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Antimicrobial effect of Dialkylcarbamoyl chloride (DACC) on infected surgical wounds. Experimental study

Efecto antimicrobial del cloruro de Dialquilcarbamoilo (DACC) en heridas quirúrgicas infectadas. Estudio experimental

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ABSTRACT

To evaluate the antimicrobial and histopathological effects of Dialkylcarbamoyl chloride (DACC) dressing on surgical wounds infected with various pathogens. In Group 1 (control), after the midline incision on interscapular region, wounds were closed with non–absorbable sutures in sterile conditions and nitrofurazone was applied externally to the surgical wounds. Wounds were covered with sterile gauze. In Group 2, 3, 4, and 5 rats were incised and wounds were contaminated with *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus*, and *Candida albicans,* respectively. Contaminated surgical wounds were covered with DACC dressing just after the incision. Dressings were changed every after 3 day. In all groups it was clearly seen that DACC showed antimicrobial effect against various microorganisms on surgical site infections. In 2nd group epithelial thickness of samples were decreased when compared to control group but it was no statistically significant. Also in this group fibrosis was statistically less than other groups. DACC covered dressing is a strategical biomechanic infection preventing material can be used against surgical site infection riscs safely. It has no any side effect known due to external uses. The hidrophobicity of DACC lets high binding capacity for microorganisms.

Key words: Dialkylcarbamoyl chloride; surgical site infection; *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Candida albicans*

RESUMEN

Con el objeto de Evaluar los efectos antimicrobianos e histopatológicos del apósito de cloruro de dialquilcarbamoilo (DACC) en heridas quirúrgicas infectadas con diversos patógenos. En el Grupo 1 (control), después de la incisión en la línea media en la región interescapular, las heridas se cerraron con suturas no absorbibles en condiciones estériles y se aplicó nitrofurazona externamente a las heridas quirúrgicas. Las heridas fueron cubiertas con gasa esterilizada. En los grupos 2, 3, 4 y 5 se realizó una incisión en las ratas y las heridas se contaminaron con *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus* y *Candida albicans*, respectivamente. Las heridas quirúrgicas contaminadas se cubrieron con un apósito DACC justo después de la incisión. Los apósitos se cambiaron cada 3 días. En todos los grupos se observó claramente que DACC mostró un efecto antimicrobiano contra varios microorganismos en las infecciones del sitio quirúrgico. En el segundo grupo, el espesor epitelial de las muestras disminuyó en comparación con el grupo de control, pero no fue estadísticamente significativo. También en este grupo la fibrosis fue estadísticamente menor que en otros grupos. El apósito cubierto por DACC es un material biomecánico estratégico que previene infecciones y se puede utilizar de forma segura contra riesgos de infección del sitio quirúrgico. No tiene ningún efecto secundario conocido debido a usos externos. La hidrofobicidad del DACC permite una alta capacidad de unión de microorganismos.

Palabras clave: Cloruro de dialquilcarbamoilo; infección del sitio quirúrgico; *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Candida albicans*

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INTRODUCTION

Surgical site infections (SSIs) are among the most common hospital acquired infections (HAIs) accounting for more than 19.6% of all HAIs in Europe between 2011–2012 [1]. The Centre for Disease Preventation and Control (CDC) decribes SSI as postoperative infection occuring within 30–90 days after a surgical procedure [2]. As a risc factor, upward trend in antimicrobial resistance seen worldwide makes wound infections an intractable situation and increases morbidity and mortality significantly in this process [3].

