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Effect of silver nanoparticles in treating and healing of burn wound

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Abstract: The paper investigates the effect of silver nanoparticles preparations on the rate of burn healing and scar quality. Three preparations for burn treatment were considered: one with silver sulfadiazine and two with silver nanoparticles woven into two types of dressing: one, of polyethylene and second, carboxymethyl cellulose. The experiment was performed on pigs, due to anatomical and pathophysiological similarities with human skin. All three silver preparations have antimicrobial properties with a beneficial effect on the healing of burns. Preparations with silver nanoparticles proved to be the most effective, since they encourage very fast burn epithelialization, affect reduction of the level of matrix metalloproteinase-9 in the environment of the burn wound, lead to faster expression of vascular endothetial growth factor – VEGF, cause less thickening of the epidermis and contractility, and improve tension characteristics of the scar compared to the preparation with silver sulfadiazine. By comparing results of healing parameters and evaluation of the scar achieved with preparations with silver nanoparticles, it was evident that the best overall results of local treatment were achieved with silver nanoparticles in crystalline form. Due to quantum-mechanics, surface and chemical oxidation–reduction (reactive oxygen species) phenomenological characteristics Ag nanoparticles in crystalline form have unique ability to catalyze rate of healing.

Keywords: Ag nanoparticles; Ag sulfadiazine; carboxymethyl-cellulose dressing; polyethylene dressing; skin recovery; burn healing.

INTRODUCTION

Over the last few decades wound care technologies have extensively evolved.[1] For wound regeneration and wound-healing bioactive agents, such as: nanoparticles, cells and molecules, which enhance the performance are applied. These agents, incorporated into various dressings, inhibit bacterial growth and replic-

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ation, give enhanced re-epithelialization, vascularization, improve recovery of the tissue functionality, and overall accelerate effective wound healing.

Research made on wounds show that Ag, as a bioactive chemical agent, has an important role in healing wounds.[2] Namely, thirty years ago it was found that the poorly soluble molecules such as the anti-infective Ag sulfadiazine aided to wound therapy. Further, it was shown that dressing with Ag sulfadiazine gives an accelerating skin wound healing effect.[3] The effect of Ag sulfadiazine in wound healing compared to saline soaked dressing was researched.[4] It was found that the healing is faster with the sulfadiazine and thus not allow the contraction of the wound. According to the fast progress in nanotechnology and nanomedicine, based on inclusion of unconventional materials, the idea to use the Ag nanoparticles in wound treatment was developed.[5] However, the question was if the Ag nanoparticles are useful for treating also high-degree burns.[6] It was found that a sandwich structure composite wound dressing with firmly anchored silver nanoparticles are appropriate for severe burn wound healing.[7] Ag nanoparticle exhibits exceptional physical and chemical properties due to the high surface area to volume ratio. In the close contact with cell membrane Ag nanoparticles produce the increased concentration of reactive oxygen species and the metal ions permeate into the cytoplasm, thus induce quick death of bacteria. Nanocomposites with Ag nanoparticles are promising candidates in the antibacterial fields and wound treating even for infected skin burns.[8]

Kaler *et al*. investigated the in vivo wound healing activity of nano-silver-based gel, formulated on the biologically synthetized silver nanoparticles.[9] the gel was obtained that has high efficiency in healing, has reduced side effect and enhanced curative activity in comparison to it counterpart (silver ions).[10] Recently, a novel hydrogel film wound dressing composed of ulvan and Ag nanoparticles was developed. Ag nanoparticles are incorporated into the hydrogel film with the aim to improve antibacterial properties and provide a potential burn treatment. Ulvan is a polysaccharide from green algae that shows good hydrogel film dressing characteristics. The result of the research show that the ulvan–silver nanoparticles hydrogel films have the ability to accelerate the healing of second--degree burns on rats skin and are potential candidates for wound dressings.[11]

Wide research on antimicrobial effect of Ag nanoparticles in polyethylene based nanocomposites has been done.[12–15] It is shown that even small amount of Ag nanoparticles, immobilized on the polyethylene surface, give high antibacterial and antiviral activities.[16]

The polyethylene terephthalate membrane (obtained from plastic waste) with Ag nano particles is suggested for a suitable wound dressings.[17] Gels prepared from a combination of carboxymethyl cellulose and poloxamer incorporated with tea tree oil and lavender together with Ag nanoparticles also promise to be the convenient wound dressings.[18] The polydopmine carboxy methyl cellulose Ag

nanaoparticles composite hydrogel coating has good antibacterial and antiadhesion properties, too.[19] The sodium carboxymethyl cellulose gels containing Ag nanoparticles improve antibacterial performance in general.[20] However, the advantage of one type of dressing over another remains to be investigated.

