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Study of the potential analgesic properties of carbon dioxide for the treatment of pain syndrome in case of osteoarthritis

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Pain syndrome is a serious global problem that causes and complicates a number of diseases, the main symptom of which is joint pain. One of them is osteoarthritis (OA). Traditional methods of treating OA often have limited efficacy and can cause side effects, so it is important to study new approaches, such as carboxytherapy (use of carbon dioxide). Objective. To investigate the analgesic effect of carbon dioxide (CO_2) and its combined use with other agents. Methods. The efficacy of carbon dioxide injections used alone and in combination with other drugs was studied in a formalin model of inflammation in rats. Results. The latent periods of phases I and II increased significantly in the experimental groups, especially in groups V, VI and VII ($p < 0.001$), indicating a delay in pain reactions. The duration of pain phase I was significantly shorter in the groups receiving CO_2 compared to the control group ($p < 0.001$). The shortest duration was observed in group V, where it decreased by 1.77 minutes. The duration of pain phase II was also significantly shorter in groups V, VI, and VII treated with CO_2 compared to group II ($p < 0.001$). The difference ranged from 7.49 to 12.54 minutes. The number of pain reactions after phase I decreased by 13.25–16.1 points in the groups receiving CO_2 compared to the control group. The data obtained indicate that CO_2 significantly increases the duration of latent periods of pain (by 55–65 %), reduces the duration of its phases (by 40–50 %) and reduces the intensity of pain reactions (by 40–50 %) in rats compared to control pathology. The most pronounced effect was observed with the combined use of CO_2 with sodium diclofenac or chondroitin sulfate. Conclusions. The results of the study expand the understanding of the analgesic effect of CO_2 on the formalin model of inflammation. The use of CO_2 significantly reduced the duration of both phases of the pain reaction and reduced the number of painful manifestations, which confirms the prospects of its use as an additional, and in some cases the main means of reducing pain and inflammation.

Больовий синдром — серйозна глобальна проблема, яка спричинює й ускладнює низку захворювань, основним симптомом яких є біль у суглобах. Одним із них є остеоартрит (ОА). Традиційні методи лікування ОА часто мають обмежену ефективність і можуть викликати побічні ефекти, тому актуальним є дослідження нових підходів, таких як карбокситерапія (використання вуглекислого газу). Мета. Дослідити можливу аналгезуючу дію вуглекислого газу (CO_2) та його комбіноване застосування з іншими засобами для лікування больового синдрому в разі остеоартриту. Методи. Ефективність ін'єкцій вуглекислого газу, застосованого окремо та в поєднанні з іншими препаратами, вивчали на формаліновій моделі запалення у щурів. Результати. Виявлено, що латентні періоди фаз I та II значно збільшились в експериментальних групах, особливо в групах V, VI та VII ($p < 0,001$), що вказує на відтермінування больових реакцій. Тривалість больової фази I була значно меншою у групах, які отримували CO_2, порівняно з групою контрольної патології ($p < 0,001$). Найменший час спостерігався у групі V, де він скоротилася на 1,77 хв. Тривалість больової фази II також була значно меншою у групах V, VI та VII, які отримували CO_2, порівняно з групою II ($p < 0,001$). Різниця становила від 7,49 до 12,54 хв. Кількість больових реакцій після фази I зменшилася на 13,25–16,1 балів у групах, які отримували CO_2, порівняно з групою контрольної патології. Отримані дані свідчать про те, що CO_2 значно збільшує латентні періоди болю (на 55–65 %), скорочує тривалість його фаз (на 40–50 %) та знижує інтенсивність больових реакцій (на 40–50 %) у щурів порівняно з контрольною патологією. Найбільш виразний ефект спостерігався за комбінованого застосування CO_2 з диклофенаком натрію або хондроїтином сульфатом. Висновки. Результати дослідження на формаліновій моделі запалення розширюють уявлення про можливості аналгезуючої дії CO_2. Застосування CO_2 значно скорочувало тривалість обох фаз больової реакції та зменшувало кількість больових проявів, що підтверджує перспективність його застосування як додаткового, а в окремих випадках — основного засобу для зменшення болю та особливо запалення. Ключові слова. Вуглекислий газ, карбокситерапія, оцінювання болю, запалення, біль, остеоартроз, хондроїтин, диклофенак

Keywords. Carbon dioxide, carboxytherapy, pain assessment, inflammation, pain, osteoarthritis, chondroitin, diclofenac

Introduction

Pain syndrome is a serious global problem that causes and complicates a number of diseases, the main symptom of which is joint pain. One of them is osteoarthritis (OA), a degenerative joint disease that affects bones, cartilage, and the synovial membrane, and is one of the main causes of chronic pain [1, 2]. Modern treatment of OA includes surgical and non-surgical methods, but it is difficult to stop joint destruction [3]. Traditional therapy is aimed at alleviating the symptom of pain with the help of nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids, which have significant side effects [3–6]. Therefore, the search for new approaches that reduce pain and inhibit the progression of the disease remains relevant.