Considering the surgical site infections there are many preventive strategies developed in time. These strategies include bacteria killer active antibiotic coated dressing materials, antimicrobial biomaterials [4], nanoparticle dressing materials [5], high hidrophobic dressing materials [6] to bind microorganisms. These materials have some advantages over antibiotics. Hemostatic effects such as inducing or accelerating the local coagulation [7], without adverse effects like foreign body reactions and granuloma formation [8]. Systemic antibiotics and/or topical antiseptics combination is used to overcome the wound infection by alleviate the bioburden on wound medically [9]. Antiseptic solutions of silver or iodine, octenidine, polyhexanide and wound dressings which contained these antimicrobials are frequently used in hospitals [10, 11, 12]. Although the antiseptic solutions and topical use of antibacterial/antifungal agents can supress the infection, since they are non–selective, cytotoxic and they may have damaging effects on some types of cells [13]. The mechanical binding of wound dress to microorganisms as a passive way may have some advantages over active Microbicidal strategies. Microbicidal effect can cause lysis of bacterial cell and may release bacterial endotoxins which increase the inflammatory response in hard–to–heal wounds [14, 15]. This type of mechanical action prevents contamination of surrounding tissues by endotoxins [13, 16].

Dialkylcarbamoyl chloride (DACC), a fatty acid derivate, has a high binding ability for bacteria by hidrophobization of surfaces [10]. This binding interaction is irreversible between DACC–coating material and bacteria [13]. During the dressing change, the microorganisms attached to the material are removed [17].

In health care settings Meticillin–resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* are frequently isolated from SSIs [18]. In several studies it was preseneted that the resistant ESKAPE (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter* spp. and *Escherichia coli*) pathogens are increasingly resistant to common antibiotics, drugs and antimicrobials due to inadequate utilization of antimicrobial agents [19, 20, 21, 22, 23, 24, 25]. During the COVID–19 pandemic, global overuse of antibiotics in healthcare settings without proper surveillance skyrocketed the antimicrobial resistance dramatically [19].

Dialkyl carbamoyl chloride was used to determine the antimicrobial effects in several *in vitro* studies before. In this study it was aimed to investigate the *in vivo* antimicrobial effect of DACC dressing material against various pathogens in SSIs.

MATERIALS AND METHODS

In this study, female Wistar albino rats (*Rattus norvegicus*) with an average weight of 250–300 grams were used. There were five groups and each group contained 8 rats.

Microorganisms

In group 2 surgical wounds were contaminated with *P. aeruginosa* strain. In groups 3, 4, and 5 we used *E. coli, S. aureus,* and *Candida albicans*, respectively.

Anaesthesia

All rats were subjected to general anaesthesia by 10 $mg \cdot kg^{-1}$ Xylazine hydrochloride (Rompun 2%, Bayer, Germany) and 150 $mg \cdot kg^{-1}$ Ketamine hydrochloride (Ketasol 10%, interhas, Turkey) IM combination before surgical procedures.

Surgical procedures and DACC dressing: In Group 1, after general anaesthesia the backs of rats were shaved and after the disinfection of skin it was made an 2 cm midline vertical incision on interscapular region in aseptic conditions. Wounds were sutured with non–absorbable suture material. Nitrofurazone pomade was applied to surgical wounds externally in this group. Wounds were covered with gauze. In groups 2, 3, and 4 the same procedure was performed for anaesthesia and surgery. In these groups the wounds were contaminated with 1 mL previously prepared microorganism solution (*P. aeruginosa, E. coli,* and *S. aureus* with 0.5 McFarland turbidity) and coated with DACC dressing (Sorbact Surgical Dressing, ABIGO Medical AB, Sweden). This material was changed every after 3 days (d) in accordance with the manufacturer's instructions. (FIG. 1). Insteadly, the wounds were contaminated with 1 mL *C. albicans* solution with 1.8 McFarland turbidity in Group 5. For all groups, we kept the rats individually. Twelve d after first incision all rats were euthanazied with over dose of anesthesia.

The wound tissues were collected in sterile conditions and has been cut in two, one piece to microbiology laboratory in sterile eppendorfs and the other for histopathological examination in 10% neutral buffered formalin solution.

Microbiological examinations

The wound tissue was divided into very little pieces by double blade method and after soluted in Mueller–Hinton Broth. One mL of solution was dropped on Blood Agar (Merck, Germany) and 1 mL for Eosin Methylene Blue (EMB) Agar (Merck, Germany) plates and incubated for over night at 37°C. In group 5 we used Sabouraud Dextrose Agar (SDA) (Merck, Germany) medium for *C. albicans* growth. The colony counts of each cultured media for each microorganisms were calculated.

