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EFFECTS OF CARBON DIOXIDE, DICLOFENAC, AND THEIR COMBINATION ON THE COURSE OF MONOIODOACETIC ACID-INDUCED OSTEOARTHRITIS IN RATS

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Osteoarthritis is the most prevalent degenerative-inflammatory joint disease. Despite the widespread use of non-steroidal anti-inflammatory drugs and physiotherapeutic approaches, the majority of patients fail to achieve sustained clinical improvement, underscoring the need for novel therapeutic strategies. In this study, osteoarthritis was induced in 60 adult male outbred white rats by a single intra-articular injection of 0.05 ml of a 3 % monoiodoacetic acid solution into the right knee joint. Animals in the control group received physiological saline, whereas experimental groups were treated with: sodium diclofenac administered intraperitoneally 1 hour prior to induction and subsequently every 3 days; carbon dioxide administered subcutaneously in the periarticular region at a dose of 0.5 ml with the same frequency; or their combination. Histological examination of the joints was performed on days 14 and 28. Administration of CO₂ and diclofenac on day 14 of therapy reduced the severity of inflammatory-destructive changes in the articular cartilage and subchondral bone. The most pronounced anti-inflammatory and chondroprotective effect was observed in the group receiving combined CO₂ and diclofenac therapy. By day 28, necrotic-degenerative changes were attenuated, accompanied by partial restoration of the morphological structure of the articular cartilage and subchondral bone. Thus, combined administration of CO₂ and diclofenac demonstrated superior efficacy compared with monotherapy with either agent alone.

Key words: carbon dioxide, diclofenac, osteoarthritis, morphological changes, histological alterations, knee joint, rats.

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ВПЛИВ ВУГЛЕКИСЛОГО ГАЗУ, ДИКЛОФЕНАКУ ТА ЇХ КОМБІНАЦІЇ НА ПЕРЕБІГ МОНОІОДАЦЕТАТ-ІНДУКОВАНОГО ОСТЕОАРТРИТУ У ЩУРІВ

Остеоартрит є найпоширеним дегенеративно-запальним захворюванням суглобів. Попри використання нестероїдних протизапальних, інших засобів і фізіотерапевтичних методів, більшість пацієнтів не досягає стійкого клінічного поліпшення, що потребує пошуку нових стратегій лікування. На 60 статевозрілих білих безпородних щурах-самцях моделювали остеоартрит введенням 0,05 мл 3 % розчину моноіодоцтової кислоти у правий колінний суглоб. Дослідним групам вводили фізіологічний розчин, диклофенак внутрішньочеревно за 1 годину до моноіодоцтової кислоти і через кожні 3 дні, СО₂ – підшкірно над ураженим суглобом у дозі 0,5 мл з та їх комбінацію. На 14-й або 28-й день проводили гістологічні дослідження. Введення СО₂, диклофенаку 14-у добу терапії зменшувало виразність запально-деструктивних процесів у хрящі та субхондральній кістці, однак більш значний протизапальний та хондропротекторний ефект відзначався у групі комбінованого застосування диклофенаку та СО₂. На 28-у добу – схеми лікування коректували некротично-дегенеративних змін, з відновленням морфологічної структури суглобового хряща та субхондральної кістки. Комбіноване використання СО₂ з диклофенаком мало більш виражений захисний ефект порівняно з монотерапією цими засобами.

Ключові слова: вуглекислий газ, диклофенак, остеоартрит, морфологічні зміни, гістологічні зміни, колінний суглоб, щури.

The work is a fragment of the research projects "Pharmacological properties of biologically active substances, medicinal products, and their combinations for the development of new therapeutic indications", state registration No. 0125U002468; "Monitoring of traumatic disease under chronic stress conditions", state registration No. 0124U002167.

Osteoarthritis (OA) is a prevalent degenerative joint disease and one of the leading causes of disability worldwide [6]. It is estimated that more than 500 million people suffer from OA, creating a considerable socio-economic burden on healthcare systems [1]. Despite the identification of major risk factors (obesity, trauma, sex, age), the pathogenesis of OA remains complex and multifactorial [15]. A key mechanism involves the progressive damage to articular cartilage, accompanied by the release of pro-inflammatory cytokines that stimulate matrix degradation and suppress the synthesis of type II collagen and proteoglycans, ultimately leading to the loss of cartilage structural integrity [9]. Therefore, the protection and restoration of cartilage tissue represent a strategic direction in OA management [8, 13].

