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*Original article*

# Preclinical Evaluation of the Treatment of Chronic Osteomyelitis Model in Rabbits

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## Abstract

***Introduction***. *Chronic osteomyelitis is one of the problems in orthopedic surgery. Recently, in the treatment of chronic osteomyelitis, biodegradable materials are increasingly used as a local antibiotic carrier. In our study, we used bone allograft, which prepared by Marburg system.*

***The purpose of the study*** *was to evaluate preclinical changes of use the antibiotic-impregnated bone allograft on osteomyelitis model in rabbit.*

***Materials and methods.*** *Osteomyelitis was caused in rabbits by the human strain Staphylococcus aureus, which is introduced into bone defects created in the distal femur. Three groups were selected depending on the filling: group 1 - antibiotic impregnated biodegradable material "PerOssal", group 2 –whole bone allograft soaked in antibiotic, group 3 - perforated bone allograft soaked in antibiotic. We used a clinical examination for the evaluating decreasing of chronic osteomyelitis process.*

***Results***. *The body temperature of all experimental animals was measured with a non-contact thermometer during the entire observation period, which was 42 days. The average temperature in rabbits in groups before surgery was 36.90 in-group 1; in-group 2 - 36.40; in-group 3 - 36.20. On the first day after the operation, in groups 1 and 3, there was no significant difference with the initial body temperature in rabbits before the operation, while in-group 2, the body temperature on the first day after the operation was 39.00. In the early postoperative period, the maximum increase in body temperature is observed on the 3rd day in-group 1 up to 39.20 and in-group 3 38.20. In-group 2, the maximum rise in temperature was on the 2nd day after surgery up to 38.60. The average weight in operated rabbits before surgery was 2983.3 g in-group 1; in-group 2 - 3206.7 gr; in-group 3 - 2300.0 gr. In the 1st group in the postoperative period in the 1st group there is a deficit on the early postoperative day amounted to 1.3 g in dynamics decreased up to 5 days and then there was a stable increase in weight, which in general by the 42nd day was 783, 4 grams. In-group 2, on the first day, there was a maximum body weight deficit of up to 92.3 g, with a subsequent increase, and in general, for the entire observation period, the increase was 200 g. In-group 3, on the first postoperative day, the body weight deficit was 13.9 grams. In the dynamics, there was a slight instability in weight, for example, on day 5, body weight was 3284.6 g, with a decrease on day 6 to 3169.2 g. Visually assessing the wound in-group 1, wound suppuration, divergence or instability of the sutures were not noted. In-group 3, on the 28th day after the operation, there was a slight infiltration of soft tissues in the area after the surgical wound. In the 2nd group on the 14th day there was a slight infiltration of soft tissues in the area after the surgical wound, and on the 28th and 42nd days there was suppuration of the postoperative wound.*

***Conclusion.*** *Thus, in this study we showed, that perforated bone allograft is an available biomaterial can be used in bone regenerative surgery.*

***Key words:*** *Preclinical evaluation algorithm, chronic osteomyelitis, rabbits model, preclinical study.*

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## Introduction

Chronic osteomyelitis is one of the most difficult to treat diseases. The difficulty of treatment is that it is necessary not only to ensure a high concentration of the antibiotic in the wound, but also to fill the resulting bone defect. Different materials in combination with antibiotics are used as an antibiotic delivery system [1-7]. Biodegradable materials like calcium sulfate, collagen, polymers and other materials have been reported to be suitable drug delivery systems in the treatment of osteomyelitis [8-13]. However, their availability is limited in different countries due to registration, supply and price. "Gold" standard for filling bone defects is autogenous bone grafting, which can impregnated with antibiotics. Disadvantages of this method are graft site restriction, small amount of material, a second operation to collect material from one patient [8-13]. As an alternative, the femoral heads from live donors, after hip joint arthroplasty, are widely used as bone allografts. There are a lot of type of preparation this type of bone allografts. In our study, we have used femoral heads allografts obtained from living donors (telos GmbH, Marburg, Germany) as antibiotic carrier.

***The aim of the study*** was to evaluate clinical changes of use the antibiotic-impregnated bone allograft on osteomyelitis model.

## Material and methods

This study was conducted at the Medical University of Karaganda, Kazakhstan.

Preparation of bone allografts. The study was approved by the University Ethics Board (approval number: 13 of 29/09/2017.) and informed consents were obtained from the donors. Femoral heads were harvested from living donors after hip replacement. All heads were boiled for 94 minutes at a maximum temperature of 82.5ºC in the "LOBATOR SD-2 system" (Telos, Germany ).