There is a growing interest in alternative therapies with a safe effect, especially in carboxytherapy — the subcutaneous injection of carbon dioxide (CO_2) [7]. This technique, applied systemically and locally, has a long history in medicine [8–10]. Carboxytherapy provides immediate effects, such as dilation of blood vessels and improvement of tissue oxygenation, as well as delayed effects, such as increased blood flow and stimulation of growth factors, in particular VEGF, which promotes the formation of new blood vessels [11, 12]. Therefore, carboxytherapy may be promising in the treatment of pain symptoms, but further research is needed to determine its analgesic effect and its combination with traditional drugs.

Purpose: to investigate the possible analgesic effect of carbon dioxide (CO_2) and its combined use with other means for the treatment of pain syndrome in the case of osteoarthritis.

Material and methods

The study was conducted on the basis of the vivarium of Poltava State Medical University, in compliance with the main provisions of the Council of Europe Convention on the Protection of Vertebrate Animals Used in Experiments and Other Scientific Purposes of 18 March 1986, Directive 2010/63/EU of the European Parliament and the Council of the EU of 22 September of 2010 on the protection of animals used for scientific purposes. The research materials were reviewed and approved by the commission on ethical issues and biomedical ethics of Poltava State Medical University (Protocol No. 225 dated 21.03.2024).

White rats of both sexes (n = 56), Me (305 ± 9.74) were taken for the study of pain assessment under theinfluence of CO_2. Rats were housed at (21 ± 2) °C, on a 12-h day/night cycle, receiving water from automatic waterers and Special One rat chow.

The animals were divided into seven groups (n = 8):

1. Intact (Group I);
2. Control disorder (formalin, F) (Group II);
3. Control disorder + sodium diclofenac (SD), 8 mg/kg (F + SD) (Group III);
4. Control disorder + chondroitin sulfate (C), 3 mg/kg (F + C) (Group IV);
5. Control disorder + sodium diclofenac, 4 mg/kg + CO_2, 0.5 ml (F + SD + CO_2) (Group V);
6. Control disorder + chondroitin sulfate, 3 mg/kg + CO_2, 0.5 ml (F + C + CO_2) (Group VI);
7. Control disorder + CO_2, 0.5 ml (F + CO_2) (Group VII).

Subcutaneous injection of CO_2 was performed using the INDAP Insuf device (Czech Republic, registration number 2012104) using a needle (BD Mikrolance 3.30 G ½) 0.3×13 mm. Diclofenac in doses of 8 and 4 mg/kg and 3 mg/kg chondroitin were administered intraperitoneally one hour before the reproduction of the formalin test.

Chemical nociception was induced by injecting 0.1 ml of 2.5 % formalin solution under the plantar aponeurosis of the right hind paw of rats. This procedure induced a biphasic pain response: an initial acute lasting 15 min, characterized by intense shivering, licking, or biting of the affected paw and reflected acute pain. It was followed by a late phase that began between 30 and 60 min, reflecting tonic pain. The acute phase indicated activation of peripheral pain pathways, while the late phase indicated sensitization of central pathways.

Pain behavior was evaluated using the following scale (in points): no reaction — 0; paw on the ground without resistance — 1; raised paw — 2; licking, biting or twitching with a paw — 3.

This study made it possible to evaluate the effectiveness of CO_2 as an analgesic agent in the case of its use both alone and in combination with sodium diclofenac and chondroitin sulfate, which helped to better understand the mechanisms of action of these agents at different stages of pain development.

Pain scores were calculated according to the formula:

$$\text{Pain assessment} = (0T0 + 1T1 + 2T2 + 3T3) / \text{time interval (min)},$$

where T0–T3 — is the number of minutes spent in each of the behavioral categories.

The results were processed by Jamovi version 2.3.21 software. Data are presented as means ± standard deviation. The Shapiro-Wilk test was used for normality, and the Levene test for homogeneity. Welch's test was used for significant differences, and Tukey's test was used to identify differences between groups. For non-normal data, the Kruskal-Wallis test with Bonferroni correction was used. The results were considered statistically significant at $p < 0.05$.

