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DYNAMICS OF INDICATORS OF THE PROOXIDANT-ANTIOXIDANT SYSTEM IN THE BLOOD AND EXUDATE UNDER THE TREATMENT OF PURULENT WOUNDS WITH NEGATIVE PRESSURE AND SILVER NANOPARTICLES

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ДИНАМИКА ПОКАЗАТЕЛЕЙ ПРООКСИДАНТНО-АНТИОКСИДАНТНОЙ СИСТЕМЫ В КРОВИ И ЭКССУДАТЕ ПРИ ЛЕЧЕНИИ ГНОЙНЫХ РАН ОТРИЦАТЕЛЬНЫМ ДАВЛЕНИЕМ И НАНОЧАСТИЦАМИ СЕРЕБРА

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The study determined the effect of silver nanoparticles (AgNPs) in the treatment of purulent wounds with negative pressure instillations (NPWTi) on the parameters of the antioxidant system of blood and exudate. The study was conducted on 72 laboratory animals, which were divided into four equal groups. In contrast, in 3 groups, it was performed by modeling a purulent wound with its further treatment in various ways. In group 1, the traditional treatment method was used under a bandage with a levomekol; in group 2, wound treatment was carried out using a preparation with AgNPs; in group 3, the NPWTi method was used. In group 4 (control), modeling of a purulent wound was not performed. During the experiment, a study was made of the parameters of the enzyme link of antioxidant protection (catalase and superoxide dismutase), as well as the total antioxidant activity due to the content of low molecular weight substrates. It should be noted that only in animals of group 3, the indicator of antioxidant activity of the blood reached the values of the control group on the 12th day. In contrast, in group 2 it remained significantly reduced by 13.2 %. The data obtained indicate the ability of AgNPs to increase the prooxidant load in the wound area mainly in the first six days, with the development of an imbalance in the work of enzymes of the 1st and 2nd lines of antioxidant protection. This may indicate the advisability of the combined use of AgNPs and NPWTi in treating the first phase of the wound process.

Keywords: wound process, silver nanoparticles, negative pressure instillations, wound treatment, oxidative stress, catalase, superoxide dismutase

В исследовании определялось влияние наночастиц серебра (AgNPs) в лечении гнойных ран отрицательным давлением с инстилляциями (NPWTi) на показатели антиоксидантной системы крови и экссудата. Исследование проведено на 72 лабораторных животных, которые были разделены на 4 равные группы, при этом в 3 группах выполнялось моделирование гнойной раны с дальнейшим ее лечением различными способами. В группе 1 использовали традиционный метод лечения под повязкой с мазью, содержащей левомеколь; в группе 2 лечение ран осуществляли с помощью препарата с наночастицами серебра; в группе 3 применяли метод NPWTi. В группе 4 (контрольной) моделирование гнойной раны не выполнялось. В ходе эксперимента было проведено изучение показателей ферментного звена антиоксидантной защиты (каталазы и супероксиддисмутазы), а также общей антиоксидантной активности, обусловленной содержанием низкомолекулярных субстратов. Следует отметить, что только у животных группы 3 показатель антиоксидантной активности крови достигал значений контрольной группы на 12 сутки, тогда как в группе 2 он оставался достоверно сниженным на 13,2 %. Полученные данные свидетельствуют о способности AgNPs увели-

чивать прооксидантную нагрузку в области раны преимущественно в первые 6 суток с развитием дисбаланса в работе ферментов 1 и 2 линии антиоксидантной защиты, что может указывать на целесообразность комбинированного использования AgNPs и NPWTi при лечении первой фазы раневого процесса.

Ключевые слова: раневой процесс, наночастицы серебра, лечение ран, отрицательное давление с инстилляциями, окислительный стресс, каталаза, супероксиддисмутаза

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AgNPs – silver nanoparticles

АОА – antioxidant activity

NPWT – negative pressure wound therapy

NPWTi – negative pressure wound therapy with instillation

SOD – superoxide dismutase

There are many methods of treating the wound process. One of the most effective methods is negative pressure treatment (NPWT). The treatment method can reduce the number of complications, accelerate the healing process and reduce the duration and cost of treatment [1, 2]. According to modern sources, the balance between prooxidant-antioxidant systems is changed by NPWT. For example, a decrease in the level of oxidative stress has been proven when modeling the wound process in rats using NPWT compared to traditional dressing changes [3]. Another publication also noted an increase in antioxidant levels and signs of a significant decrease in the intensity of free radical oxidation when NPWT was used to treat chronic wounds [4].

