THE STUDY OF EFFECTS OF “CHONDROLIFE” COMBINED CREAM-GEL IN THE SPONTANEOUS PAIN SENSITIVITY EXPERIMENT

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Key words: osteoarthritis; glucosamine; chondroitine; local therapy; pain; analgesimetry

The leading areas of pathogenetic treatment of osteoarthritis include: modulation of inflammation, regulation of metabolism of chondrocytes and stimulation of the cartilage synthesis. Relief of pain is another no less important aspect of the therapy. Today, along with the use of drugs the treatment of the articular syndrome in osteoarthritis focuses on the local therapy, including the use of ointments and gels. The aim of this work was to study the analgesic action of the original cream-gel under the conditional name “Chondrolife” containing glucosamine hydrochloride, chondroitin sulphate, camphor and menthol. The antinociceptive effect of “Chondrolife” cream-gel compared to the reference drugs “Chondroxide®” gel and “Diclac gel®” was studied when externally applied on the model of carrageenan-induced acute gonarthritis in rats by the impact to the severity of spontaneous pain using an Incapacitance Tester MkV (“Linton Instrumentation”, Great Britain). “Chondrolife” cream-gel has shown a significantly better antinociceptive effect compared to the reference drug “Chondroxide®” gel and is not inferior “Diclac gel®” by the antinociceptive activity on the 6th hour (in 1 hour after applying the drugs under study). Although on the seventh hour the activity (in 2 hours after applying the drugs under study) of “Chondrolife” cream-gel gradually reduces and is slightly inferior the activity of “Diclac gel®”, it is likely higher than that of “Chondroxide®” gel. It allows continuing our study of “Chondrolife” combined cream-gel as a chondroprotective analgesic agent for local application.

According to various studies the frequency of pain in the knee joints in the presence of radiographic osteoarthritis ranged from 40 to 80%, and increase in the frequency of pain was observed in people aged over 50 years [1, 13]. According to the current data the main directions of pathogenetic treatment of osteoarthritis (OA) include: modulation of inflammation, regulation of metabolism of chondrocytes and stimulation of the cartilage synthesis [15]. Relief of pain is another no less important aspect of therapy since the overwhelming number of OA patients suffers from chronic pain [5].

Experts of the European Anti-rheumatic League (EULAR) and the American Association of Rheumatology (OARSI) have developed recommendations for treating OA, which include non-pharmacological, pharmacological and surgical treatments [8]. There are 3 main principles of OA treatment: pain relief, removal of inflammation, further delayed cartilage degeneration [11].

All drug treatments of OA are divided into 3 main groups: rapid acting symptom-modifying drugs (simple analgesics, nonsteroidal anti-inflammatory drugs, opioid analgesics, intraarticular injections of glucocorticoids, transdermal drug forms); Symptomatic Slow Acting Drugs for Osteoarthritis (SYSDOA) (chondroitine sulphate, glucosamine sulphate, piasclidine, drugs of hyaluronic acid) [8, 11].

Therapy of OA is a long, almost life-long process, and a special attention should be paid to the effective and safe use of drugs [9]. SYSDOA combine all the necessary qualities for long-term rehabilitation. Monotherapy with SYSDOA is recommended in the non-acute condition. It is recommended to combine SYSDOA with NSAIDs when the pain syndrome exacerbates since the analgesic action of the last develops much faster. The combined use can reduce the dose of NSAIDs, thus preventing a number of undesirable side effects [10, 12].

Today, along with the regular use of drugs the treatment of the articular syndrome in osteoarthritis focuses on the local therapy, including the use of ointments and gels [14]. The reference should be given to the local treatment over the systemic therapy, especially in case of a mild or moderate pain, and when only a few joints are involved [13].

Inclusion of the local therapy in the complex of therapeutic measures in OA has a number of advantages: a purposeful effect on the main inflammatory focus (the most affected joints) and reduction of the need for prescribed drugs with a negative impact on the condition of the gastrointestinal tract, cardiovascular and nervous systems, etc. The latest OARSI recommendations for OA therapy regulate the use of different groups of drugs, including local NSAIDs [15].

The aim of this work was to study the analgesic action of the original cream-gel under the conditional name “Chondrolife” with...
the following composition: glucosamine hydrochloride – 5.0 g, chondroitin sulfate – 5.0 g, camphor – 3.2 g, menthol – 0.5 g, excipients – up to 100 g. “Chondroxide®” gel (manufactured by Nizpharm-STADA, Russia) containing 5% of chondroitin sulfate and “Diclac gel®” (manufactured by Sandoz AG, Slovenia) containing 5% of diclofenac sodium were chosen as reference drugs.