*Animals.* 54 specific pathogen free adult non-bred rabbits were used in this study. The accommodation, feeding and care conditions were the standard according to the rules in force.

*Bacterial strain and inoculum preparation.* The ATCC 43.000 strain of Staphylococcus aureus (SA) was used to induce infection. After sterilized broth cultivation, 3 passages were performed over 24 hours in nutrient agar tubes incubated at 37°C. From the third passage of the strain the concentration of 5 x 106 CFU / ml was determined.

*Surgery.* As an alternative to classical treatment, bone allografts and biodegradable material "PerOssal" were used. All allografts impregnated with 4% gentamicin sulphate. Chronic osteomyelitis model in rabbit was created in all groups before treatment.

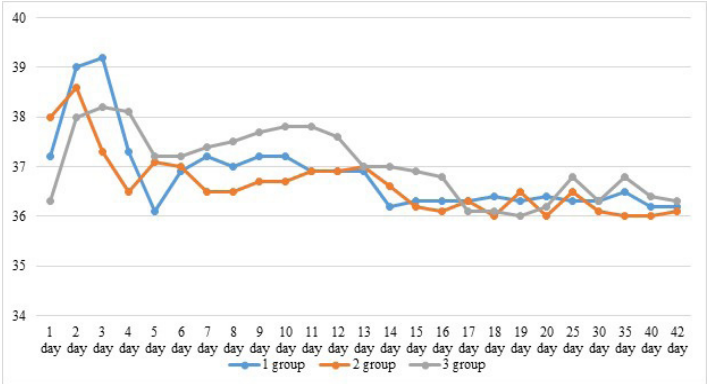
All rabbits under total anesthesia (ketamine 35 mg/kg+xylazine 5 mg/kg, IM) were approached for surgical treatment. The hair was removed by trimming, and the disinfection was done. In all groups surgery included debridement, abscess drainage and reconstruction technique. Reconstruction technique involved filling the resulting bone cavity after necroectomy with a bone allograft. In all groups, resorbable sutures was applied. Three groups were selected depending on the filling (n=18): (1) antibiotic impregnated biodegradable material "PerOssal"; (2) whole bone allograft soaked in antibiotic; (3) perforated bone allograft soaked in antibiotic.

*Clinical analysis.* Clinical evaluation was based on the activity of the rabbit, measurements of temperature and body weight, and the condition of the postoperative wound. A visual assessment of the severity of the inflammatory process in the area of the postoperative wound and soft tissues was carried out, which was assessed in points: 0 points - no inflammation, 1 point - soft tissue infiltration in the projection of the postoperative wound, 2 points - suppuration of the postoperative wound.

*Statistical analysis.* Statistical analysis was performed. The statistical data was performed with software IBM SPSS Statistics 20. Mean values and standard deviations were calculated. Groups were statistically compared using the chi-squared test with p value ≤0.05 to consider statistical significant (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

## Results

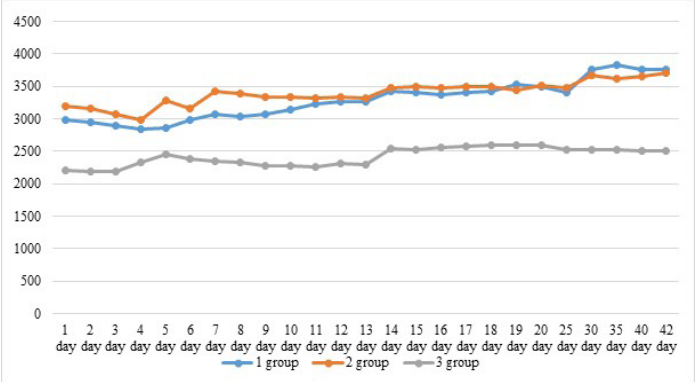
The body temperature of all experimental animals was measured with a non-contact thermometer during the entire observation period, which was 42 days. The average temperature in rabbits in groups before surgery was 36.90 in-group 1; in-group 2 - 36.40; in-group 3 - 36.20.




*Picture 1 - The body temperature changes*

As shown in Figure 1, on the first day after the operation, in groups 1 and 3, there was no significant difference with the initial body temperature in rabbits before the operation, while in-group 2, the body temperature on the first day after the operation was 39.00. In the early postoperative period, the maximum increase in body temperature is observed on the 3rd day in-group 1 up to 39.20 and in-group 3 38.20. In-group 2, the maximum rise in temperature was on the 2nd day after surgery up to 38.60. There was no significant difference between the groups after the operation.

