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Experimental evaluation of the effectiveness of CO_2 application in a carrageenan model of inflammation: new perspectives in the treatment of osteoarthritis

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Osteoarthritis (OA) is a chronic degenerative joint disease that leads to pain and limited mobility. Inflammation is a key pathogenetic factor in OA, which is accompanied by the activity of pro-inflammatory cytokines. One of the most promising methods of treating inflammation is carboxytherapy (CO_2), which has low toxicity and physiological safety, but its interaction with other anti-inflammatory drugs is not well understood. Objective. To evaluate the anti-inflammatory effect of CO_2 in animal models of carrageenan inflammation and to study its combined use with diclofenac and chondroitin. Methods. The study was conducted on 56 Wistar rats, which were randomly divided into 7 groups. Inflammation was modelled by injecting carrageenan into the limb of the animals. Prophylactic injections of anti-inflammatory drugs (diclofenac, chondroitin) were performed intraperitoneally and CO_2 subcutaneously one hour later. The size of the edema was analysed 1, 2, 3 and 5 hours after the injection. The rectal temperature of the animals was also measured to determine the overall inflammation. Results. One hour after the administration of carrageenan, the volume of the limb in group VII decreased to (0.429 ± 0.020) ml ($p < 0.001$), and in group VI — to (0.441 ± 0.017) ml ($p < 0.001$). After 2 hours, the maximum decrease in limb edema was observed in group VII — (0.491 ± 0.017) ml (by 52 %, $p < 0.001$), and in group VI — (0.495 ± 0.012) ml (by 38 %, $p < 0.001$). After 5 hours, the size of the limb edema in group VI decreased to (0.559 ± 0.030) ml (by 51 %, $p < 0.001$), and in group VII — to (0.571 ± 0.016) ml (by 46 %, $p < 0.001$). Rectal temperature in group VI decreased to (37.7 ± 0.3) °C (by 1.5 °C, $p < 0.001$), and in group VII — to (38.3 ± 0.2) °C (by 0.9 °C, $p < 0.001$). Conclusions. Carboxytherapy has a pronounced anti-inflammatory effect, which is manifested in the reduction of edema and temperature, especially when combined with diclofenac or chondroitin. Further research may be aimed at studying the possible mechanisms of the positive effect of CO_2, optimising therapeutic regimens and determining the long-term effects of carboxy therapy.

Остеоартрит (ОА) — хронічне дегенеративне захворювання суглобів, що призводить до болю та обмеження рухливості. Запалення є ключовим патогенетичним фактором ОА, який супроводжується активністю прозапальних цитокінів. Однією із перспективних методик лікування запалення є карбокситерапія (CO_2), яка має низьку токсичність і фізіологічну безпечність, проте її взаємодія з іншими протизапальними засобами недостатньо вивчена. Мета. Оцінити протизапальну дію CO_2 на моделі карагенінового запалення в тварин і дослідити його комбіноване застосування з диклофенаком і хондроїтином. Методи. Експеримент проведено на 56 щурах лінії Wistar, яких рандомізували на 7 груп. Запалення моделювали шляхом введення карагеніну в кінцівку тварин. Профілактично за годину робили ін'єкції протизапальних засобів (диклофенак, хондроїтин) внутрішньочеревинно та CO_2 підшкірно. Аналіз розміру набряку проводили через 1, 2, 3 та 5 год після ін'єкції. Також вимірювали ректальну температуру тварин для визначення загального запалення. Результати. Через годину після введення карагеніну обсяг кінцівки у групі VII зменшився до (0,429 ± 0,020) мл ($p < 0,001$), а у групі VI — до (0,441 ± 0,017) мл ($p < 0,001$). Через 2 год максимальне зменшення величини набряку кінцівки спостерігалося у групі VII — (0,491 ± 0,017) мл (на 52 %, $p < 0,001$), а у групі VI — (0,495 ± 0,012) мл (на 38 %, $p < 0,001$). Через 5 год розмір набряку кінцівки у групі VI зменшився до (0,559 ± 0,030) мл (на 51 %, $p < 0,001$), а у групі VII — до (0,571 ± 0,016) мл (на 46 %, $p < 0,001$). Ректальна температура в групі VI знизилася до (37,7 ± 0,3) °C (на 1,5 °C, $p < 0,001$), а у групі VII — до (38,3 ± 0,2) °C (на 0,9 °C, $p < 0,001$). Висновки. Карбокситерапія має виражений протизапальний ефект, який проявляється в зменшенні набряку та температури, особливо за комбінованого застосування з диклофенаком або хондроїтином. Подальші дослідження можуть бути спрямовані на вивчення можливих механізмів позитивної дії CO_2, оптимізації терапевтичних схем і визначення довготривалих ефектів карбокситерапії. Ключові слова. Карагенінове запалення, карбокситерапія, CO_2, диклофенак, хондроїтин, протизапальна дія.

