EFFECTS OF LOW-DOSAGE RADIOTHERAPY FOR KNEE OSTEOARTHRITIS ON THE INCIDENCE OF KNEE ARTHROPLASTY: RESULTS OF A RANDOMIZED CONTROLLED TRIAL WITH 9-YEAR FOLLOW-UP

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ABSTRACT

The aim. *To compare the incidence of knee arthroplasty in patients receiving standard treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in combination with symptomatic slow acting drugs for osteoarthritis (SYSADOA), or combination of NSAIDs and SYSADOA with low-dose radiation therapy (LDRT) in patients with stage 0–2 knee osteoarthritis (OA).*

Materials and methods. *The article presents the results of randomized controlled study of 292 patients with confirmed knee OA according to Altman's criteria (1991) and Kellgren – Lawrence radiographic stages 0–2 who were randomized into two groups. The control group (n = 146) received standard therapy of NSAIDs + SYSADOA. Patients of the study group (n = 146) received combination of standard therapy and LDRT up to a total dose of 4.5 Gy. The cumulative risk of knee arthroplasty was assessed using actuarial analysis and the Kaplan – Meier method. Attributable (AF) and population attributable (PAF) fractions were calculated to assess LDRT preventive potential.*

Results. *The total observation period was 2131.2 person-years. Knee arthroplasty was performed in 4.1 % (n = 6) of patients in the study group against 7.5 % (n = 11) in the control group. The incidence density ratio was 0.60 (95% CI: 0.18–1.88), which corresponds to a risk reduction by 67 %, but the differences were not statistically significant due to the small number of cases (p = 0.340). The AF was 40 % while the PAF was 21 %.*

Conclusions. *The use of LDRT reduces the risk of knee arthroplasty by two-thirds and has the potential to prevent 21 % cases of knee arthroplasty in patients with knee OA. A study on a larger sample is required.*

Key words: *osteoarthritis, knee joint, joint arthroplasty, low-dose radiation therapy*

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ВЛИЯНИЕ НИЗКОДОЗНОЙ ЛУЧЕВОЙ ТЕРАПИИ ОСТЕОАРТРИТА КОЛЕННОГО СУСТАВА НА ЧАСТОТУ ЭНДОПРОТЕЗИРОВАНИЯ: РЕЗУЛЬТАТЫ РАНДОМИЗИРОВАННОГО КОНТРОЛИРУЕМОГО ИСПЫТАНИЯ С 9-ЛЕТНИМ НАБЛЮДЕНИЕМ

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РЕЗЮМЕ

Цель исследования. *Сравнить частоту эндопротезирования коленного сустава у больных, получавших стандартное лечение нестероидными противовоспалительными препаратами (НПВП) в комбинации с симптоматическими лекарственными средствами замедленного действия (SYSADOA, symptomatic slow acting drugs for osteoarthritis) либо их сочетание с низкодозной лучевой терапией (НДЛТ), при остеоартрите коленных суставов 0–2-й стадий.*

Материалы и методы. *Представлены отдалённые результаты рандомизированного контролируемого испытания в выборке из 292 пациентов с подтверждённым остеоартритом (ОА) коленных суставов по критериям Altman (1991), рентгенологической стадией 0–2 по Kellgren – Lawrence, случайным образом распределённых в две группы. Контрольная группа (n = 146) получала терапию комбинацией НПВП и SYSADOA. В группе исследования (n = 146) пациенты дополнительно к стандартному лечению получали НДЛТ до суммарной дозы 4,5 Гр. Кумулятивный риск эндопротезирования оценивали с помощью актуарного анализа и метода Каплана – Майера. Для оценки профилактического потенциала НДЛТ рассчитывали предотвратимые доли для выборки (AF, attributable fraction) и для генеральной совокупности (PAF, population attributable fraction).*