The average weight in operated rabbits before surgery was 2983.3 g in-group 1; in-group 2 - 3206.7 g; in-group 3 - 2300.0 g.




*Picture 2 - The body weight changes*

As shown in Figure 2 - in the 1st group in the postoperative period in the 1st group there is a deficit on the early postoperative day amounted to 1.3 g in dynamics decreased up to 5 days and then there was a stable increase in weight, which in general by the 42nd day was 783, 4 grams. In-group 2, on the first postoperative day, the body weight deficit was 13.9 grams. In the dynamics, there was a slight instability in weight, for example, on day 5, body weight was 3284.6 g, with a decrease on day 6 to 3169.2 g. Subsequently, in dynamics, the weight stabilized from 3420 grams, and the total weight gain for 42 days was 493.3 grams. In-group 3, on the first day, there was a maximum body weight deficit of up to 92.3 g, with a subsequent increase, and in general, for the entire observation period, the increase was 200 g.

*Table 1 - Comparative clinical analysis in the study groups of the experiment*

| Group Number | 14 day | 28 day | 42 day |
|---|---|---|---|
| 1 group | 0 | 0 | 0 |
| 2 group | 1 | 2 | 2 |
| 3 group | 0 | 1 | 0 |

As can be seen from Table 1, when visually assessing the wound in-group 1, wound suppuration, divergence or instability of the sutures were not noted. In-group 3, on the 28th day after the operation, there was a slight infiltration of soft tissues in the area after the surgical wound. In the 2nd group on the 14th day there was a slight infiltration of soft tissues in the area after the surgical wound, and on the 28th and 42nd days there was suppuration of the postoperative wound.

## Discussion

We conducted a comparative morphological study of the reparative process of bone tissue after different methods of surgical treatment of chronic osteomyelitis in an animal model. The PerOssal group was an experimental control group.

Osteomyelitis remains a formidable complication after injuries or surgical interventions on the bones [14,15]. The study we describe was performed to provide insight into the post-treatment changes in chronic osteomyelitis, including concomitant bone remodeling, and the use of a bone allograft of an antibiotic-impregnated Marburg bone bank.

Animal models of experimental osteomyelitis are used to evaluate the effectiveness of the use of resorbable biomaterials and antibacterial drugs [16-18]. For this reason, sclerosing agents are best not used, as they pose a threat to resorbable biomaterials due to the denaturing ability of such drugs [19].

Staphylococcus aureus bacterial culture is considered the gold standard for detecting active bone infections [20]. Additionally, the use of standard histological staining indicates morphological bone changes initiated by bacterial infection.

Calcium-binding fluorophores have previously been studied to track bone remodeling and tooth mineralization [21-23]. In contrast to such studies, our data suggest that the use of a bone allograft of an antibiotic-impregnated Marburg-prepared bone bank may be of great value in monitoring and quantifying bone remodeling associated with osteomyelitis, in particular periosteal eminence mineralization [16]. Furthermore, when these data are combined with hematological data, they show that infection-

mediated bone mineralization continues to progress even after reductions in ESR and CRP levels, reinforcing the indication for acute stabilizing (potentially chronic) infection. Moreover, in combination with our previously published data [16,17], these data show that these changes in bone remodeling are infection dependent and not associated with the presence or absence of an implant.

Our collected data provide new insight into the development of osteomyelitis and suggestions for the use of parameters in both preclinical and clinical perspectives. Under preclinical conditions, body weight and temperature provide general information about the condition of the animal and should be considered as such. Weekly assessment of CRP levels and leukocyte differentiation is recommended, combined with weekly x-rays, histology, and cultures. X-ray provides additional information about infection and associated bone mineralization, is not absolutely necessary to determine the effectiveness of an antibacterial drug or biomaterial in preventing osteomyelitis. While combined follow-up with radiographs, histology, bacterial culture, and hematology analysis will provide sufficient information to determine antimicrobial efficacy.

However, when translated into a clinical setting, the situation is different, and CRP and leukocyte differentiation will still be useful, as will radiographs.

## Conclusions

Our study describes the detection of various parameters of bone infection and their correlation in an experimental animal model of osteomyelitis (regardless of the presence of an implant) and provides information on which parameters would be the most optimal infection parameters to use in preclinical and potentially clinical settings.