In the paper the effect of silver nanoparticles on treating burns is investigated. The research is done on pigs and their skin. Three dressings on burn injury are considered: one, with Ag-sulfadiazine, second, Ag nanoparticles in a carrier made of polyethylene and the third, Ag in a carrier made of carboxymethyl--cellulose. The aim was to compare the influence of the three dressings on burn wound and to obtain the optimal one which would substantially reduce the healing time, also reduce the risk of recurrent infections as well as costs associated.

EXPERIMENTAL

Plan of experiment

The experiment was done on 10 pigs of the age of 2 months and with weight of 20 kg. On the skin 8 burns were created: 4 on one and 4 on the other side of the backbone. Burns are of the same size, properly arranged and at the appropriate distance, at the same height, and equidistant from the spinal column, in order to have approximately the same thickness of the dermis. After shaving, the preparation of the operative field of skin was carried out by an aerosol and not by rubbing, in order not to cause hyperemia, which can affect the depth of the burn. The full-thickness burn wounds were created under anesthesia with the special equipment. The equipment consists of a heater (with voltage of 150–230 V), a thermo regulator (with accuracy 0.5 %) and a brass extension which is specially made with a smooth contact surface (of dimensions 47 mm×47 mm) with an integrated PT100 probe. Contact burns, with a surface area of 22.09 cm^2, were created with a brass attachment heated to a temperature of 92 °C for 15 s with uniform pressure.

Immediately, after the injury, various dressings with Ag were used for burn treatment and the research on effect of Ag on burn wound healing was done. For testing, the Ag was incorporated into various compress materials in elemental or ionic form. Two considered dressing materials applied in the experiment are: polyethylene and the carboxymethyl cellulose with Ag nanoparticles. For both dressings the incorporated silver is released gradually as an integral part of a certain material. Thus, one of them is the sandwich dressing with outside polyethylene layers and an absorbent inner core, made of artificial silk and polyester, in which silver in the form of nanocrystal, smaller than 20 nm, is woven (Acticoat – Smith & Nephew). Nanocrystalline silver protects the wound from bacterial contamination, and the inner core maintains optimal validity, which is essential for wound healing. At the other side, Ag nanoparticles are pressed into the carboxymethyl cellulose whose fibers absorb exudate, form a gel (Aquacel Ag, Convatec) and thereby maintain a moist wound environment. The silver ions are slowly released in this compression through hydration. These ions act as counterions in carboxymethyl cellulose. The third considered dressing is with sulfadiazine. In contrast to the aforementioned ones, Ag cations are counter-ions of deprotonated sulfadiazine anion.

Four groups were formed according to the utilized dressing:

K control group	sterile saline-soaked dressing,
SSD group	dressing with 1% Ag-sulfadiazine,
NP group	dressing with Ag nanoparticles in crystalline form in polyethylene and
NKC group	dressing with Ag nanoparticles in carboxymethyl cellulose.

Burns of each pig were randomly treated with 4 dressings: 2 with K, 2 with SSD, 2 with NP and 2 with NKC. It means, the total number of burns was 80 and each treatment was applied for two times on each pig, *i.e.*, 20 samples. The experiment lasted for 70 days at the Scientific Institute for Veterinary Medicine in Novi Sad, Serbia. In the postoperative course, the analgesic agent Diclofenac 50 mg was prescribed for the first ten days. The animals were kept in individual boxes with a surface area of 5 m^2 to prevent possible mutual injury. The feeding of pigs was standard. Dressing was carried out at regular intervals, using a standardized procedure with the same topical agent until complete healing. Sampling was done on 1, 4, 7, 11, 14, 18, 21, 24, 28, 32, 35 and 38 day. During this time the healing of the wound was monitored and the formed scar was analyzed using morphometric, histological, immune biochemical, microbiological and clinical parameters. On the 70th day after the experiment, the animals were sacrificed, and the skin samples were analyzed morpho-metrically, histologically and tensometrically.