Histopathological examinations

The wound pieces were fixed in 10% neutral buffered formalin (NBF, pH=7.26) for 48 h, dehydrated in different concentrations (70%, 90%, and 100%) of ethanol and embedded in paraffin. The sections obtained this parafin block with a thickness of 5 µm were stained with Haematoxylin & Eosin (HE), Masson Trichrome (MTC),

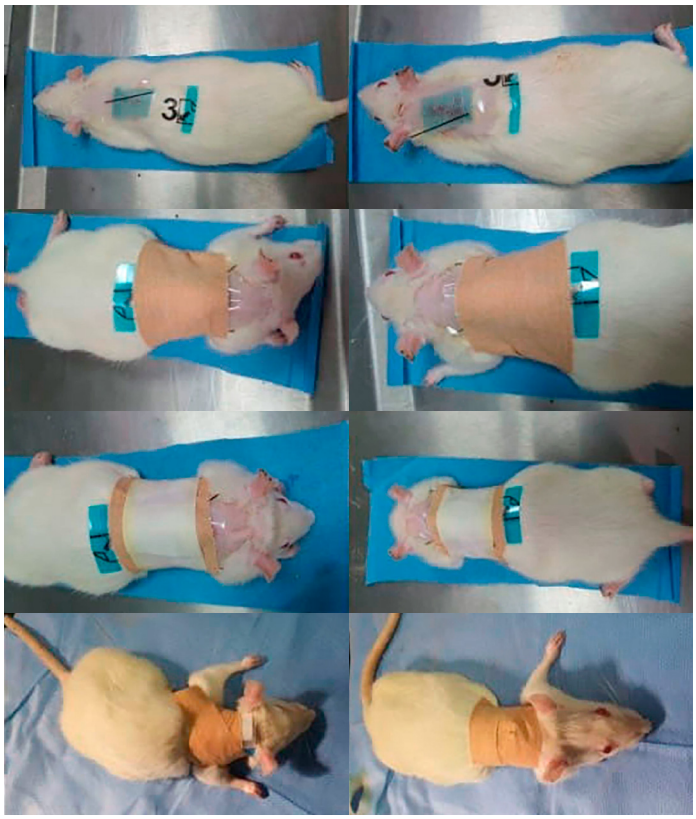

FIGURE 1. Rat (*Rattus norvegicus*) covering the wounds with Dialkylcarbamoyl chloride (DACC) dressing and sterile gauze

and Anti–CD31 (DAKO, Monoclonal Mouse Anti–Human, Clone JC70A, ready–to–use, Denmark). All sections were systematically evaluated with fields 40×, 100×, 200×, 400× using an Olympus DP72 microscope digital camera system with Olympus DP2BSW software connected to an Olympus BX51 (Olympus corp., Tokyo, Japan) light microscope. The inflammation was evaluated with H&E stained samples. Collagenization was evaluated with Masson–Trichrome stained samples and neo–vascularization was observed with immunohistochemical analysis.

Assessment of Inflammation

In 100× ocular, the microscopic area was scanned and the most intense area of inflammation selected, the cell count was performed in 200× large magnification area (LMA). For evaluation of acute inflammation neutrophile leucocytes (PMNL) were counted. Lymphocytes, macrophages and plasma cells were counted for determine the chronic inflammation and based to all datas scoring was performed. Accordingly;

- Score 0 : 0–4 inflammatory cells/200 LMA
- Score 1 : 5–20 inflammatory cells/200 LMA
- Score 2 : 21–60 inflammatory cells/200 LMA
- Score 3 : >60 inflammatory cells/200 LMA

Assessment of Fibrosis

The ratio of collagen fibers stained blue with Masson trichrome to the tissue covering 200× LMA calculated and scored as follows [26].