Materials and Methods

The antinociceptive effect of “Chondrolife” cream-gel compared to the reference drugs “Chondroxide®” gel and “Diclac gel®” was studied when externally applied on the model of carrageenan-induced acute gonarthritis in rats by the impact to the severity of spontaneous pain in the hind limbs at a fixed position of the animal in the chamber. Data on distribution of the weight on the right and left limb (g) were calculated as a percentage of the total weight of animals using the formula:

\[ ID = \frac{MRL}{MRL + MLL} \times 100, \]

where ID – is the index of disability (%);
MRL – is the body weight of the animal distributed to the right (affected) limb;
MLL – is the weight of the animal distributed to the left (healthy) limb.

The analgesic activity (AA) was calculated according to the ability of the drugs under study to decrease the signs of stress and improve the measurement accuracy during the experiment.

Development of spontaneous pain in animals with carrageenan-induced acute gonarthritis and distribution of the load on the hind limbs were studied using an Incapacitance Tester MkV (“Linton Instrumentation”, Great Britain). Measurement of the intensity of the spontaneous pain reaction was performed in 1 and 2 hours after application of the gels under study. For this purpose, each animal was placed into the fixing chamber of the tester and left there for 5 min to acclimatize until the animal adapted and took a comfortable position. The rat’s hind limbs should be at plates of the loading device separately, and fore limbs on the sloping front wall of the chamber. Thus, the entire weight of the animal was redistributed through the hind limbs on the weight sensors of the tester. Redistribution of the body weight was measured three times with an interval of 5 seconds, and the average of the body weight falling on the right and left limb separately was recorded. This test allowed assessing the severity of pain in the injured paw by the nature of distribution of the weight on the hind limbs at a fixed position of the animal in the chamber. Data on distribution of the weight on the right and left limb (g) were calculated as a percentage of the total weight of animals using the formula:

\[ AA = \frac{ID - ID_{sg}}{ID_{sg}} \times 100, \]

where AA – is the analgesic activity;
ID_{sg} is the index of disability in the experimental group of animals with the control pathology;
ID – is the index of disability in the experimental group of animals treated with the gels under study.

Statistic processing of the results obtained was performed by the methods of variation statistics using Student t-test and non-parametric methods for analysis (Mann-Whitney U Test) with STATISTICA 7.0 and MS Excel 2007 PC software.

Results and Discussion

In the intact animals distribution of the weight on the right and left limbs was in the range of 50:50% of the body weight, and the pain that spontaneously developed in animals with acute carrageenan-induced gonarthritis was...
The effect of "Chondrolife" cream-gel on the spontaneous pain reaction on the model of carrageenan-induced acute gonarthritis in rats

| Conditions of the experiment | n    | Index of disability, ID (%) | Analgesic activity, AA (%) |
|-----------------------------|------|-----------------------------|---------------------------|
| Control pathology (in 1 hour after applying the drugs under study) | 10   | 73.9±1.8                    | -                         |
| "Chondrolife" cream-gel     | 10   | 53.4±2.0/*/**              | 27.74±0.53***/***         |
| "Chondroxide®" gel          | 10   | 68.7±1.6*/**               | 7.04±0.36                 |
| "Diclac gel®"              | 10   | 55.4±2.4*/**               | 25.04±0.63*/**            |
| Control pathology (in 2 hours after applying the drugs under study) | 10   | 70.7±1.6                   | -                         |
| "Chondrolife" cream-gel     | 10   | 60.4±2.0/*/**              | 14.57±0.47**/*/*/*         |
| "Chondroxide®" gel          | 10   | 66.4±2.0/*/**              | 6.08±0.71                 |
| "Diclac gel®"              | 10   | 53.6±2.4*                  | 24.19±0.65*/**            |

Notes:
1) * – deviation is significant compared to control, p<0.05;
2) ** – deviation is significant compared to the reference drug "Chondroxide®" gel, p<0.05;
3) *** – deviation is significant compared to the reference drug "Diclac gel®", p<0.05;
4) n – is the number of animals in the group.

The rapid and strong analgesic effect is typical for "Chondrolife" cream gel due to the presence of menthol and camphor with their revulsive and cooling action in its composition. However, it is known that the effect of these drugs is not long, and our experiment confirms it. On the other hand, the analgesic activity of "Diclac gel®" is due to diclofenac sodium in it. At the same time the analgesic effect of glucosamine and chondroitin develops more slowly and acquires its maximum due to inhibition of inflammation and positive morphological and structural changes in the joint cartilage [6]. Thus, this combined cream-gel possesses the properties of symptom-modifying drugs (due to inhibition of pain) and disease-modifying properties (due to a marked effect of "Chondrolife" cream-gel on the morphological and structural characteristics of the articular cartilage) as shown in the previous experiments [3].