Results

The table shows the indicators of the analgesic effect of CO_2, they are presented in the form of the average value ± standard deviation for each group (n = 8). The difference between the average values of the studied groups and the control group was considered statistically significant at $p < 0.05$. Statistical processing was performed using univariate analysis of variance followed by Tukey's a posteriori test.

Latent period of phase I

Comparison of the time of the latent period of phase I of the pain reaction in groups of rats under the influence of CO_2 on the formalin model of inflammation showed significant differences (Kruskal-Wallis $\chi^2 = 50.7$; $p < 0.001$). The distribution is different from normal (Shapiro-Wilk test: W = 0.913; p = 0.002), so the non-parametric Kruskal-Wallis test and the Dwass-Steel-Critchlow-Fligner method were used for pairwise comparison.

The results of the comparison of the mean values of the groups determined significant differences between Group II and experimental groups. Comparison of Groups II and V, II and VI, II and VII showed that exposure to CO_2 and its combined use significantly increased the latent period of phase I of the pain reaction (Table).

The comparison between Groups III and V indicated that CO_2 was able to enhance the effect of diclofenac and exert an antinociceptive effect by increasing the latent period of phase I. The comparison between Groups IV and VI showed a significant increase in the analgesic effect of chondroitin when combined with CO_2, confirming the antinociceptive effect of CO_2.

According to the ability to prolong the duration of the latent period of phase I of the pain reaction caused by the introduction of formalin, the groups can be divided as follows: V > VII > VI > III > IV.

The difference in the time of the latent period of the phase I pain reaction under the influence of CO_2 on the formalin model of inflammation between the control Group II and the experimental groups turned out to be statistically significant. In particular, between Group II and V there was a significant decrease in the latent period with an average value of 4.76 min (p = 0.014). A similar trend was found when comparing Group II with VI (4.76 min, p = 0.014) and VII (4.76 min, p = 0.014). Additionally, the difference between Groups III and V was 4.75 min (p = 0.014). When comparing Groups IV and VI, the difference was 4.68 min (p = 0.016), and for Groups V and VI it was 4.75 min (p = 0.014). A similar difference of 4.75 min (p = 0.014) was observed between Groups V and VII.

The obtained data indicated that CO_2 significantly affected the duration of the latent period of phase I of the pain reaction, confirming its ability to enhance the analgesic effect.

Table

Analgesic effect of CO2 in the formalin model of pain reaction in rats (M ± SD, n = 8)

Response to a stressor	II	III	IV	V	VI	VII	Probable intergroup differences
Latent period of phase I, min	1.28 ± 0.05	1.40 ± 0.06	1.33 ± 0.07	2.81 ± 0.40**	2.20 ± 0.34**	2.25 ± 0.11**	$\chi^2 = 50.7$ p < 0.001
Latent period of phase II, min	16.66 ± 1.47	25.61 ± 1.67	19.41 ± 1.05	28.50 ± 1.08***	23.11 ± 2.28***	23.13 ± 2.36***	F = 82.7 p < 0.001
Duration of pain phase I, min	7.28 ± 0.79	6.92 ± 0.61	6.86 ± 0.51	5.51 ± 0.82**	5.61 ± 0.48	5.51 ± 0.41	F = 13.8 p < 0.001
Duration of pain phase II, min	23.30 ± 2.60	12.38 ± 2.00	23.22 ± 1.97	10.76 ± 1.35***	15.81 ± 2.41***	15.66 ± 1.99***	F = 55.1 p < 0.001
Reaction to pain after phase I, points	43.75 ± 4.03	42.00 ± 3.66	40.00 ± 2.56	27.63 ± 2.67***	28.75 ± 3.20***	30.50 ± 3.07***	F = 36.1 p < 0.001

Notes: *** — p < 0.001; ** — p < 0.01; * — p < 0.05. In comparison with the group of control disorder (formalin).

This indicates a peculiar principle of the analgesic effect of CO_2, which may differ from the mechanisms of action of diclofenac and chondroitin.

Latent period of phase II

The intergroup difference in the duration of the latent period of the phase II pain reaction under the influence of CO_2 on the formalin model of inflammation remained statistically significant ($F = 82.7$; $p < 0.001$).