- Score 0 : no collagenization
- Score 1 : < 10% collagenization
- Score 2 : 10% – 49% collagenization
- Score 3 : ≥ 50% collagenization

Assessment of Neovascularization

Immunohistochemical analysis were performed for evaluation of neovascularization. Sections prepared for immunohistochemical study were stained using CD31/PECAM–1 (endothelial cell marker) antibody using the combination method of streptavidin–biotin–peroxidase and microwave antigen retrieval. Monoclonal antibody CD31 was used for assessment of microvascular density. Microvascular density was measured as the number of new microvessels per 200× optical field. The sections were detected in 40× and 100× optical magnification initially and counted on the invazive graft front. Three random fields with high vascular densities were selected at 100× magnification and counted microvessels at 200× magnification. The final microvessel score was calculated as the average number of vessels from these three fields [27].

Protein analysis

To perform immunohistochemical analysis, wound tissues were collected to determine the level of Bax and Bcl-2 apoptopic protein expressions.

Statistical analysis

All data were analysed using the Statistical Package for the Social Sciences V.21.0 software package (SPSS Inc., Armonk, NY, US). Shapiro–Wilk test was performed to assess normality. Epithelial thickness and neo–vascularization were normally distributed. Inflammation and fibrosis were not normally distributed. Quantitative data were given as mean±standard deviation, and ordinal data were given as median (min–max). One–way ANOVA followed by Tukey test as a post–hoc test was used to analyze quantitative data. Kruskal Wallis test was used to analyze ordinal data. A value of $P<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Today antimicrobial dressings are widely use in surgical procedures in many cases. Mupirocin, film, silver, hydrocolloid, silver–film, silver–alginate, silver–hydrocolloid, dialkyl carbamoyl chloride (DACC) and vitamin E (VE)–silicone are some of these dressings. Jiang and co–workers recently demonstrated that DACC significantly reduce the rate of postoperative SSI [28]. The mechanism of DACC dressings relies on the irreversible binding of dialkylcarbamoyl chloride to microorganisms on the basis of interactions between hydrophobic particles, thus resulting in a decreased number of pathogenic microorganisms [29]. Due to its ease of use, reliability, no toxic effects on tissue, irreversible

microorganism binding ability, and cost–effectiveness, DACC is feasible for clinical application [28].

The mean bacterial/fungal load of the infected wounds was observed and for groups 2, 3, 4, and 5; 2×10^3 CFU·mL^{-1} (P=0.01), 2×10^3 CFU·mL^{-1} (P=0.01), 5×10^3 CFU·mL^{-1} (P=0.01), and 0 CFU·mL^{-1} values were found respectively in this study.

In rats in Group 2 which were infected with *P. aeruginosa* the wound tissues were all ulserated. Primer wound healing in other groups was observed (FIG. 2).