Результаты. *Общее время наблюдения составило 2131,2 человеко-лет. 4,1 % (n = 6) пациентам группы исследования проведено эндопротезирование против 7,5 % (n = 11) в контрольной группе. Отношение плотностей инцидентности составило 0,60 (95% ДИ: 0,18–1,88), что соответствует снижению риска на 67 %, но результаты не достигали уровня статистической значимости по причине малого числа эндопротезирований (p = 0,340). Предотвратимая доля эндопротезирований составила 40 % для выборочной совокупности и 21 % для генеральной совокупности пациентов с рентгенологической стадией 0–2.*

Заключение. *Применение НДЛТ снижает риск эндопротезирования на две трети и потенциально способно снизить частоту эндопротезирования на 21 % у больных ОА коленного сустава. Требуется исследование на большей выборке.*

Ключевые слова: *остеоартрит, коленный сустав, эндопротезирование, низкодозная лучевая терапия*

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INTRODUCTION

Osteoarthritis (OA) of the major joints, more commonly affecting those over 40 years of age, is the most common musculoskeletal disease. In 2020, it is estimated that 654 million people worldwide could have knee OA [1]. According to Russian statistics, up to 13 % of the adult population suffer from knee and hip OA [2].

Current OA therapy is primarily aimed at pain relief. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been prescribed for this purpose [3, 4]. Following the clinical recommendations of the Association of Rheumatologists of Russia, symptomatic slow acting drugs for osteoarthritis (SYSADOA), including tissue repair stimulators (chondroitin sulfate, glucosamine, etc.), as well as bone and cartilage metabolism correctors, can also be used to treat knee OA [4]; in the anatomical-therapeutic-chemical classification they are included along with NSAIDs and anti-rheumatic drugs in "basic therapy" [3]. However, meta-analyses of studies conducted without the support of pharmaceutical companies have not confirmed the benefits of using chondroitin sulfate and glucosamine, so many international professional communities of rheumatologists do not recommend their use [3, 5].

Osteoarthritis often progresses steadily to advanced stages, resulting in a high incidence of disability and referral for surgical treatment. Among all reported cases of permanent disability, 30 % are associated with OA progression [1]. Among them, about 15 % of patients are referred for total knee replacement [6]. Meanwhile, the long-term results of knee arthroplasty cannot be recognized as completely satisfactory. As many as 25 % of patients are dissatisfied with the results of surgery, as several studies have reported. Within two to five years, revision surgeries are performed in 60–80 % of cases [7, 8]. In more than half of all cases of unsatisfactory results caused by endoprosthetics, patients are suffering from pain in the operated joint [9]. The incidence of infectious complications after surgery is 0.2–4.5 % in primary prosthetics and 4.5–12 % in revision (repeat) prosthetics [6, 7].

As a result, a search for more effective techniques for conservative treatment of OA is required. Since the 1970s, low-dose radiation therapy (LDRT) has been used for the OA treatment of various localisations, which is able to provide long-term pain relief [10, 11]. LDRT has been successfully used in Germany and Spain for the therapy of gonarthritis [12, 13]. Russia has a long experience with this approach [14], but further evidence of its efficacy is required for inclusion of this treatment. LDRT has been previously demonstrated in a randomized study that it could prevent the progression of pain syndrome and pathological changes in the joint over a horizon of three years [15, 16]. A long-term preservation of the analgesic effect has the potential to delay the need for surgical treatment.

THE AIM OF THE STUDY

To conduct a comparative analysis of the knee arthroplasty incidence in patients who received low-dose radiation therapy in combination with baseline therapy with non-steroidal anti-inflammatory drugs in combination with symptomatic slow-acting drugs or standard treatment alone, in patients with osteoarthritis of knee joints of stages 0–2 within the framework of an open randomized trial with long-term prospective follow-up.

MATERIAL AND METHODS

Patient characteristics

The details of the patient sample have been described previously [15, 16]; briefly, they can be summarized as follows. The study, conducted from October 2012 to October 2014, included patients with clinically confirmed OA of the knee joints of stage 0–2 according to the criteria of Altman, 1991 [17] Kellgren – Lawrence [18] in combination with or without laboratory and radiological manifestations and baseline pain level of 30 mm or more on the visual analogue scale (VAS).