The Shapiro-Wilk test ($W = 0.962$; $p = 0.118$) confirmed the normal distribution of the data. The latent period of phase II of the pain reaction increased significantly in Groups V, VI, and VII compared to Group II (Table). Addition of CO_2 to the combination to correct the pain syndrome caused by the injection of formalin led to the following distribution of the duration of the latent period of phase II of the pain reaction between groups of experimental animals: V > III > VII > VI > IV.

The difference in time of the latent period of phase II of the pain reaction between the groups was as follows: II and V — 11.84 min ($p < 0.001$); II and VI — 6.45 min ($p < 0.001$); II and VII — 6.47 min ($p < 0.001$), which indicated sufficient effectiveness of the proposed therapy. Comparison of Groups III and V showed a difference of 2.89 min ($p = 0.021$), indicating the possibility of increasing the analgesic effect of diclofenac by combining it with CO_2. In addition, the difference between Groups V and VII was 5.37 min ($p < 0.001$), clearly indicating a direct analgesic effect of CO_2, as there was an increase in the latency period of the phase II pain response and a preference under the conditions of CO_2 use.

Duration of pain phase I

The results of the study showed that the effect of CO_2 on the duration of pain phase I on the formalin model was statistically significant ($F = 13.8$; $p < 0.001$). The normality test also confirmed the statistical significance of the results ($W = 0.980$; $p = 0.576$).

The experiment proved a significant effect of CO_2 on the time of the painful phase I of inflammation, reducing it compared to the group of control disorder. The shortest duration of pain phase I was found in Group V, which was significantly different from Group II (Table). Reduction of pain phase I under the influence of CO_2 can be given in the following order: V < VII < VI < IV < III. The obtained data demonstrate that CO_2 has a pronounced effect on reducing the duration of pain phase I, enhancing the analgesic effect of diclofenac.

The intergroup differences in the reduction of the duration of pain phase I on the formalin model under the influence of CO_2 are as follows in comparison with Group II: Group V by 1.77 min, ($p < 0.001$); in VI it was 1.67 min ($p < 0.001$); in VII by 1.76 min ($p < 0.001$). Between Groups III and V, the difference in the time of pain phase I reached 1.41 min ($p < 0.001$). These indicators indicated a significant effect of CO_2 on reducing the duration of pain phase I, confirming its potential in enhancing the analgesic effect of diclofenac and chondroitin.

Duration of pain phase II

The next stage of this study was to determine the time of the painful phase II of inflammation under the influence of CO_2.

During the experiment on the duration of pain phase II, it was found that the average values ± SD in Groups V, VI, VII were significantly smaller compared to Group II. The analysis showed statistical significance of $F = 55.1$; $p < 0.001$ (Table). The reduction in the time of phase II inflammation under the influence of CO_2 was as follows: V < III < VII < VI < IV.

The normality of these groups was confirmed by the Shapiro-Wilk test ($W = 0.965$; $p = 0.159$). Further post-hoc analysis according to Tukey's test revealed differences between groups in the duration of phase II under the influence of CO_2: between II and V 12.54 min, $p < 0.001$; II and VI 7.49 min, $p < 0.001$; II and VII 7.64 min, $p < 0.001$. The probable difference between Groups IV and VI of 7.41 min, $p < 0.001$ indicated that combining CO_2 with chondroitin enhanced the analgesic effect of the latter during the second phase of the pain reaction. This shows that exposure to CO_2 significantly reduced phase II, which clearly proves its analgesic properties.

Reaction to pain after the I phase, points

The number of pain reactions after phase I on the formalin model of disorder was also determined. When comparing the mean value ± SD between groups, the number of pain responses after phase I (points) in Groups V, VI, VII was less than in Group II. The analysis showed significant differences between groups ($F = 36.1$; $p < 0.001$) (Table). The reduction in the number of pain reactions under the influence of CO_2 was as follows: V < VI < VII < IV < III.

The reliability of indicators in groups was checked using the Shapiro-Wilk test ($W = 0.979$; $p = 0.541$). Further post-hoc analysis according to the Tukey test revealed differences between groups in the number of pain reactions after phase I under the influence of CO_2: between II and V — 16.1 points ($p < 0.001$), between II and VI — 15.0 points ($p < 0.001$), between II and VII — 13.25 points ($p < 0.001$). In addition, there was a difference in the number of pain reactions after phase I between Groups III and V, which was 14.4 points ($p < 0.001$). This may indicate that CO_2 enhances the analgesic effect of diclofenac when they are used together, which shows a significant reduction

in pain under conditions of CO_2 addition. The difference between IV and VI was 11.25 points ($p < 0.001$), indicating an improvement in the analgesic effect of chondroitin with the addition of CO_2.