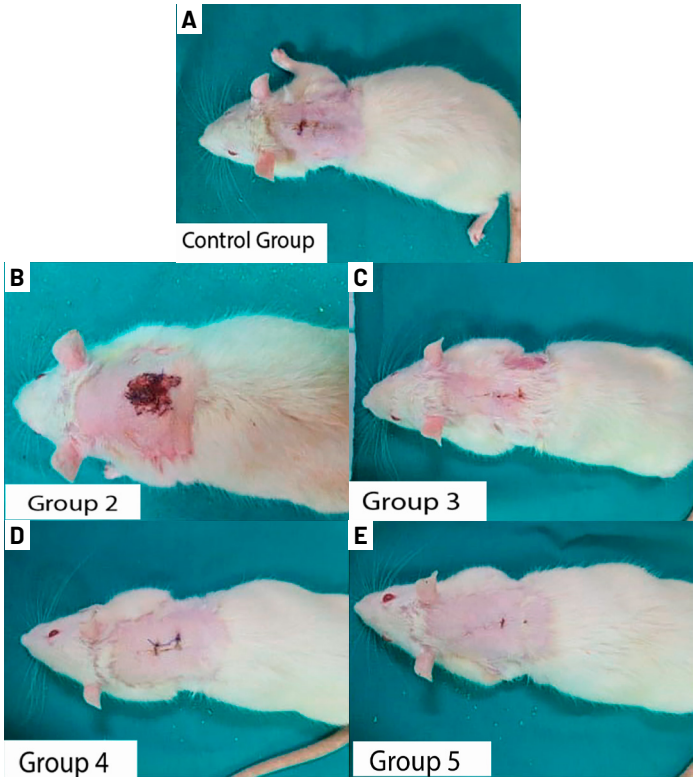

FIGURE 2. Wound healing in each groups on postoperative 12th day. Primer wound healing was detected in Control Group, Groups 3, 4, and 5. In Group 2, the wounds were all ulcerated. A: Control Group, B: Group 2, C: Group 3, D: Group 4, E: Group 5

When skin integrity is disrupted fibroblasts and keratinocytes rush to the wound to repair the damaged area. These restorative cells take a leading role on inflammation. Nonetheless this effect can not overcome the regional infection and antimicrotherapy should be administered in this case. Beside the antibiotic treatment antimicrobial mechanical approaches/strategies are considered to removal the potential bacterial cells may be on wound as a supporting mechanism. This double effect can be more effective than alone, on particularly non–healing wounds. Hydrophobic interaction is one of these mechanical prevention options against SSIs beside the antibiotherapy and ensure strongly binding to microorganisms possibly found on surgical wounds [30]. DACC dressings have a great ability to bind the microorganisms and the findings in various clinical studies was promising on both prevention and treatment of wound infections [13, 31, 32]. It was founded similar results in this study which present the antimicrobial effects of DACC dressing material on infected wounds *in vivo*. According to findings minimal bacterial growth on plates was observed in each groups.

In histopathological examination, severe delayed acute inflammation was detected in *P. aeruginosa* group and therefore wound healing process was paused and the epithelial tissues were ulserated in all surgical wounds clinically. It has been thought that DACC does not bind equally to all microorganisms. The *in vitro* study performed by Geroult and co–workers supports the results of this study. Accordingly it was explained that bonding differeneces between species probably reflect the distinct adhesins present on the surface of each species and the sticky nature of the extracellular polymeric material produced by *Pseudomonas* spp. [33]. The findings of this study were also verified with a previous *in vitro* study. The JIS L 1902 against *S. aureus* and *P. aeruginosa* achieves a great antibacterial activity through a binding mechanism was presented in contact tests which performed by Husmark and colleagues. It was also indicated that binding strenght of the DACC dressing was enough resistant to not let the bacteria release from even after extensive washing with a surfactant. They demonstrated that this kind of dressing may control wound bioburden [34].

It has been aforementioned that DACC dressing material prevents SSIs to a large extent, although not completely, and this is supported by a study performed by Stanirowski and co–workers. According to their findings using of DACC dressing limited the SSIs at a level of 2.8% while standart dressing showed a rate of SSIs as 9.8% [35]. In an *in vitro* study, endotoxin–binding capacity of DACC was evaluated by Susilo and co–workers. The study team reproted that DACC reduced the *P. aeruginosa* endotoxin with a rate of >99.95% by binding the free endotoxin. The researchers thought that DACC dressing was able to bind the bacterial cells and even endotoxins [36].

A group of researchers presented enhanced proliferation and augmented migration of fibroblasts treated with DACC in a cell culture model. The objective was to determine the cellular safety of the DACC dressing in a wound healing process. DACC dressing presented positive and increased healing progression when compared with control group with a percentage of 70%–80% and showed a complete scratch closure (99%) after 48 h [37]. In this present study there were observed similar findings on epithelial thickness (P=0.771) rates and in groups 3, 4, and 5 there were no statistically differences when compared with control group (P=0.921, P=0.971, and P=0.999 respectively). One more study performed by Sudetja and co–workers, have demonstrated perivascular changes in a patient with lupus erythematosus profundus with multiple overlying cutaneous ulcerations when treated with 2% mupirocin cream and DACC dressing. They have observed perivascular, periadnexal, and periadiposal lymphocytic, eosinophilic, and plasmacytic infiltration in the dermis, after two weeks of treatment [38]. In Group 2, neovascularization was significantly less than control group was observed (P=0.013) histopathologically in this study. In histopathological examination there was a statistically significant difference between groups in terms of neo–vascularization according to ANOVA test results (P=0.001). Similar findings were observed in the control group and groups 3, 4, and 5 with post–hoc tests (P values are P=0.971; P=0.999; P=0.921, respectively). Significantly less neovascularization was detected in group 2 compared to the control group (P=0.013) (FIG. 3) (TABLE I).

