al.*, 2001). Typical planned wounds are surgical wounds and these have been classified as clean, clean-contaminated, contaminated or infected. The classification however has not proved useful in predicting occurrence of wound infection, which is the key to its effective prevention (Haley, *et al.*, 1985). The number and diversity of microorganisms in any wound is influenced by the wound type, depth, location, quality, and level of tissue perfusion and antimicrobial efficacy of the host immune response (Bogaard *et al.*, 2002).

Wound healing is a complex physiological process that may be divided into three main overlapping stages; inflammation, tissue formation and tissue remodeling (Singer and Clark, 1999). Once the

tissue is injured, inflammation occurs leading to hemostasis and clot formation; after which the fibroplasia and neovascularization follows with formation of granulation tissue, re-epithelization and finally the formation of new extracellular matrix and tissue remodeling (Bowler *et al.*, 2001). In planned wounds, proper surgical technique including asepsis is important to prevent wound infection, promote wound healing and ensure likelihood of a satisfactory outcome to the surgical procedure (Baines, 1996; Mangram *et al.*, 1999; Ichikawa, 2010).

Wound infection occurs when microorganisms have the opportunity to proliferate in the tissue and the body's defense cannot combat the organism or its proliferation (Hotston, 1995). Certain patient characteristics can be associated with a higher incidence of wound infections including old age, chronic immunosuppressant, diabetes mellitus, corticosteroid use, obesity, malnutrition, and chronic renal failure (Beauchamp *et al.*, 2001). Infecting organisms are often part of the resident flora of the skin or nearby mucous membranes. *Staphylococcus aureus* is most commonly isolated in cutaneous wound infections although *Escherichia coli*, *Streptococcus*, *Pseudomonas*, and *Proteus species* may also be responsible (Bowler *et al.*, 2001; Kobayashi *et al.*, 2015) Inadequate

postoperative wound care and poor hygiene can introduce bacteria into a wound, which can lead to infection (Haley, *et al.*, 1985).

Antibiotics have been extensively used in treating various bacterial diseases and in wound management. Broad-spectrum antibiotics with activity against bacteria and protozoa are preferred for prophylactic purposes (Hawkey, 1998; Davies and Davies, 2010). Some formulations of OTC when administered intramuscularly take 30 minutes to several hours to reach peak levels in tissues depending on the volume and site of injection. The long acting products have significant slower absorption after intramuscular injection. OTC is eliminated unchanged primarily via glomerular filtration (Donald and Pharm, 1995). Timing of antibiotics administration is critical to efficacy, since the efficacy depends on the presence of peak antibiotic levels in the tissues at a time when the local concentration of microorganisms would otherwise be high (Jenney *et al.*, 2001). Appropriately administered antibiotics as prophylaxis, reduces the incidence of surgical wound infections (Dellinger *et al.*, 1994). Classen *et al.* (1992) suggested the first antibiotic dose to be given preferably within 30 minutes before surgical incision and re-administered at one to two half-lives of the antibiotics for the duration of the procedure. Since antibiotics are also being administered to cases attended aseptically, and in view of the possibility of occurrence of antibiotic resistance following abuse and overuse of these, there is a need to put on record proven recommendations regarding the use of antibiotics in surgery. The present study was aimed at assessing the appropriate time of antibiotics administration for effective prevention of wound infections in surgical interventions.

MATERIALS AND METHODS

Experimental animals

Sixty-four clinically healthy adult male (n=20) and female (n=44) guinea pigs (*Cavia porcellus*) were used for the study that was carried out at the College of Veterinary Medicine and Biomedical Sciences, Sokoine University of Agriculture, Morogoro, Tanzania. All animals were fasted for 12 hours before operation in order to get actual weight and prevent regurgitation during the procedures.

Antibiotic choice

Oxytetracycline hydrochloride (OTC) was used as it is a broad-spectrum antibiotic as well as the most

common used antibiotic in treatment of different conditions (bacterial and protozoan infection) in animals.

Experimental design and procedure

The 64 experimental animals were randomly allocated into four equal groups (n=16) i.e. preoperative, postoperative, topical and control groups. Animals in group one, (preoperative) received intramuscular injection of OTC two hours before the operation; group two (postoperative) received OTC intramuscularly immediately after the operation whereas animals in group three (topical) received topical OTC spray immediately after the operation. Animals in the control group were treated with intramuscular water for injection two hours before the operation.

Wound models

Animals were sedated by intramuscular injection of 5.0 mg/kg Xylazine and anesthetized with intramuscular injection of 44.0 mg/kg Ketamine Hydrochloride (Hall and Clarke, 1991). The surgical sites were aseptically prepared by shaving the hairs around the ventral abdomen, cleaning with water and application of Chlorhexidine, alcohol 70%, and finally iodine. A 3cm ventro-midline laparotomy incision was performed cutting through the skin, subcutaneous tissues, *linea alba* and the peritoneum. The incision was sutured using Surgical gut 3/0 for the peritoneum, *linea alba* and subcutaneous tissues while the skin was sutured with Silk 3/0. Animals were treated as shown on the experimental design. After recovery from anesthesia, the animals were taken back to their respective cages.