More effective than the NPWT method is the NPWTi method. This method is similar to the classical NPWT but also involves periodic treatment of the wound with various medicinal solutions without removing the dressing components. Sanitation contributes to the cleaning of wounds and more effective disposal of necrolysis products [5, 6]. Sanitation, saline, and hypochlorous acid solutions are used. The use of NPWTi allows you to clean the wound quickly. Also, it reduces the level of inflammatory changes in the tissues of the walls and bottom of the wound [7, 8]. One of the potential sanitation solutions using NPWTi may be solutions containing silver compounds, including silver nanoparticles (AgNPs).

Silver nanoparticles are actively used to treat wounds of different origins [9]. Their use makes it possible to accelerate wound healing and, thanks to the pronounced antibacterial activity of such nanoparticles, reduce the probability of purulent septic complications [10]. At the same time, antimicrobial activity is associated with the ability of AgNPs to destroy the bacterial membrane. Also, their ability to increase the production of reactive oxygen species violates the integrity of the bacterial cell [11]. Such a mechanism of action of silver nanoparticles can potentially prevent the use of AgNPs solutions for wound debridement within NPWTi due to their multidirectional effect on the state of the prooxidant-antioxidant system in situ. At the same time, it is known that a slight increase in the formation of active oxygen species may contribute to a decrease in microbial load and faster wound healing [12]. Thus, it can be assumed that using silver nanoparticle solutions for NPWTi is possible, depending on the phase of the wound process. However, it should be considered that AgNPs may have cytotoxicity [13].

Therefore, it seems appropriate to study the state of the prooxidant-antioxidant system at the local and systemic levels using the NPWT method, which will potentially make it possible to identify the optimal period for using solutions with AgNPs. Thus, to assess the course of the wound process, the determination of the activity and enzymes of antioxidant protection in the blood and wound discharge can be used.

The aim of the study was to compare the efficacy of both NPWT and AgNPs by the parameters of the antioxidant blood and exudate system in the treatment of purulent wounds in the experiment.

Material and Methods. The study was provided on 72 outbred male rabbits weighing 2.5 to 3.0 kg, eight months old. The rabbits were divided into four equal groups, including 3 with purulent wound modeling, which differed depending on the treatment method. Group 1 (n=18) used the traditional treatment method under a bandage with an ointment containing Levomekol (Nizhpharm, Russia). In group 2 (n=18), a commercial preparation with silver nanoparticles Argogel (Vector-Vita, Russia) was used for wound treatment following the manufacturer's recommendations. Group 3 (n=18) received NPWT treatment. Control group 4 consisted of 18 rabbits, which did not undergo modeling of a purulent wound.

The activity of catalase, dismutase superoxide (SOD), and antioxidants in blood and exudate was studied during the experiment. The study of catalase activity in blood and exudate was performed on a Chem Well 2900 T biochemical analyzer (Awareness Technology, USA) according to a method based on measuring the decomposition of hydrogen peroxide [14]. Catalase activity was calculated from the difference in extinction in the experiment and control according to the Bouguer-Lambert-Beer law, considering the molar light absorption coefficient of hydrogen peroxide at a wavelength of 260 nm $\epsilon = 22 \text{ M}^{-1} \cdot \text{cm}^{-1}$.

SOD activity was determined on a Chem Well 2900 T biochemical analyzer (Awareness technology, USA) based on the quercetin oxidation reaction [15]. Oxidation of 1.4 μM quercetin was carried out at room temperature in phosphate buffer pH=8.0 with dimethyl sulfoxide after adding tetramethylethylenediamine to a final concentration of 0.8 mM in a final volume of the reaction mixture equal to 2.0 ml.