Key words. Carrageenan inflammation, carboxytherapy, CO_2, diclofenac, chondroitin, anti-inflammatory effect

Introduction

Osteoarthritis (OA) is a chronic joint disease that affects the knees, hips, hands, and spine, causing pain, stiffness, and limited mobility [1]. According to the Global Burden of Disease (2019), OA is the 16th leading cause of disability in terms of years lost due to incapacitation [2]. Inflammation is a major factor in the development of OA, which is accompanied by the activity of pro-inflammatory cytokines such as IL-6 and vascular endothelial growth factor [2]. The acute phase involves vascular changes and cell activation. Macrophages play a key role in regulating the inflammatory response [3]. Carrageenan is used to model acute inflammation in animals, as it activates specific mediators and induces vascular changes [4].

New and improved treatments for inflammation are constantly being sought. One of them is carboxytherapy (CO_2 administration), which is characterized by safety and low toxicity [5]. CO_2 is administered subcutaneously or transdermally, providing both local and systemic therapeutic effects. Carboxytherapy is effective for the treatment of vascular diseases, osteoarthritis, rheumatic diseases, as well as in physiotherapy and balneotherapy [6]. It also improves oxygenation, angiogenesis, reduces oxidative stress and increases blood flow, which makes it effective in various pathological conditions [7]. Despite its widespread use, the effects of the interaction of CO_2 with other agents for the correction of inflammation are not well studied.

Purpose: to evaluate the anti-inflammatory effect of CO_2 in the carrageenan inflammation model in animals, as well as to study its combined use with other anti-inflammatory agents.

Materials and methods

The study protocols were approved by the institutional ethical committee for the use of animals and the bioethics commission of Uzhhorod National University (Protocol No. 9/2 dated 07.06.2023) and Poltava State Medical University (Protocol No. 225 dated 21.03.2024). The experiments were performed on 56 white sexually mature Wistar rats, weighing 285–315 g, of which 34 (60.70 %) were females. The animals were kept in standard vivarium conditions at a temperature of (22 ± 2) °C, relative humidity (55 ± 5) %, and a 12-hour light regime, in cages of 4–5 rats, were on a food ration in the form of a feed mixture and had free 24-hour access to water from automated drinkers. The experimental studies that were conducted comply with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes (Strasbourg, 1985), the Law of Ukraine on the Protection of Animals against Cruelty (No. 3446-IV of 21.02.2006). Rats were randomized by sex and divided into 7 groups of 8 individuals each (n = 8):

– I — intact control (saline);

– II — control disorder (carrageenan 1 %, 0.1 ml);

– III — control disorder + diclofenac sodium (8 mg/kg, intraperitoneally);

– IV — control disorder + chondroitin sulfate (3 mg/kg, intraperitoneally);

– V — control disorder + carbon dioxide (CO_2, 0.5 ml, s/w);

– VI — control disorder + diclofenac sodium (4 mg/kg) + CO_2 (0.5 ml);

– VII — control disorder + chondroitin sulfate (3 mg/kg) + CO_2 (0.5 ml).

To study the anti-inflammatory activity, a model of limb edema induced by carrageenan was used. Inflammation was induced by injection of 0.1 ml of 1 % carrageenan solution into the subaponeurotic area of the right hip of a rat. The size of the edema was measured before the disorder simulation and 1, 2, 3 and 5 h after the injection using a plethysmometer. One hour before the reproduction of the carrageenan test, diclofenac was administered intraperitoneally at a dose of 8 and 4 mg/kg and chondroitin — 3 mg/kg, as well as carbon dioxide subcutaneously — 0.5 ml per animal. The intact control group received saline solution in an equivalent volume. CO2 administration was performed using the INDAP Insuf apparatus (Czech Republic) using a BD Mikrolance needle — 3.30•G×½ (0.3×13) mm. Additionally, the rectal temperature of the rats was measured using a digital thermometer. Data were processed using the Jamovi software version 2.3.21. The results are presented as mean values ± standard deviation. The Shapiro-Wilk test was used to check normality. For comparison of groups, Welch's t-test or Tukey's test was used under normal distribution conditions, and for non-normal distribution conditions, Kruskal-Wallis test with Bonferroni correction was used. Results were considered statistically significant at $p < 0.05$.