Scientists are still looks for a treatment, but any treatment must be verified on an experimental model. The experimental model reproduced in this project used clinical evaluation as analysis method. The clinical evaluation allowed detailed observations of analyses, that showed dynamical changes on different types of treatment.

**Conflict of interests.** The Authors declare no conflict of interests.

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**Author Contributions**. Conceptualization – B.T.; Methodology – B.T., D.S. and M.T.; Formal Analysis - D.S., E.K. and A.S.; Writing - Original Draft Preparation - A.A. and A.S.; Writing - Review and Editing – D.S. and E.K.; Supervision – B.T. and M.T.; Project Administration – D.S., E.K. and A.A.

All authors have read and agreed to the published version of the manuscript.

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## Қояндардағы созылмалы остеомиелит үлгісін емдеудің нәтижелерін клиникаға дейінгі бағалау

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**Түйіндеме**

*Созылмалы остеомиелит бүгінге дейін ортопедиялық хирургиядағы күрделі мәселе болып табылады. Соңғы уақытта созылмалы остеомиелитті емдеуде жергілікті антибиотик тасымалдаушысы ретінде биоыдыраушы материалдар жиі қолданылады. Біздің зерттеуде Марбург жүйесі бойынша дайындалған сүйек аллографты қолданылды.*

*Зерттеу мақсаты: қояндардағы остеомиелит үлгісінде антибиотикке байытылған сүйек аллографтын қолдану арқылы жүргізілген созылмалы остеомиелит емінен кейінгі клиникалық өзгерістерді бағалау.*

*Материалдар мен әдістер. Остеомиелит Staphylococcus aureus-тың адамдық штаммын жұқтыру көмегімен жасалды. Ол ортан жіліктің дисталды бөліміне арнйы жасалған сүйек ақауларына енгізілді. Сүйек ақауын толтыру тәсіліне байланысты эксперименттік жануарлар үш топқа бөлінді: 1 топта сүйек ақауы антибиотикке байытылған биоыдыраушы PerOssal материалымен толтырылды, 2 топта сүйек ақауы антибиотикке малынған тұтас сүйек аллографтымен толтырылды, 3 топта сүйек ақауы антибиотикке малынған тесілген сүйек аллографтымен толтырылды. Созылмалы остеомиелит дамуының бәсеңдеуін бағалау үшін клиникалық бақылау жүргізілді. Тәжірибедегі барлық жануарлардың дене қызуы 42 күндік бақылаудың барлық кезеңінде қашықтықтан өлшенетін термометрмен өлшенді.*

*Нәтижелері. Топтардағы қояндарда отаға дейінгі ортоаша температура 1 топта - 36,90; 2 топта - 36,40; 3 топта 36,20 құрады. Отадан кейінгі бірінші тәулікте 1 және 3 топтарда бастапқы температурамен салыстырғанда айтарлықтай айырмашылық болған жоқ, ал 2-ші топта отадан кейінгі бірінші тәулікте жануарлардың дене температурасы 39,00 дейін көтерілді. Ерте отадан кейінгі кезеңнің 3-ші тәулігінде 1-ші және 3-ші топтарда дене температурасының максималды жоғарылауы анықталды. 1-ші топта 39,20 дейін және 3-ші топта 38,20 дейін. 2-ші топта дене температурасының максималды жоғарлауы 2-ші тәулікке сәйкес келді және 38,60 құрады. Ота жасалған қояндардың отаға дейінгі орташа дене салмағы 1-ші топта 2983,3 гр.; 2-ші топта - 3206,7 гр.; 3-ші топта - 2300,0 гр. құрады. Отадан кейінгі кезеңде 1-ші топта отадан кейінгі бірінші күні дене салмағының тапшылығы 1,3 граммды құрады, динамикада 5 күнге дейінгі уақытта төмендеді, содан кейін дене салмағының*

*тұрақты өсуі байқалды да, 42-ші күні 783,4 грамды құрады. 2-ші топта бірінші күні дене салмағының максималды тапшылығы 92,3 гр-ға дейін, кейіннен жоғарылауы байқалды, ал жалпы алғанда, бүкіл бақылау кезеңінде дене салмағының тұрақты өсуі 200 гр. құрады. 3-ші топта отадан кейінгі бірінші күні дене салмағының тапшылығы 13,9 гр. құрады. Динамикада дене салмағының шамалы тұрақсыздығы байқалды, мысалы, 5-ші күні дене салмағы 3284,6 гр., 6-шы күні 3169,2 гр-ға дейін төмендеген. 1-ші топтағы жараны жалпы бағалау кезінде бүкіл бақылау кезеңінде жараның іріңдеуі, тігістердің ажырауы немесе тұрақсыздығы байқалмады. 3-ші топта отадан кейінгі 28-ші күні отадан кейінгі жара аймағында жұмсақ тіндердің аздап инфильтрациясы анықталды. 2-ші топта 14-ші күні отадан кейінгі жара аймағында жұмсақ тіндердің аздап инфильтрациясы, ал 28-ші және 42-ші күндері отадан кейінгі жараның іріңдеуі анықталды.*