The use of CO_2 significantly reduced the number of pain reactions after phase I in groups V, VI and VII. These results suggest that CO_2 may reduce the production of inflammatory mediators and thus affect nociception by reducing thermal nerve stimulation.

The study showed that the combined use of carbon dioxide (CO_2) with diclofenac and chondroitin significantly improved their analgesic properties, which is confirmed by differences in scores between the groups that received combined therapy.

Discussion

Taking into account the obtained data, it is possible to assert the highly probable effect of CO_2 on the nociceptive system. This is evidenced by an increase in the latent period of both pain phase I and phase II, a decrease in the duration of these phases, and a decrease in the number of pain reactions on the formalin model of nociception.

Pain nerve endings are key molecular transducers of stimuli that express a variety of ion channels, such as members of the transient receptor potential (TRP) family of ion channels, including TRP vanilloid 1 (TRPV1), TRP melastatin 3 (Transient Receptor Potential (M — melastatin)) (TRPM3), TRP ankyrin 1 (TRPA1) and members of potential-dependent sodium channels, including Nav1.8 and Nav1.7 [13, 14]. When stimuli such as chemical or thermal sensations are detected, the terminals are activated with the release of neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P antibodies [15].

It was shown that the algogenic effect of formalin is due to the activation of TRPA1 channels on the surface of nociceptors, which normally respond to cold and stimulate the development of inflammation, which is accompanied by thermal and mechanical hyperalgesia. The latter, caused by formalin, leads to both local and systemic changes, resulting in the release of inflammatory mediators, in particular prostaglandins [16]. Substance P and bradykinin are involved in the first phase, while histamine, serotonin, prostaglandins and bradykinin are involved in the second.

Previous reports have suggested that CO_2 administration with inhibition of peptide release is associated with the calcitonin gene (CGRP), the increase of which is provoked by formalin administration [17]. Apparently, CO_2 prevents the increase in CGRP secretion that occurs with chemical depolarization, capsaicin or NO. The inhibitory effect of CO_2 on CGRP secretion involves a decrease in intracellular pH and inhibition of calcium channels, as CO_2 has been shown to block the typical physiological increase in intracellular calcium [18].

Transcutaneous use of gaseous CO_2 has been considered for analgesia in several cases [19–21]. The substantiation of its analgesic properties was that after application it increased the oxygenation of tissues as a result of the vasodilator effect. Along with this, it is believed that the increased content of CO_2 in the tissues encourages hemoglobin to release oxygen with the help of the Bohr effect and thus increases oxygenation [22].

Conclusions

The results of the research allow us to draw the following conclusions: the use of carbon dioxide (CO_2) in the model of formalin inflammation in rats leads to a significant reduction in the duration of pain phase I. The most pronounced reduction of this phase was observed in the case of combining CO_2 with diclofenac (Group V) and under the conditions of its use with chondroitin sulfate (Group VII). This indicates potentiation of the analgesic activity of CO_2 when combined with other anti-inflammatory/analgesic agents for the treatment of OA.

CO_2 has been shown to significantly reduce the duration of pain phase II on the formalin model. The most pronounced reduction in the duration of this phase was observed in the case of the use of CO_2 both in monotherapy and in combination with diclofenac (Group V) and chondroitin sulfate (Group VII). The obtained results indicate a pronounced analgesic effect of CO_2 on the late inflammatory phase of the pain reaction.

It has been proven that CO_2 significantly reduces the number of pain reactions after phase I on the formalin model in rats. The greatest decrease in pain reactions was observed in groups receiving CO_2 in combination with diclofenac (Group V) and chondroitin sulfate (Group VII).

Therefore, the findings of this experiment emphasize the possibility of using carbon dioxide to reduce pain and can obviously become the basis for future scientific research, in particular clinical research. These results may contribute to the development of personalized combination therapeutic strategies to reduce joint pain and inflammation. Especially if there are contraindications to the use of basic therapy. Further studies are needed to establish the mechanisms underlying the observed relationships and to evaluate the potential of carbon dioxide as an additional element in the therapeutic strategy of patients with OA.

Conflict of interest. The authors declare no conflict ofinterest.

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STUDY OF THE POTENTIAL ANALGESIC PROPERTIES OF CARBON DIOXIDE FOR THE TREATMENT OF PAIN SYNDROME IN CASE OF OSTEOARTHRITIS

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