Results

A study of the effect of carbon dioxide (CO_2) on carrageenan inflammation in rats showed significant changes in the volume of limb edema and rectal temperature after its administration. The table shows the mean values ± standard deviations (Mean ± SD) of the volume of the limbs of animals before and 1, 2, 3 and 5 hours after carrageenan administration, as well as changes in rectal temperature.

After the administration of carrageenan, a significant increase in the size of the limb edema was immediately observed in all experimental groups compared with the intact control group, which indicates the development of an inflammatory reaction.

In 1 hour

After the induction of carrageenan inflammation, significant changes in the size of the limb edema were observed in all groups. The greatest decrease was observed in group VII (CO_2 + chondroitin), where it reached (0.429 ± 0.020) ml, which was 0.10 ml less than in group II (control disorder) ((0.529 ± 0.022) ml, $p < 0.001$). This corresponded to a 49 % decrease, which was the best result. In group VI (CO_2 + diclofenac), the edema size also decreased significantly to (0.441 ± 0.017) ml, which was less compared to the control disorder group.

In 2 hours

The anti-inflammatory effect continued to increase 2 hours after drug administration. In group VII (CO_2 + chondroitin), the limb volume decreased to (0.491 ± 0.017) ml, which was 52 % less compared to the control disorder group (difference 0.118 ml, $p < 0.001$). In group VI (CO_2 + diclofenac), the edema volume was (0.495 ± 0.012) ml, which meant a 38 % reduction (difference 0.114 ml, $p < 0.001$). This indicated a significant anti-inflammatory effect of CO_2 in combination with chondroitin and diclofenac.

In 3 hours

In the combined therapy groups, the reduction in edema volume remained the greatest 3 h after inflammation induction. In group VII (CO_2 + chondroitin) — (0.579 ± 0.020) ml, which was 51 % less than in the control disorder group (difference 0.161 ml, $p < 0.001$). In group VI (CO_2 + diclofenac), the edema volume decreased to (0.586 ± 0.026) ml, which was 49.2 % less than in group II (difference 0.154 ml, $p < 0.001$). These results emphasize the long-term efficacy of the combined therapy.

In 5 hours

After inflammation induction, the combined use of CO_2 continued to demonstrate a high anti-inflammatory effect even after 5 h. In group VI (CO_2 + diclofenac), the edema volume decreased to (0.559 ± 0.030) ml, which was 51 % less than in the control disorder group (difference 0.136 ml, $p < 0.001$). In group VII (CO_2 + chondroitin), it decreased to (0.571 ± 0.016) ml, which was a 46 % decrease compared to group II (difference 0.124 ml, $p < 0.001$). In group V (CO_2), a significant decrease in edema volume of 30 % ($p < 0.001$) was also noted, which emphasizes the effectiveness even when CO_2 is used as monotherapy.

Thus, the results demonstrate the high anti-inflammatory activity of CO_2, especially when used in combination with diclofenac and chondroitin. The greatest effect was observed within 2–5 h after the induction of inflammation, which emphasizes the promising use of CO_2 in the complex therapy of inflammatory diseases.

In the time course of the study, changes in the size of limb edema in rats in different experimental groups were observed, which reflected the reduction of the inflammatory process. In group II (control disorder), the greatest increase was recorded after 3 h — +80; hour — +29, 2 h — +48, after 5 h — +69 %.

Group III (diclofenac) — the reduction in edema after 1, 2, 3 and 5 h was (in %): –27; –38; –30.67; –29. The greatest effect (–38 %) was observed after 2 h.

Group IV (chondroitin) — the decrease in edema volume after 1, 2, 3 and 5 h was (in %): –31, –44, –35, –27. The maximum decrease (–44 %) was after 2 h.

Group V (CO_2) — after 1, 2, 3 and 5 h, the decrease (in %) was found: –35, –47, –33, –30. The highest effect (–47 %) was found after 2 h, after which the effectiveness gradually decreased.