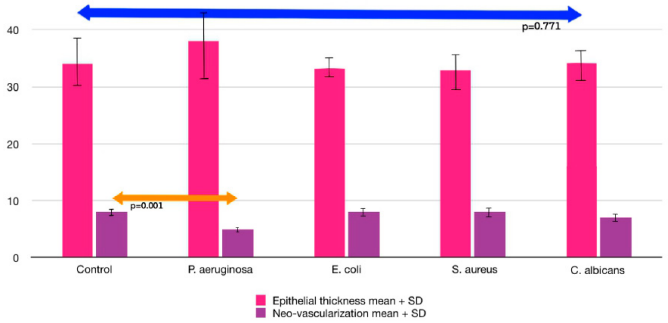

FIGURE 3. Comparison of control group and infected wounds with various pathogens IHC staining analysis in terms of epithelial thickness (*P*=0.771) and neo–vascularization (*P*=0.001)

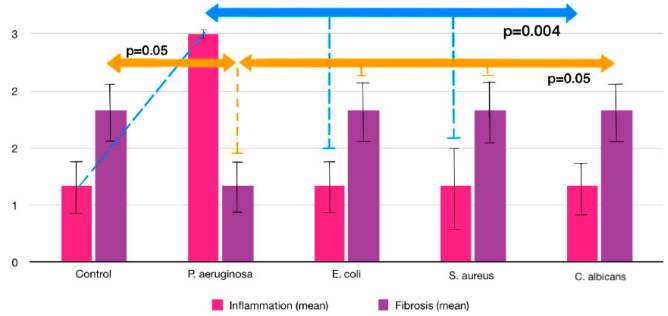

FIGURE 4. Comparison of control group and infected wounds with various pathogens IHC staining analysis in terms of inflammation (*P*=0.004) and fibrosis (*P*=0.05)

TABLE I
Histopathological scoring

Group (n)	Epithelial thickness (µm) mean+SD	Neo–vascularization mean+SD	Inflammation median (min–max)	Fibrosis median (min–max)
1 (6)	34.15 + 9.02	7.68 + 1.23	1 (1-2)	2 (1-2)
2 (6)	38.52 + 9.43	4.83 + 0.89	3 (3-3)	1 (0-1)
3 (6)	33.4 + 5.00	8.35 + 1.57	1 (1-2)	2 (1-2)
4 (6)	33.37 + 7.39	8.18 + 1.75	1 (1-3)	2 (1-2)
5 (6)	34.15 + 7.75	7.47 + 1.41	1 (1-2)	2 (1-2)

Morgner *et al.* [6] demonstrated the molecular mechanisms of wound healing process by RT–PCR. Accordingly, *in vitro* evaluation was performed to investigate the effects of DACC–coated samples and uncoated reference material on cell responses related with inflammation, growth factor induction and collagen synthesis, as well as antimicrobial defense. The inflammatory mediator gene expression after wounding *in vivo* and *in vitro* was shown in several studies [39, 40, 41, 42]. This expression contributes growth factor release, cell migration towards the wound site to reparation of wound. In inflammation keratinocytes actively participate the process by releasing chemokines and pro–inflammatory cytokines [43 ,44].

According to results of this study inflammation between groups was significantly different according to Kruskal Wallis test and was statistically more severe in group 2 when compared with others (*P*=0.004). Ulceration was seen in all rats (100%) in group 2 and it was not detected in other groups. Microabscess, a finding of acute inflammation, was seen in 5 rats in group 2 (83.3%) while it was not detected in other groups. It was previously shown that a DACC–coated dressing potentially increased fibroblast proliferation and migration *in vitro* and it has been suggested that this type of dressing may further accelerate the healing process in wounds those are difficult to heal [37]. According to Kruskal Wallis test fibrosis was significantly different between groups in this study. Fibrosis was milder in group 2 when compared with other groups (*P*=0.05) (FIG. 4) (TABLE I). Histopathological images are shown in FIG. 5.