Treatment regimen

Randomisation using a number generator was used for allocation into groups. In the control group, the patients received basic therapy with selective NSAIDs and combined preparation SYSADOA glucosamine (500 mg) and chondroitin sulphate (400 mg) according to the scheme: 1 capsule 3 times a day for 3 weeks, from the fourth week – 1 capsule 2 times a day for up to 12 weeks. After an 8-week break, a repeat course in the same regimen was administered for 12 weeks. Low-dose orthovoltage X-ray therapy to the affected joint at a dose of 4.5 Gy in 10 sessions every 48 hours was administered to the patients of the study group against the background of standard treatment similar to that in the first group.

A total of 292 patients were included in the analysis, 146 in each treatment group. Patients in the comparison groups were comparable in terms of age-sex composition and baseline disease characteristics. Female patients were 48 % and the mean age was 36–40 years. The mean body mass index was 27 kg/m^2 in both groups, and the duration of pain syndrome before treatment varied from 9.2 to 9.7 months. Radiological stages 0 (symptomatic OA with changes characteristic of OA according to magnetic resonance imaging (MRI) but no changes on radiographs), 1 and 2 were established in 15 (10.3 %), 89 (60.9 %) and 42 (28.8 %) patients of the control group and in 24 (16.4 %), 86 (58.9 %) and 36 (24.7 %) patients of the study group, respectively. No statistically significant differences between the two groups were observed for all the compared indices.

Statistical analysis

The cumulative risk of endoprosthetic replacement was assessed using actuarial analysis and the Kaplan – Meier method. Knee arthroplasty, the data on which were obtained from the Unified State Information System in the sphere of healthcare of the Arkhangelsk region as of December 31, 2021, was considered as an event.

The incidence of endoprosthetic replacement in both groups was calculated per 100 person-years. Relative (AF,

attributable fraction) and population (PAF, population attributable fraction) fractions were calculated to estimate the proportion of endoprosthetic replacements that could have been prevented if all patients had received LDRT in addition to standard treatment in the study and in the general population. Differences in the incidence of outcome between groups were assessed using the Wilcoxon – Jihan test.

The results of the analyses are presented with 95 % confidence intervals (95% CI) as they are more informative than traditional levels of statistical significance [19]. The Stata software package version 17 (Stata Corp., USA) was used for all calculations [20].

The study was approved by the Ethical Committee of the Northern State Medical University (minutes No. 10 dated December 21, 2011), informed consent was obtained from all patients.

RESULTS

The number of patients who underwent knee arthroplasty by radiological stage is summarized in Table 1. The cumulative risk of endoprosthetic replacement for the two groups is summarized in Figure 1.

The incidence of knee arthroplasty was significantly associated with the initial OA stage. In the initial absence of radiological signs of OA, none of the patients required surgery during 9 years of follow-up. Endoprosthesis was performed half as often in more advanced OA stages when LDRT was used. The total time to either endoprosthesis or censoring was 2131.2 person-years. A total of 4.1 % (n = 6) of patients in the study group underwent endoprosthetics as compared to 7.5 % (n = 11) of patients in the control group. The incident density ratio was 0.60 (95% CI: 0.18–1.88), meaning that the use of the new method has the potential to significantly reduce the time to need for endoprosthesis, but the results did not reach the level of statistical significance as the number of endoprosthetics was not significant (p = 0.340).