The study of blood and exudate AOA was done by evaluating the total antioxidant activity of biologically

active substances [16] in the modification [17] on the TsvetYauza-AAA-01 antioxidant activity analyzer (Khimavtomatika, Russia) using an amperometric method based on measuring the electrical current arising from the oxidation of the test substrate at a certain voltage (1.3 V) on the surface of the working carbon disulfide electrode and subsequent comparison of the obtained signal, recorded in nanoamperes per second (nA · sec), with the accepted standard (ascorbic acid solution).

Collection of exudate in groups 1 and 2 was performed on days 1, 4, 6, 9, and 12. In group 3, exudate was collected on day 1, then when replacing the sponge bandage on days 4 and 9. Blood sampling in groups 1, 2, and 3 was carried out on days 1, 4, 6, 9, and 12, and blood sampling in group 4 was carried out on day 12.

Simulation of the wound process was carried out based on the method of formation of abscess. For anesthesia, a combination of Zoletil 100 at 10 mg/kg and Xylazine 2 % at a dosage of 0.1 ml/kg was used, with additional local anesthesia with novocaine (0.5 % solution). Modeling of the NPWT method was performed based on a device for local treatment and dynamic observation of superficial purulent wounds [18] using a porous spongy bandage Askina Foam (B-Braun, Germany).

Ranges of silver nanoparticle sizes were evaluated by SEM with a field emission cathode at an accelerating voltage of 10 kV in the reflected electron detection mode (COMPO) with a magnification of 30,000× («Center for collective use of diagnostics of structures and properties of nanomaterials», Kuban State University, Krasnodar, Russia, FZEN-2023-0006).

Statistical processing of the obtained experimental data was carried out using the methods of variation statistics with the package Statistica10.0 (StatSoft Inc., USA). The value of the differences found between the parameters in the groups was estimated using the Mann – Whitney non-parametric U-test. The differences were considered significant at $p < 0.05$.

Results and Discussion. The study found that in group 1, an increase in AOA was observed in the exudate

within six days of treatment (Table 1). This indicator was 46.2 % higher on the 4th day compared to the data on the 1st day and another 10.5 % more on the 6th day compared to the values on the 4th day, which indicates the accumulation in the wound discharge of low molecular weight substrates capable of act as restorers. Subsequently, in the exudate in animals from group 1, a progressive decrease in AOA was noted on days 9 and 12 to values that did not significantly differ from those on day 1 in the same group.

In group 2, an increase in AOA was observed only on day 4 (by 33.3 % compared to day 1). Subsequently, in group 2, this indicator decreased, and from days 6 to 12 did not significantly differ from the data on day 1 of the same group, as well as similar values in group 1 on days 9 and 12 ($p > 0.05$). Completely different dynamics were characteristic of changes in AOA in group 3 compared with groups 1 and 2. Thus, on day 4 in group 3, a decrease in AOA by 33.4 % compared with day one was detected, which was also 57.9 % and 55.6 % lower than in groups 1 and 2, respectively (Table 1). On day 9, this indicator in group 3 also remained significantly lower than in groups 1 (by 52.0 %) and 2 (by 53.8 %). Such dynamics indicate the ability of AgNPs to increase the prooxidant load on tissues in the wound of laboratory animals, thereby reducing their local antioxidant defense capacity.

Catalase activity in the exudate of animals from group 1 increased 1.5 times on day 4 and 2.7 times on day six compared with day 1 of the experiment. Further, a decrease in catalase activity was noted in group 1 on days 9 and 12, although these values remained elevated compared to day one by 83.3 % and 66.7 %, respectively ($p < 0.05$, Table 1). In group 2, catalase activity increased less pronounced than on day 1 (maximum 1.7 times on day 6, 25.0 % less than in group 1), reaching a plateau from day 6 to day 12. In group 3, the greatest increase in the catalase index was noted on day 4 (at the same time, it exceeded the values in group 1 by 1.3 times, Table 1), and then sharply decreased on day 9, being 45.4 % and 40.0 % lower than in groups 1 and 2, respectively ($p < 0.05$).