CONCLUSIONS
1. "Chondrolife" cream-gel has shown a significant antinociceptive effect in acute pain on the model of carrageenan-induced acute gonarthritis in rats.
2. The antinociceptive activity of "Chondrolife" cream-gel is statistically higher than that of the reference on the 6th hour of the experiment (in 1 hour after applying the drugs under study).
3. The antinociceptive activity of "Chondrolife" cream-gel is statistically higher than that of the reference drug "Chondroxide®" on the 7th hour of the experiment (in 2 hours after applying the drugs under study), but is slightly lower than that of the reference drug "Diclac gel®".
4. The analgesic activity of "Chondrolife" cream-gel in acute pain on the model of carrageenan-induced acute gonarthritis in rats is due to the presence of menthol and camphor in its composition.
5. The data provide the basis for further preclinical study of "Chondrolife" combined cream-gel as a chondroprotective and analgesics drug of topical application.
ЕКСПЕРИМЕНТАЛЬНОЕ ВИЧЕНИЕ ВЛИЯНИЯ КОМБИНИРОВАННОГО КРЕМ-ГЕЛЯ «ХОНДРОЛАЙФ» НА СПОНТАННУЮ БОЛЬСУ ЧУВСТВИТЕЛЬНОСТЬ

С.К.Шебeko, С.М.Зимин

Ключевые слова: остеоартроз; глюкозамин; хондроитин; местное лечение; боль; анальгезиметрия

Проведенными напряжённостью патогенетического лечения остеоартроза являются: модификация воспаления, регуляция метаболизма хондроцитов и стимуляция синтеза хряща. Уменьшение болевого синдрома - ещё один важный аспект терапии. С целью создания лекарственных средств, позволяющих эффективно уменьшить болевой синдром, были проведены эксперименты с использованием комбинированного крем-геля под условным названием «Хондролайф» с содержанием глюкозаминола, хондроитина сульфата, камфоры и ментола. Лечебное антиноцицептивное действие крем-геля «Хондролайф» было изучено на модельной системе, а именно, на модели карагенин-индуцированного гострого гонартроза у щурят. Крем-гель «Хондролайф» показал значительный антиноцицептивный эффект в сравнении с контрольными препаратами «Хондроксид®» и «Диклак гелем®», а также с другими препаратами, используемыми в клинической практике. Эти результаты подтверждают возможность использования комбинированного крем-геля «Хондролайф» в качестве эффективного метода лечения остеоартроза, особенно в местном применении.

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ЭКСПЕРИМЕНТАЛЬНОЕ ИЗУЧЕНИЕ ВЛИЯНИЯ КОМБИНИРОВАННОГО КРЕМ-ГЕЛЯ «ХОНДРОЛАЙФ» НА СПОНТАННУЮ БОЛЬСУ ЧУВСТВИТЕЛЬНОСТЬ

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Ведущими направлениями патогенетического лечения остеоартроза являются: модификация воспаления, регуляция метаболизма хондроцитов и стимуляция синтеза хряща. Уменьшение болевого синдрома – ещё один не менее важный аспект терапии. На сегодняшний день наряду с системным применением препаратов, в терапии суставного синдрома остеоартроза большое внимание уделяется местной (местной) терапии, в том числе с применением мазей и гелей. Целью данного исследования стало изучение анальгетического действия оригинального крем-геля под условным названием «Хондролайф» с содержанием глюкозамина гидрохлорида, хондроитина сульфата, камфоры и ментола. Лечебное антиноцицептивное действие крем-геля «Хондролайф»
по сравнению с референс-препаратами «Хондроксид®» гелем и «Диклак гелем®» исследовали при наружном нанесении на модели карагенин-индукированного острого гонартрита у крыс по влиянию на выраженность спонтанного болевого синдрома с помощью ‘тестера инвалидности’ – Incapacitance Tester MkV (‘Linton Instrumentation’, Великобритания). Крем-гель «Хондролайф» показал значительно лучшую антиноцицептивную активность по сравнению с контрольным препаратом «Хондроксид®» и не уступает антиноцицептивной активности «Диклак геля®» на шестом часу эксперимента (через 1 час после нанесения исследуемых препаратов), и, хотя на седьмом (через 2 часа после нанесения исследуемых препаратов) часу активность крем-геля «Хондролайф» постепенно снижается и несколько уступает активности «Диклак геля®», она достоверно выше, чем у геля «Хондроксид®», что дает основание для продолжения изучения комбинированного крем-геля «Хондролайф» в качестве хондропротекторного и анальгетического средства местного применения.