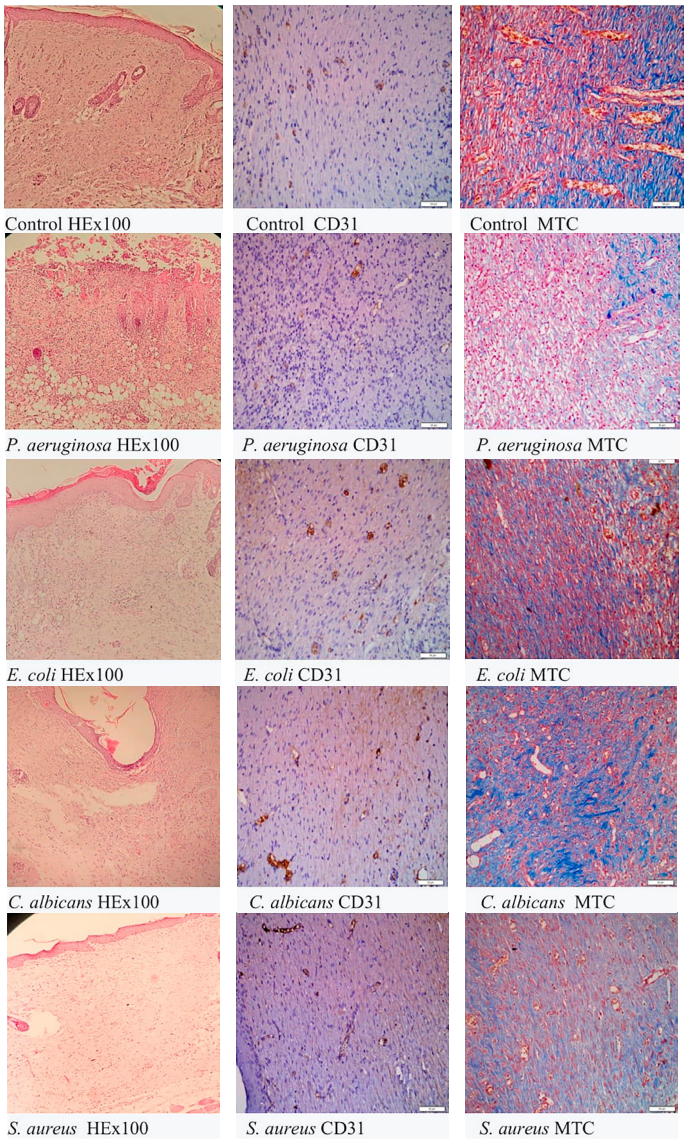

FIGURE 5. Histopathological images of control group and infected tissues

CONCLUSION

In this study it was investigated the potential antimicrobial effect of DACC dressing against various pathogens on an experimental surgical site infection model. Wound healing and wound scores were better than expected except group 2. In this group, prolonged acute inflammation, stromal edema and microabcess formations are thought to be the cause of the milder fibrosis compared to other groups. According to these findings it can be said that use of DACC dressing significantly effective as an alternative antimicrobial strategy on surgical site infections beside antibiotherapy. The combine use od DACC with antibiotics will be beneficial and preventive fort he aim of prophylaxis in this context. Further studies are needed to elucidate the effects of DACC on other pathogens *in vivo*.

Limitations

Due to limited source of rats and pathogens, this work can be evaluated as a preliminary *in vivo* study. Further detailed studies about DACC coating dressing material are needed and the number of rats and pathogens should be enlarged.

Ethical Statement

This study was performed with the permission of Animal Experiments Local Ethics Committee with a decision number of 2021/04-04.

Conflicts of Interest

The authors declare no conflict of interest for his study.

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