Table 1

Dynamics of indicators of the antioxidant system in the exudate with various methods of treating purulent wounds in laboratory animals

Group/ index	Day of the experiment, Me [P ₂₅ -P ₇₅]				
	1	4	6	9	12
Group 1, AOA, nA · sec	0.26 [0.24-0.27]	0.38 [0.34-0.39] ^	0.42 [0.39-0.43] ^	0.25 [0.24-0.26] ^	0.23 [0.22-0.25]
Group 2, AOA, nA · sec	0.27 [0.26-0.31]	0.36 [0.32-0.38] ^	0.28 [0.27-0.30] * ^	0.26 [0.25-0.31]	0.23 [0.20-0.24]
Group 3, AOA, nA · sec	0.24 [0.23-0.26]	0.16 [0.13-0.17] *# ^	-	0.12 [0.09-0.14] *# ^	-
Group 1, catalase, activity units	0.06 [0.05-0.07]	0.09 [0.08-0.10] ^	0.16 [0.14-0.17] ^	0.11 [0.09-0.12] ^	0.10 [0.09-0.12]
Group 2, catalase, activity units	0.07 [0.06-0.08]	0.08 [0.07-0.09] * ^	0.12 [0.11-0.13] * ^	0.10 [0.09-0.11] ^	0.11 [0.10-0.12]
Group 3, catalase, activity units	0.07 [0.05-0.08]	0.10 [0.09-0.11] # ^	-	0.06 [0.05-0.07] *# ^	-
Group 1, SOD, activity units	0.08 [0.07-0.09]	0.12 [0.11-0.13] ^	0.17 [0.16-0.18] ^	0.13 [0.12-0.14] ^	0.11 [0.10-0.12] ^
Group 2, SOD, activity units	0.07 [0.06-0.08]	0.13 [0.12-0.13] ^	0.18 [0.15-0.19] ^	0.15 [0.14-0.16] * ^	0.12 [0.11-0.13] ^
Group 3, SOD, activity units	0.07 [0.05-0.10]	0.08 [0.07-0.09] * #	-	0.05 [0.04-0.07] *# ^	-

Note: * – statistically significant differences ($p < 0.05$) from group 1; # – statistically significant differences ($p < 0.05$) from group 2; ^ – statistically significant differences ($p < 0.05$) from previous measurements in the same group; Me – median; P₂₅ – 25 percentile; P₇₅ – 75 percentile.

The activity of SOD in the exudate of group 1 reached its maximum values on day 6 (2.1 times more than on day 1), decreasing further by 35.2 % on day 12. The dynamics of SOD in group 2 were characterized by an even more pronounced increase on day 6 (2.6 times higher than on day 1), with a further gradual decrease on days 9 and 12 of the experiment (Table 1). Different changes were observed in this indicator in group 3, which was lower than the medians in groups 1 and 2 by 33.3 % and 38.4 % on day four and by 61.5 % and 66.7 % on day 9 of the experiment, respectively ($p < 0.05$). The described changes in the group treated with silver nanoparticles indicate an excessive load on the prooxidants and an imbalance in the enzyme bond of the antioxidant system with the predominance of dismutation activity, which can lead to excessive peroxide in the first phase of the wound process. It can also activate cell decay by accumulating regenerative equivalents in the wound. The analysis of micrographs revealed the presence of AgNPs in the following size ranges: less than 10 nm – 22.8 %, from 10 to 25 nm – 12.3 %, and more than 25 nm – 64.9 % (Figure). It is known that metal nanoparticles up to 10 nm in diameter have the highest antimicrobial activity [19]. In comparison, the predominance of AgNPs larger than 25 nm can cause an increased prooxidant load on wound tissues.

In blood plasma in group 1, AOA decreased by 10.7 %, and 9.4 % were found on days 4 to 6, compared with day 1, respectively ($p < 0.05$). At the same time, on days 9 and 12, this indicator increased by 13.7 % and 18.8 % in group 1 compared to days 6, respectively ($p < 0.05$, Table 2). At the same time, in group 2, the different dynamics of AOA were noted, which was characterized

by its more pronounced inhibition not only on day six but also on day 12 of the experiment (by 9.4 % compared to group 1). In group 3, the increase in AOA was detected already on the 6th day, which was higher by 18.6 % and 22.1 % compared with the data in groups 1 and 2, respectively (Table 2). At the same time, the values in group 3 did not differ statistically significantly from those in control group 4 ($Me [P_{25}-P_{75}] = 94.1 [92.6-96.5]$, $p > 0.05$).