Observation and Data collection

Wounds were assessed daily until complete healing by re-epithelialization. Body temperature and signs of infection were monitored and recorded daily for 2 weeks. Presence or absence and nature of exudates and smell of the wound were assessed. Wound size measurement was performed at intervals by using veneer calipers and recorded accordingly.

Data analysis

Data were handled using Microsoft excel and analyzed using STATISTICA program version 8. Means and standard deviation for body temperature, infection cases, wound contraction and wound healing rates were calculated. The contingency 2x2 table was employed to check if there were statistically significant differences between and

within the treatment groups. Values of $p \leq 0.05$ were considered significant.

RESULTS

Significant wound contraction was noted in pre-operative and the topical treated groups (Figure 1). Wound healing in the pre-operative group was

observed to be between 7 to 8 postoperative days while in topical, post-operative and control groups healing was between 10 to 12, 13 to 15 and 13 to 15 days, respectively (Figure 2). Significant difference ($p \leq 0.05$) was observed between the post-operative, preoperative and topical groups but there was no statistical significant difference in healing durations between the post-operative and control groups.

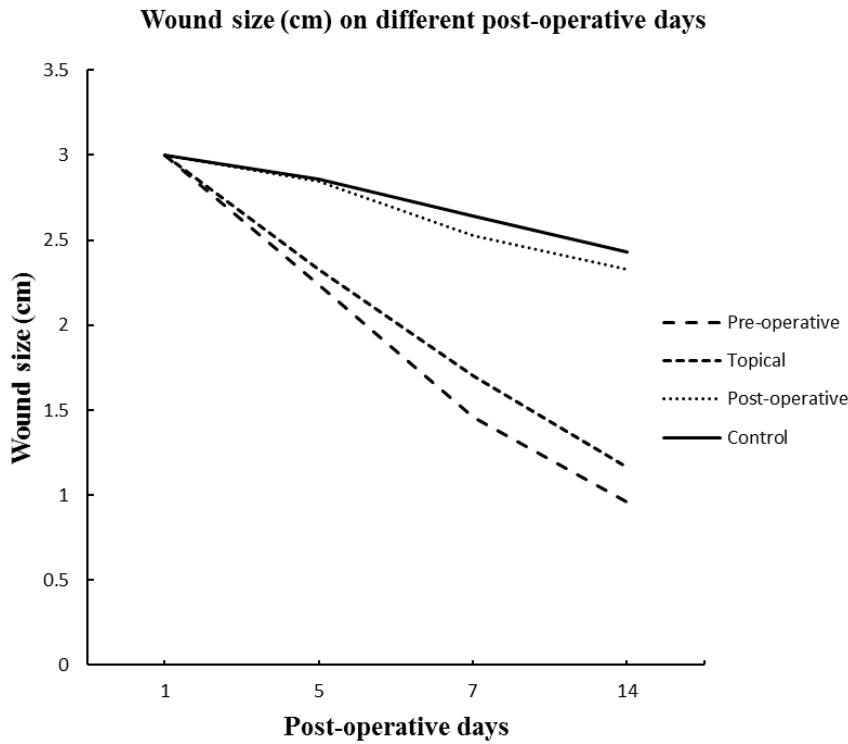


Figure 1. Wound sizes measured at different post-operative days.