Calculation of the preventable fractions (AF and PAF) of the studied outcome showed that 40 % of knee arthroplasties could have been prevented in the study sample population if all patients had received the experimen-

TABLE 1

THE TOTAL NUMBER OF JOINT REPLACEMENTS IN PATIENTS WITH KNEE OSTEOARTHRITIS OVER A A 9-YEAR PERIOD

Baseline stage	Control group	Study group
X-ray stage 0, abs. (%)	0/24 (0.0 %)	0/15 (0.0 %)
X-ray stage 1, abs. (%)	2/86 (2.3 %)	1/89 (1.1 %)
X-ray stage 2, abs. (%)	9/36 (25.0 %)	5/42 (11.9 %)

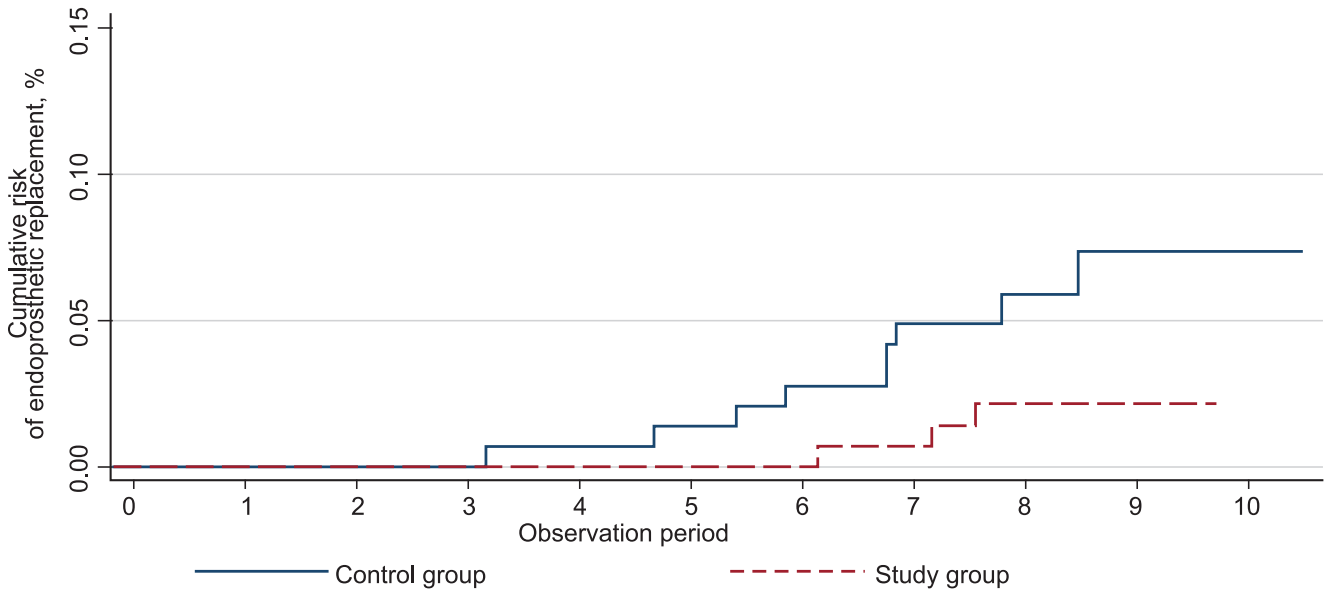

FIG. 1.

Cumulative risk of total knee replacement as affected by treatment of osteoarthritis

tal treatment, while in the general population of patients with knee osteoarthritis with radiological stage 0–2 this proportion would have been 21 %.

DISCUSSION OF RESULTS

The article contains a comparative analysis of the knee arthroplasty frequency in patients in the framework of an open randomized trial depending on the previous treatment of knee OA stages 0–2. The study's inclusion of data from symptomatic knee OA allowed us to follow the results of therapy for the disease when changes are not yet radiologically evident (stage 0). There were no adverse effects of low-dose radiation therapy on the disease course in symptomatic OA, which confirms our results of no endoprosthetic incidence in both the control and study groups. A two-fold reduction in the risk of arthroplasty was observed in patients treated with LDRT compared with the control group, but despite the magnitude of the effect, no differences reached the level of statistical significance for conventional alpha and beta error rates as a result of the small number of outcomes studied.