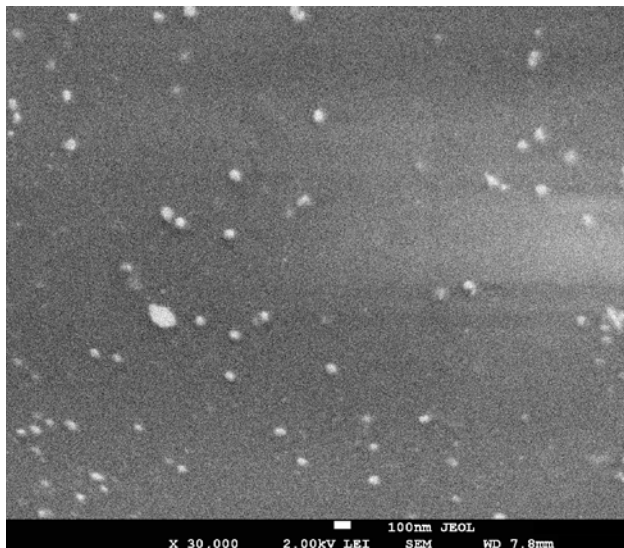


Fig. Electron micrograph of the gel with silver nanoparticles in the COMPO mode with a magnification of 30000 times

Changes in the indicators of antioxidant protection in the blood of laboratory animals with various methods of treating purulent wounds in the experiment

Table 2

Group/ index	Day of the experiment, Me [P ₂₅ -P ₇₅]				
	1	4	6	9	12
Group 1, AOA, nA · sec	83.9 [82.4-85.6]	74.9 [73.6-75.7] ^	76.0 [75.3-76.4]	86.4 [85.3-87.2] ^	90.2 [89.4-91.9] ^
Group 2, AOA, nA · sec	81.5 [80.4-82.5]	76.2 [75.4-76.8] ^	73.8 [72.5-74.2] *^	86.6 [86.1-87.4] ^	81.7 [80.6-82.3] *^
Group 3, AOA, nA · sec	83.1 [82.3-84.1]	79.6 [78.6-81.0] #*^	90.1 [88.9-91.7] #*^	93.0 [91.4-95.6] #*^	93.6 [91.7-95.4] #*
Group 1, catalase, activity units	0.97 [0.94-0.98]	0.98 [0.96-0.99]	0.94 [0.93-0.95]	0.91 [0.88-0.92] ^	0.78 [0.75-0.79] ^
Group 2, catalase, activity units	0.96 [0.94-0.97]	0.97 [0.96-0.99]	0.93 [0.91-0.94] ^	0.77 [0.76-0.79] *^	0.83 [0.81-0.85] *^
Group 3, catalase, activity units	0.90 [0.84-0.94]	0.93 [0.87-0.95]	0.82 [0.79-0.84] #*^	0.78 [0.75-0.79] *^	0.75 [0.72-0.78] #^
Group 1, SOD, activity units.	0.58 [0.57-0.59]	0.59 [0.58-0.61]	0.59 [0.57-0.61]	0.54 [0.53-0.55]	0.48 [0.46-0.48] ^
Group 2, SOD, activity units	0.57 [0.56-0.58]	0.60 [0.58-0.62]	0.58 [0.57-0.59]	0.49 [0.48-0.50] ^	0.48 [0.47-0.50]
Group 3, SOD, activity units	0.53 [0.49-0.55]	0.55 [0.54-0.56]	0.52 [0.50-0.53]	0.43 [0.41-0.44] #*^	0.42 [0.40-0.45] #*^

Note: * – statistically significant differences ($p < 0.05$) from group 1; # – statistically significant differences ($p < 0.05$) from group 2; ^ – statistically significant differences ($p < 0.05$) from previous measurements in the same group; Me – median; P₂₅ – 25 percentile; P₇₅ – 75 percentile.