In group VI (diclofenac + CO_2), a decrease in edema volume (in %) was recorded: –44; –38; –49.2; –51 after 1, 2, 3 and 5 h. respectively. The maximum decrease (–51 %) was observed after 5 h, which indicated a synergistic effect in the case of combining diclofenac with CO_2.

In group VII (chondroitin + CO_2), a decrease in the size of limb edema (in %) was found: –49; –52; –51.44; 46 after 1, 2, 3 and 5 h, respectively. The greatest decrease (–52 %) occurred after 2 h.

These results demonstrate that CO_2 in combination with diclofenac and chondroitin has a pronounced anti-inflammatory effect, especially after 2–5 h after administration.

The effect of CO_2 and its combinations with diclofenac and chondroitin on rectal temperature in rats in the carrageenan model of inflammation

Body temperature is an important parameter that was evaluated during the study. The results obtained show that the body temperature of rats in group II (control disorder) significantly increased to (39.2 ± 0.2) °C compared to the indicators of intact animals (37.3 ± 0.2) °C (Table). This hyperthermic reaction verified the development of carrageenan inflammation.

In the process of analyzing the results of the experimental groups, significant changes in temperature were found compared to group II.

Group III (diclofenac) — decreased to (38.0 ± 0.2) °C, which is 1.2 °C, or –3.06 % less than group II

($p < 0.001$). This confirms the pronounced anti-inflammatory and hypothermic effect of diclofenac under the conditions of carrageenan inflammation.

Group IV (chondroitin) — decreased to (38.9 ± 0.4) °C, which is 0.3 °C lower than in group II. However, this difference was not statistically significant ($p = 0.146$).

Group V (CO_2) — decreased to (38.6 ± 0.3) °C, which was 0.6 °C, or –1.53 % less than in group II ($p < 0.001$). This indicated a moderate hypothermic and anti-inflammatory effect of CO_2.

Group VI (diclofenac + CO_2). The greatest decrease in temperature was observed in this group — to (37.7 ± 0.3) °C, which was 1.5 °C (or 3.83 %, $p < 0.001$) less than in group II. This confirmed the synergistic effect of diclofenac and CO_2, which significantly reduced the temperature and, accordingly, the intensity of the inflammatory process.

Group VII (chondroitin + CO_2) — decreased to (38.3 ± 0.2) °C, which was 0.9 °C (or 2.30 %, $p < 0.001$) less than group II. This indicated the effectiveness of the combination of chondroitin with CO_2 in reducing inflammatory hyperthermia, although the effect was not as strong as the combination of diclofenac with CO_2. The results obtained show that carboxytherapy exhibits an independent hypothermic effect, but the most noticeable result is achieved when it is combined with other anti-inflammatory agents. In groups VI and VII, a pronounced systemic anti-inflammatory effect of CO_2 was recorded, which may be associated with its effect on the general condition of the body and a decrease in the inflammatory response. The most significant temperature changes were observed in the combination of CO_2 with diclofenac (group VI), which confirms the synergistic effect of these substances. CO_2 exposure also significantly improved the anti-inflammatory efficacy of chondroitin, which is also an important addition to traditional therapy of inflammatory reactions, in particular joints.

Thus, the use of carboxytherapy in the carrageenan inflammation model in rats demonstrated a significant anti-inflammatory effect, which was manifested in a decrease in the size of the edema throughout the observation period and a decrease in body temperature.

Discussion

The results of the study showed that the use of CO_2 alone and in combination with diclofenac and chondroitin leads to the suppression of carrageenan inflammation (swelling of the limb and hyperthermic reaction). Edema can be described as a two-phase reaction: the early phase lasts for an hour and includes the production of histamine and bradykinin, while the late phase is accompanied by neutrophil infiltration [4]. CO_2 as monotherapy inhibited both phases of edema, although more the first. At the same time, the time course changed when CO_2 was added to

Table

Effect of CO_2 on limb volume and rectal temperature in rats in a carrageenan model of inflammation (Mean ± SD, n = 8)