*Қорытынды. Бұл зерттеудің нәтижесі бойынша перфорацияланған сүйек аллографтының қолжетімді биоматериал екені және сүйектердің регенеративті хирургиясында қолданылуы мүмкін екені көрсетілді.*

*Түйін сөздер: клиникаға дейінгі бағалау алгоритмі, созылмалы остеомиелит, қояндардағы остеомиелит үлгісі, клиникаға дейінгі зерттеу.*

## Доклиническая оценка лечения на модели хронического остеомиелита у кроликов

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### Резюме

*Хронический остеомиелит является сложной проблемой ортопедической хирургии. В последнее время в лечении хронического остеомиелита все чаще применяются биодеградируемые материалы в качестве местного носителя антибиотика. В нашем исследовании мы использовали костный аллографт, заготовленный по Марбургской системе.*

*Цель исследования состояла в том, чтобы оценить клинические изменения при применении импрегнированного антибиотиком костного аллографта на модели остеомиелита у кроликов.*

*Материалы и методы. Остеомиелит формировали у кроликов человеческим штаммом Staphylococcus aureus, который вводился в костные дефекты в дистальном отделе бедренной кости. В зависимости от заполнения дефекта были сформированы три группы: в 1 группе – дефект заполнен биодеградируемым материалом PerOssal, импрегнированным антибиотиком, во 2 группе – дефект заполнялся цельным костным аллографтом, замоченным в антибиотике, в 3 группе – дефект заполнялся перфорированным костным аллографтом, замоченным в антибиотике. Клиническое наблюдение использовано для оценки уменьшения процесса хронического остеомиелита. Температуру тела всех экспериментальных животных измеряли бесконтактным термометром в течение всего срока наблюдения, который составил 42 дня.*

*Результаты. Средняя температура у кроликов в группах до операции составила 36,90 в 1-й группе; во 2-й группе - 36,40; в группе 3 - 36,20. В первые сутки после операции в 1 и 3 группах достоверной разницы с исходной температурой тела у кроликов до операции не было, а во 2-й группе температура тела в первые сутки после операции повысилась до 39.00. В раннем послеоперационном периоде максимальное повышение температуры тела наблюдается на 3-и сутки в 1-й группе до 39,20 и в 3-й группе 38,20. Во 2-й группе максимальное повышение температуры было на 2-е сутки после операции до 38,60. Средняя масса оперированных кроликов до операции составила 2983,3 гр. в 1-й группе; во 2-й группе - 3206,7 гр.; в группе 3 - 2300,0 гр. В послеоперационном периоде в 1-й группе дефицит в первые послеоперационные сутки составил 1,3 гр., в динамике уменьшился до 5-х суток, а затем наблюдался стойкий прирост массы тела, который в целом к 42 дню составил 783,4 грамма. Во 2-й группе в первые сутки отмечался максимальный дефицит массы тела до 92,3 гр., с последующим увеличением, и в целом за весь период наблюдения прирост составил 200 гр. В 3-й группе в первые сутки после операции дефицит массы тела составил 13,9 гр. В динамике отмечалась незначительная нестабильность массы тела, например, на 5-е сутки масса тела составила 3284,6 гр., со снижением на 6-е сутки до 3169,2 гр. При визуальной оценке раны в 1-й группе нагноения раны, расхождения или нестабильности швов за весь период наблюдения не отмечалось. В 3-й группе на 28-е сутки после операции отмечалась незначительная инфильтрация мягких тканей в области послеоперационной раны. Во 2-й группе на 14-е сутки отмечалась незначительная инфильтрация мягких тканей в области послеоперационной раны, а на 28-е и 42-е сутки - нагноение послеоперационной раны.*

*Выводы. Таким образом, в данном исследовании показано, что перфорированный костный аллографт является доступным биоматериалом и может быть использован в костно-регенеративной хирургии.*

*Ключевые слова: алгоритм доклинической оценки, хронический остеомиелит, модель на кроликах, доклиническое исследование.*