Statistical procedures for data processing

For data processing the statistical package SPSS 14.0 for Windows was applied. Using the *T*-test, for comparison of 2 groups of data, and the one-way analysis of variance (ANOVA), for three or more groups of data, the average mean values were compared with the normal distribution for certain parameters. To check the differences in the distribution frequency of variables non-parametric tests were used. In addition, the Mann–Whithey test (for two independent samples) and the χ test are applied for comparing the frequencies of attributive features with a normal measurement scale. For all statistical tests it is accepted that there is a statistically significant difference if the probability of the null hypothesis is less than 0.05 ($p < 0.05$).

RESULTS AND DISCUSSION

Results of microbiological and histological wound swabs analysis

After application of dressing on burn, the quantitative and qualitative histological and microbiological analyses were done. The presence of bacteria on certain preparations only on the surface of the wound, and not inside the tissue was investigated. It was recorded that on the first day after the infliction of burns, the presence of bacteria was not observed in any group. On the 4th day, only a few individual cases of bacterial contamination were recorded in the control group. The highest contamination was found on the eleventh day after injury in all groups, except in the SSD group where it was on the fourteenth day. The presence of bacteria on the wound surface was in 40 % of the burns of the control group, 13 % of the burns of the SSD group, 12 % of the burns of the NCD group and 11 % of the burns of the NK group.

In addition, there was a significant statistical difference between the results of the control group in relation to all other groups ($\chi^2 = 9.267$, $p < 0.05$). In the control group, the number of histologically positive findings was significantly higher in all phases in which healing was monitored. When comparing the 3 remaining tested groups that were treated with different Ag preparations, no significant statistical differences were observed.

Analyzing and separating the bacteria types on the wound groups it was observed that in the group with saline-soaked dressing more types of bacteria are evident than in other groups (see Table I). Thus, in K there are 6, in SSD and NP there are 3 and in NKC only 2 types of bacteria. Comparing the control K group result with other ones, significant statistical differences was noted ($\chi^2 = 17.039$, $p < 0.01$). At the other side, the differences between the NP group, the SSD and NKC groups, in which burns were also treated with Ag-based preparations, is very small and does not show statistical significance ($\chi^2 = 1.625$, $p > 0.05$). For these three examined groups, the uniform diversity of bacterial strains is also a characteristic.

TABLE I. Bacteria isolated from variously treated burn wounds

Bacteria isolated from burn wounds	K	SSD	NP	NKC
Staphylococcus sp. Coagulasa neg.	+	+	+	+
Staphylococcus saprophzticus	+	+	+	-
Enterobacter sp.	+	-	-	-
Escherichia coli	+	-	-	+
Proteus sp.	+	+	-	-
Klebsiella oxytoca	+	-	-	+
Summary of positive counts, %	55	18	20	16

Clinical parameters on local infection

In all three groups of burns that were treated with different Ag preparations (SSD, NP, NKC), in most cases no indicators were recorded that would declare state of the presence of local infection. The condition of these burn wounds was characterized with a score of 1.

There was no statistically significant difference between these groups treated with different Ag preparations. However, greater number of burn wounds in the control K group, whose condition was characterized by a score of 2, differed statistically significantly compared to the other groups ($\chi^2 = 7.703$, $p < 0.05$).

Results of wound surface planimetric measurement during healing

The kinetic rate of healing of a burn wound is the most authoritative way to determine the effectiveness of the applied topical agent. Burns that were treated with Ag nanoparticles in ionic and crystalline form (NKC and NP) had, on average, a faster onset of healing compared to the other two groups. A statistically significant difference was observed when comparing the NP and K group and the NP and SSD group on the fourteenth day after injury.