Animal group	Before disorder n = 8	After 1 hour n = 8	After 2 hours n = 8	After 3 hours n = 8	After 5 hours n = 8	Rectal temperature, °C, n = 8
Intact control	0.427 ± 0.029	0.427 ± 0.029	0.427 ± 0.029	0.427 ± 0.029	0.427 ± 0.029	37.3 ± 0.2
II (control disorder)	0.410 ± 0.028	0.529 ± 0.022	0.609 ± 0.022	0.740 ± 0.025	0.695 ± 0.037	39.2 ± 0.2
III	0.404 ± 0.019	0.455 ± 0.019***	0.496 ± 0.016***	0.644 ± 0.030***	0.617 ± 0.026***	38.0 ± 0.2***
IV	0.395 ± 0.019	0.459 ± 0.029***	0.506 ± 0.012***	0.676 ± 0.025***	0.624 ± 0.030***	38.9 ± 0.4***
V	0.406 ± 0.019	0.463 ± 0.027***	0.514 ± 0.023***	0.659 ± 0.031***	0.613 ± 0.026***	38.6 ± 0.3***
VI	0.395 ± 0.019	0.441 ± 0.017***	0.495 ± 0.012***	0.586 ± 0.026***	0.559 ± 0.030**	37.7 ± 0.3***
VII	0.401 ± 0.014	0.429 ± 0.020***	0.491 ± 0.017***	0.579 ± 0.020***	0.571 ± 0.016***	38.3 ± 0.2***
Statistical significance of the intergroup difference	F = 1.34 p = 0.282	F = 16.40 p < 0.001	F = 35.20 p < 0.001	F = 92.10 p < 0.001	F = 50.10 p < 0.001	F = 80.10 p < 0.001
Normality Test (Shapiro-Wilk)	W = 0.984 p = 0.657	W = 0.984 p = 0.682	W = 0.988 p = 0.841	W = 0.983 p = 0.602	W = 0.988 p = 0.830	W = 0.992 p = 0.966

Notes: Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test.
***p < 0.001, **p < 0.01, *p < 0.05.
Compared to the control disorder group (carrageenan).

diclofenac or chondroitin, which contributed to the prolongation of the action of these combinations. This effect is probably due to the reduction in the release of inflammatory mediators under the influence of CO_2. The anti-inflammatory effect of CO_2 has also been established, which may be associated with improved microcirculation and a decrease in the level of oxygen stress in the tissues, which led to a decrease in the inflammatory response [4]. In addition, carboxytherapy can influence immune responses by modulating the activity of pro-inflammatory cytokines and mediators of inflammation [8–11], thereby limiting its manifestations. Apparently, CO_2 can reduce the activity of neutrophils and macrophages, which play a key role in the development of inflammation [12].

The introduction of CO_2 as an anti-inflammatory agent led to a noticeable decrease in temperature in rats. The results obtained are consistent with the data of other authors who showed the ability of CO_2 to reduce inflammation [13]. A possible mechanism of the anti-inflammatory effect of CO_2 may be the creation of a hypoxic environment that suppresses the production of pro-inflammatory cytokines and reduces the inflammatory response [11, 13]. This mechanism underlies the ability of CO_2 to block macrophage activation and prostaglandin synthesis, which further enhances its effectiveness in the anti-inflammatory process [4]. Literature sources confirm that carboxytherapy is a promising method of treating inflammatory diseases [4, 14–16]. Our previous studies also showed that CO_2, both alone and in combination with diclofenac or chondroitin, significantly reduced inflammation in rats [17]. Thus, carboxytherapy is an effective tool in combating acute inflammation and may be useful as a stand-alone agent or in combination with other therapeutic agents to enhance anti-inflammatory effects.

Further studies may be aimed at studying the possible mechanisms of the positive effect of CO_2, as well as optimizing dosages to achieve maximum therapeutic effect; studying alternative routes of administration and different regimens of administration, which will improve and justify the clinical use of this agent.

Conclusions

The administration of carrageenan caused the development of a classic inflammatory reaction, which was accompanied by an increase in the volume of limb edema in rats and an increase in body temperature.

The use of a combination of carboxytherapy with diclofenac or chondroitin effectively corrected the inflammatory phenomena.

CO_2 monotherapy showed a local anti-inflammatory effect against the background of carrageenan.

Conflict of interest. The author declare the absence of a conflict of interest.

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EXPERIMENTAL EVALUATION OF THE EFFECTIVENESS OF CO_2 APPLICATION IN A CARRAGEENAN MODEL OF INFLAMMATION: NEW PERSPECTIVES IN THE TREATMENT OF OSTEOARTHRITIS

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