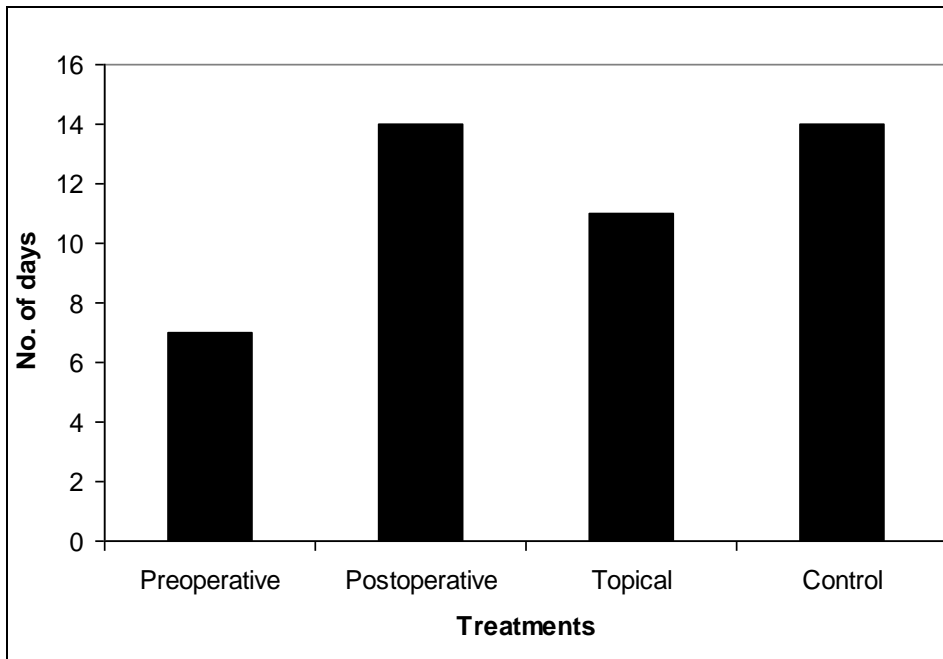


Figure 2. Wound healing durations (days)

Signs of infection such as pyrexia, edema, discharges and pus formation were observed in twelve animals (75%) and ten animals (62.5%) in control and postoperative groups' respectively (Table 1).

Table 1. Animals with signs of wound infections

Treatment	Number of animals (%)
Preoperative (n=16)	0 (0.0)
Postoperative (n=16)	10 (62.5)
Topical (n=16)	0 (0.0)
Control (n=16)	12 (75.0)
Total (n=64)	22 (34.4)

DISCUSSION

All surgical wounds are contaminated with bacteria, but not all become infected. The microflora associated with clean, surgical wounds is expected to be minimal, but the presence of foreign materials and devitalized tissue in a traumatic wound is likely to facilitate microbial proliferation unless early prophylactic antibiotic treatment and surgical debridement is implemented (Bowler *et al.*, 2001). Antibiotics have been widely used in veterinary practice to prevent infection in wounds in the perioperative period as it is not easy to define with precision which surgical procedures do and don't warrant prophylactic antibacterial use.

In the present study wounds treated with antibiotic two hours before the procedure healed faster than in the other groups (7-8 days post-operative). Incised wounds begin to heal by 5–8 days with re-establishment of epidermal continuity and a proliferation of fibroblasts from the subcutaneous tissues (Slatter, 1985). The faster uncompromised wound healing in the preoperatively treated animals was attributed to the effect of the antibiotic. During the time of operation, the antibiotic level in tissues was at a peak concentration enabling these animals to fight against the microorganisms thus preventing post-operative wound infection and promote healing.

There was a delay in wound healing in animals under the postoperative group and the control group where most of them (62.5% and 75% respectively) showed typical signs of infection i.e. high body temperature, edema, discharges, and pus formation on the wound. The delayed wound healing in these groups might be explained by the fact that there was no antibiotic in the tissues at the time of intentional tissue damage caused by surgical operation since antibiotic in this group was administered after the

operation. The results of this study correlate with the findings of Burke (2001) who reported that administration of antibiotic either shortly before or after inoculation of microorganisms resulted in lesions that were histologically identical to lesions induced by intra-dermal inoculation with killed organisms. Also, our findings are in line with the reports of Page *et al.* (1993) and McDonald (1998) that prophylactic antibiotics administration before operation minimizes or prevents the postoperative infection in surgical patients. Classen *et al.* (1992) noted that delaying administration of antibiotic resulted in lesions identical to those in animals not receiving antibiotic. Since surgical site infection is mostly likely due to colonization of the wound by animal's own endemic flora, inappropriate use of antibiotics peri-operatively may increase the risk of surgical site infection with opportunistic organisms (Hotston, 1995). In the postoperative group and the untreated animals, the body's immune defenses were overwhelmed by the microorganisms and failed to fight and prevent infections. In these animals, the delayed wound healing is thus partly attributed to wound infection.

Wounds that were topically treated with antibiotics had a faster healing rate than the control animals. In this group, no animal showed signs of infection. This is explained by the fact that antibiotic was applied directly to the site of action thus enabled to reduce bacterial proliferation and prevent infection on the surgical incision. When antibiotics are administered locally the effective drug concentration goes straight to the site for action while when administered through parenteral routes, it takes time to be absorbed and distributed to tissues for effective action (Bergamini *et al.*, 1989; Classen *et al.* 1992; Page *et al.*, 1993).

The results of this study justify the use of antibiotics especially in animals because the operation might be conducted aseptically but animals may acquire infection from the surrounding environment after the operation. Normal flora also from the animal itself might take the opportunity after the surgical stress to cause the secondary bacterial infection. Prophylactic antibiotics administration using broad spectrum antibiotics or antibiotics which are effective against the suspected contaminants is therefore useful if administered before the operation in order to prevent or minimize postoperative infections. It should however be noted that where the risk of infection is low, inappropriate use of antibiotics is likely to result in unnecessary cost for the client and can increase the risk of development of antibacterial resistance.

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