In Table II, the re-epithelialization rate as the function of the date is shown. It is directly evident that there is the most significant difference in re-epithelialization during the eighteenth and twenty first day. The NP group had the best result, followed by the NKC group. A statistically significant difference was

manifested on the eighteenth day when comparing the NP and the NKC group with SSD and the K group. On the twenty first day, a significant difference in epithelialization was determined only in the NP group and the NKC group compared to the control K group. On the twenty fourth day the biochemical rate of re-epithelialization was still the best in the NP group and then, NKC, SSD and the control K group, but these differences did not have statistical significance. In the final healing phase, the differences between the groups were also not statistically significant. However, it is seen that 50 % of burnt is healed after 21 days, while the 75 % of re-epithelialization is after 28 days except the group K. For all groups the 100 % healing is in 38 days.

TABLE II. Re-epithelialization in time for all four groups

Re-epithelialization, %/day	K	SSD	NP	NKC
14	17	16	20	19
18	28	48	50	45
21	60	63	80	67
24	70	77	87	78
28	85	96	95	95
32	95	96	97	98
35	97	97	99	99
38	100	100	100	100

On the first day after inflicting injury, no expression of MMP-9 was observed. The first signs were evident on the fourth day in all groups. During the eleventh and fourteenth days a higher presence of MMP-9 was verified in the tissue of the burn wound in the K control, SSD and NKC groups compared to the NP group. The differences in expression were even more pronounced on eighteenth day. On the twenty fourth day a lower expression of MMP-9 was observed in the two groups treated with Ag nanoparticles compared to the other two groups. Finally, by monitoring of this protease from the first to twenty fourth day of burn treatment, the increase of the total expression of MMP-9 was observed.

Measured results of the scar surface and skin properties after burn treatment

By comparing the groups, it was observed that the highest percentage of contraction of the scar in relation to the surface of the skin before the injury was observed in the control group, where it was 38.3 %. In the group in which Ag-sulfadiazine was used, it was slightly lower (37.3 %), while the lowest percentage of contraction was recorded in the remaining two groups, in the NKC group it was 36 %, and in the NP group 35.2 %. A statistically significant difference (ANOVA, F.3.204, $p < 0.05$) was found when comparing the control K group with NKC ($t = 2.396$, $p < 0.05$), as well as when comparing the control K group with the NP group ($t = 2.485$, $p < 0.05$) which indicates that the topical treatment with Ag

nanoparticles in crystalline and ionic form had an effect on the reduction of the total contraction of the scar.

Thickness of epidermis

It was shown that the thickness of the epidermis in all examined groups was significantly greater in relation to healthy skin samples from the same region of the body where the cut thickness was 70 μm ($t = 2.664$, $p < 0.01$). A difference in the thickness of the epidermis can be observed in the burn groups that were treated with preparations with Ag nanoparticles compared to the control group and the one that was treated with Ag-sulfadiazine. A statistically significant difference was observed when comparing the results of the control and NKC groups ($t = 2.396$, $p < 0.05$), as well as the control and NP groups ($t = 2.485$, $p < 0.05$).

Thickness of dermis

The average total thickness of the dermis in the control group was 1000 μm, 980 μm in the SSD group, 960 μm in the NKC group, and 950 μm in the NP group. Hence, the average total thickness of the dermis in the studied groups was 970 μm. It differed minimally, that is, it was somewhat thicker than the average thickness of the dermis of healthy skin of the same region, which was 940 μm. These differences did not show statistical significance. (ANOVA, $F = 1.732$, $p > 0.05$).

Tensiometry results

Tensiometric analysis was performed on the seventieth day after the injury. It was observed that the scar tissue is on average 1.6 times weaker than intact skin, i.e. that it reached 63.9 % of the strength of healthy skin taken from the body region. The average ability to stretch the scarred skin when tearing was 3.7 times less compared to the intact skin, respectively, it reached only 27.3 % of the extension length of healthy skin of the same region.