Blood catalase activity in group 1 progressively decreased (Table 2), reaching a minimum on day 12 (by 19.6 % compared to day 1 of the experiment, $p < 0.05$). The decrease in blood catalase activity in group 2 was more pronounced on day 9 when the indicator was 22.1 % lower than in group 1. At the same time, in group

3, the decrease in catalase activity was the largest on day 12, yielding to the value in group 2 at least 9.6 %, and the control group was 27.2 % ($Me [P_{25}-P_{75}] = 1.03 [0.96-1.05]$, $p < 0.05$). The change in SOD activity had similar trends in all groups and was characterized by a decrease in the index on the 12th day, more pronounced in group 3

(12.5 % less than in groups 1 and 2, Table 2). At the same time, this indicator of all three groups significantly differed from the values of group 4 (Me [P₂₅–P₇₅] = 0.36 [0.34–0.41], p<0.05), which indicates a significant imbalance of the prooxidant-antioxidant system, primarily in the first six days with a predominance of prooxidant link and may be due to a violation of the processes of regeneration of antioxidant protection factors during the development of the 1st phase of the wound process.

The study confirmed the AgNPs ability to increase tissue load in the wound, which is accompanied by an imbalance in the enzyme link of the antioxidant system with a predominance of dismutase activity, most pronounced on day 6 (2.6 times higher than on the first day of the experiment). The latter can be due to the increased formation of the superoxide anion radical in the wound. At the same time, SOD values in the exudate did not increase significantly with the use of NPWTi in the experiment. However, an adaptive increase in catalase activity by 42.9 % was found on the four days. Considering that, according to the number of studies, it was noted that an increase in SOD activity has a positive effect on wound treatment when using NPWTi by accelerating the healing process [20], the combined use of AgNPs and NPWTi is a perspective approach in the treatment of purulent wounds.

Also, separate studies indicate the accumulation of pathogenic microflora in the dressing during wound treatment using the NPWTi method [21], which may contribute to maintaining the inflammatory process. Therefore, the additional use of AgNPs can help reduce the contamination of the dressing, reducing the risk of developing infectious complications in NPWTi, especially in the first phase of the wound process. It should also be noted that only in group 3 animals did blood antioxidant

activity reach 12-day control group values, while in group 2, it remained significantly reduced by 13.2 %.

Conclusion. Thus, the use of AgNPs with a diameter of more than 25 nm in treating purulent wounds is accompanied in the first phase of the wound process by an imbalance in the functioning of antiradical protection enzymes. At the same time, the NPWTi method provides less pronounced changes in the antioxidant system and faster normalization of its enzyme and low molecular weight parameters, both in exudate and in the blood of laboratory animals.

Informed consent. The studies were conducted after the approval of the training protocol by the local ethical committee of the Kuban State Medical University of the Russian Ministry of Health (protocol № 45) in compliance with the Directives of the European Community 86/609EEC, recommendations RD-APK 3.10.07.02-09 «Methodological recommendations for keeping laboratory animals in vivarium, research institutes and educational institutions» Ministry of Agriculture of the Russian Federation (2007), Sanitary Rules 2.2.1.3218-14 «Sanitary and epidemiological requirements for the arrangement, equipment and maintenance of experimental biological clinics (vivariums)», requirements of GOST 33215–2014 dated 07.01.2016 «Guidelines for the maintenance and care of laboratory animals. Rules for equipping premises and organizing procedures» and GOST 33216–2014 «Rules for working with laboratory rodents and rabbits», the Declaration of Helsinki on the humane treatment of laboratory animals that were kept under standard vivarium conditions on a standard diet.

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ANGIOARCHITECTONICS OF THE SUBEPICARDIAL VASCULAR BED OF THE HEART ON THE LATERAL SURFACE OF THE LEFT VENTRICLE IN YOUNG ADULTHOOD

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АНГИОАРХИТЕКТОНИКА СУБЭПИКАРДИАЛЬНОГО СОСУДИСТОГО РУСЛА СЕРДЦА НА БОКОВОЙ ПОВЕРХНОСТИ ЛЕВОГО ЖЕЛУДОЧКА У ЛИЦ ЮНОШЕСКОГО ВОЗРАСТА

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In young adulthood, 28 hearts with a uniform variant of coronary branching were studied. The vascular bed of the heart was examined using X-ray, anatomical, histological, and morphometric methods. On the lateral surface of the left ventricle, the spatial relationship of the circumflex branch and the posterior vein of the left ventricle is considered. The average distance