Low-dose radiation therapy is not a common approach in the treatment of knee OA. A major obstacle in the expansion of its use is the lack of evidence from high quality studies. This is, for example, the conclusion reached by the authors of a recently published systematic review of the literature [12]. They analyzed heterogeneous studies, the earliest of which was dated 1980; a total of 26 studies were included in the analysis. Many of the studies analyzed were retrospective in nature with an observational design, had no control group and / or contained a small number of observations.

Up to date, a very few randomized studies examining the effect of LDRT in knee OA have been published [11, 13, 16]. A positive effect of LDRT was obtained in a study from Germany. In a retrospective analysis, S. Keller et al. evaluated the clinical response to LDRT in 1,037 patients with painful knee OA immediately or within two months after completion of irradiation. Pain reduction after LDRT was observed in 79.3 % (10.5 % complete response, 68.8 % partial response) [21]. O.J. Ott et al. assumed that LDRT is less effective for the treatment of severe pain syndrome in advanced OA with already documented destruction of the bone joint and damage to periarticular soft tissues, which may be resistant to the anti-inflammatory effect of LDRT [22].

By contrast, in a double-blind randomised trial from the Netherlands, the authors observed no reduction in pain among patients in the study group compared with the control group of simulated irradiation (relative risk, 1.09; 95% CI: 0.37–3.19), and no significant synovial changes or reduction in synovitis volume on MRI. One should note that the total number of observations ($n = 55$ in both groups) and the limited follow-up period (3 months) do not allow a definitive conclusion about the efficacy of the approach [11].

Our randomized trial has a high degree of maturity. LDRT for the included knee OA patients was performed 8–10 years ago. It has previously been demonstrated that the addition of orthovoltage radiotherapy to standard conservative treatment leads to a persistent reduction in pain syndrome, improvement of joint function and, in general, quality of life of patients for a horizon of at least three years [15, 23, 24].

The decision to proceed with a joint endoprosthesis is determined not only by the radiological stage, but also, to a greater extent, by the severity of the pain syndrome and the patient's disability with persistent impairment of static and dynamic functions (third and fourth). With an initial more severe radiological stage of OA, the deterioration of statico-dynamic functions in these patients occurs more rapidly [25]. In Europe, the incidence of arthroplasty among patients over 65 years of age was an average of 0.6 per 1,000 population in the 2010s [6, 8]; in Russia, this rate was somewhat lower during the same period, being up to 0.2 per 1,000 adults [2].

This study was the first to analyze data about the incidence of total knee arthroplasty depending mainly on the previous treatment received in a randomized analysis; thus, assessing the impact of a specific therapy on the course of OA. Patient outcomes were followed over a long period of time, which is an important feature of our study. In most other studies, the duration of follow-up is limited to one, maximum three years of follow-up [11, 13] without studying the long-term outcomes of the disease. From this study, it was demonstrated that one in five cases of endoprosthetic replacement could be prevented if all patients in the general population received the experimental treatment.

The comparatively small total number of observations (292 patients in total) and 17 events represent limitations of the study. Considering, however, that the incidence of knee arthroplasty was half as frequent in the study group compared with the control group, a longer follow-up period is required, as well as replication of the study in other studies using larger sample populations.

Other limitations include the fact that there is no mandatory patient registration for OA to date, so there is a risk of patients "dropping out" of the study. However, in the present study, we had access to patients' personal data; they were called personally for appointments and evaluated for long-term treatment outcomes. However, when analyzing larger data sets, such personalization may not be available; this is an important motivation for mandatory registration of OA patients and possibly the creation of an OA registry along the lines of population-based cancer registries [26].

CONCLUSION

The integration of LDRT into OA treatment regimens can not only permanently reduce pain syndrome and improve the quality of life of such patients, but also potentially reduce the risk of knee arthroplasty by two-fold. With few-

er patients requiring endoprosthetics, the financial burden on the health care system is potentially reduced.

Conflict of interest

The authors of this article declare no conflicts of interest.

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