By comparing the average values of the force required to tear the tissue between the groups, it was shown that the lowest force was reached by the control group, which was 8168 N, then the group treated with Ag-sulfadiazine 8644 N, the NP group 10330 N and the NKC group 11253 N. A statistically significant difference between the force was established tearing in healthy skin compared to these examined groups (ANOVA, $F = 91{,}980$, $p < 0.01$). In addition, a statistically significant difference ($p < 0.05$) was found when comparing the NKC and also the NP group with the control K group, and also of the NKC with SSD group.

The average values of the stretching limit of the skin were the least in the control K and SSD groups and amounted to 964 and 1070 μm respectively; while in the remaining two groups they were significantly higher and amounted to 1185 μm in the NP group and 1210 μm in the NKC group. A statistically significant difference was found between the extension of healthy skin in relation to all

examined groups (ANOVA, $F = 2715.205$, $p < 0.01$). A statistically significant difference ($p < 0.05$) was verified when comparing the NKC group and the NP group with the control C and SSD group.

CONCLUSIONS

The following is concluded:

1. All tested preparations with Ag in their composition had strong and approximately equal antimicrobial properties. By comparing histological, clinical and microbiological parameters, no statistically significant difference in antimicrobial action was observed between the groups of burns treated with Ag-sulfadiazine and Ag nanoparticles in crystalline or ionic form.

2. Nanocrystalline Ag has intensive anti-inflammatory properties and affect the reduction of MMP-9 levels in the environment of the burn wound. Burn epithelisation of 50, 75 and 100 % occurred faster in the group of burns treated with Ag nanoparticles in crystalline form than in ionic form. Ag nanoparticles in crystalline and ionic form showed proangiogenic properties and cause the increase of VEGF in burn already ten days after the injury. In addition, the reduction of the surface area of the open wound over time was the fastest in the group of burns treated with Ag nanoparticles in crystalline form, and then with Ag nanoparticles in carboxymethyl-cellulose.

3. Summarizing results related to the analysis of scars, it can be concluded that the groups in which Ag nanoparticles were used, showed the best research results as the catalyzer: significantly less thickening of the epidermis, less contractility of the scar, as well as better tension characteristics.

4. By comparing all the results of the examined parameters of healing and evaluation of scars, it was determined that the best overall results were obtained when using preparations with Ag nanoparticles in crystalline form. This result can be primarily explained by the surface high impact of Ag nanoparticles on the wound environment during healing and scar formation. Ag nanoparticles have unique quantum-mechanics, surface (nano size/amphiphilicity) and chemical oxidation–reduction (reactive oxygen species) properties permitting the antimicrobial and cytotoxicity catalytic characteristics.

Future research in burn wound treatment would be directed toward improving the considered dressing with Ag nanoparticles in crystalline form by adding substances which would have not only anti-inflammatory and anti-infective properties but also anesthetic effect. The recent research shows that the clove oil[21] may be a good candidate.

ИЗВОД

УТИЦАЈ НАНОЧЕСТИЦА СРЕБРА НА ЛЕЧЕЊЕ И ЗАРАСТАЊЕ ОПЕКОТИНЕ

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У раду је истраживано деловање три препарата сребра, једног са сребро-сулфадиазином и два са наночестицама сребра у јонском и кристалном облику, на брзину зарастање опекотине и квалитет насталог ожиљка. Експреимент је извршен на кожи свиња због анатомске и патофизиолошких сличности са људском кожом. Истраживања су показала да сва три препарата са сребром имају антимикробне особине и благотворно делују на зарастање опекотина. Препарати са наночестицама сребра су се показали као високо ефикасни, јер каталишу врло брзу епителизацију опекотина, утичу на смањење нивоа матрикс маталопротеиназе-9 у окружењу опекотиинске ране и доводе до брже експресије васкуларног ендотелног фактора раста. Поред тога, изазивају мање задебљања епидерма, мању контрабилност и боље тензионе карактеристике ожиљка у односу на препарат са сребро-сулфадиазином. Компарацијом резултата параметара зарастања и евалуације ожиљка остварених препаратима са наночестицама сребра утврђено је да су најбољи укупни резултати локалног лечења постигнути наночестицама сребра у кристалмон облику као резултат квантно механичких, физичких, површинских, а посебно оксидоредуктивних (активне кисеоничне специје) карактеристика, а потом и у јонском облику.

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