Standard pharmacotherapy includes non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and intra-articular injections of hyaluronate or corticosteroids; however, these approaches are largely aimed at symptom control [7]. This highlights the need for novel adjuvant strategies capable of targeting the pathogenetic mechanisms underlying disease progression. The contemporary concept views OA as a pathology of the entire osteochondral unit-comprising cartilage, subchondral bone, synovium, and periarticular tissues-characterized by microenvironmental disruption, chronic inflammation, and degenerative changes [2]. Therefore, the use of physiologically active agents, in particular carboxytherapy (CO₂), appears to be a promising approach.

Nevertheless, data on the combined use of CO₂ with conventional pharmacological agents remain limited. It has been demonstrated that the combination of CO₂ with diclofenac may exert beneficial effects, reduce the dosage burden of NSAIDs, and lower the risk of their adverse effects [11]. Therefore, investigating the effects of CO₂ as monotherapy and in combination with diclofenac is highly relevant for the development of novel multifactorial approaches to OA treatment.

The purpose of the study was to evaluate the efficacy of CO₂ in combination with diclofenac based on histological assessment of the articular cartilage, synovial membrane, and subchondral bone in an experimental model of knee osteoarthritis in rats.

Materials and methods. The study was conducted on 60 adult male albino outbred rats weighing 180–220 g. Animals were housed in the vivarium under standard laboratory conditions. Prior to the experiment, all animals underwent a seven-day acclimatization period to handling. All procedures were carried out in compliance with Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes. Euthanasia was performed in accordance with the AVMA Guidelines for the Euthanasia of Animals (2020).

Osteoarthritis was induced according to modified protocols [10]. Under ether anesthesia, a single intra-articular injection of 0.05 ml of a 3 % solution of monoiodoacetic acid (MIA; Sigma-Aldrich, Germany), prepared *ex tempore* in 0.9 % NaCl, was administered into the right knee joint of rats. The control group received an equivalent volume of physiological saline. The following groups were studied: Group I – Intact control; Group II – Intact animals + physiological saline (intraperitoneally); Group III – Pathological control (MIA-induced osteoarthritis); Group IV – MIA + diclofenac sodium (8 mg/kg, intraperitoneally); Group V – MIA + CO₂ (0.5 ml, subcutaneously); Group VI – MIA + diclofenac sodium (4 mg/kg, intraperitoneally) + CO₂ (0.5 ml, subcutaneously).

Diclofenac was administered intraperitoneally 1 hour before the injection of MIA and subsequently every 3 days, whereas CO₂ was applied subcutaneously above the affected joint at a dose of 0.5 ml with the same periodicity. On day 14 or 28 of the experiment, euthanasia of the rats was performed under thiopental anesthesia (50 mg/kg, intraperitoneally) by cardiac blood collection until cardiac arrest. The right knee joints of the rats were excised and fixed in 10 % neutral formalin. Decalcification was carried out in 5 % HNO₃ solution, after which the material underwent dehydration through a graded series of isopropanol and was embedded in paraffin. Serial sections of 3–5 μm thickness were prepared using a rotary microtome and stained by various methods: hematoxylin Gill II and eosin (H&E), Masson's trichrome, and Van Gieson's picrofuchsin.

Morphological analysis included the evaluation of the articular cartilage, the structure of the synovial membrane, vascular architecture, and the remodeling of the subchondral bone. The histological processing methods employed corresponded to classical protocols [3].

Results of the study and their discussion. It was established that in rats (intact and those administered physiological saline) the morphological organization of the main joint structures remained preserved at both observation time points (day 14 and day 28). The articular cartilage demonstrated a clear zonal differentiation: the superficial zone consisted of flattened chondrocytes without a distinct orientation, the intermediate zone displayed columnar arrays of rounded chondrocytes with large nuclei, while the deep zone was predominantly represented by extracellular matrix with a small number of scattered cells. The subchondral bone exhibited a typical trabecular structure, with the intertrabecular space filled by normal hematopoietic bone marrow. The synovial membrane retained its characteristic organization, showing a clear demarcation between the outer fibrous layer and the inner synoviocyte layer, which formed villous projections into the joint cavity. Periarticular soft tissues were represented by striated muscle fibers, areas of fibrous connective tissue, and adipose tissue (Fig. 1A, 1B).

In animals with experimentally induced osteoarthritis, pronounced dystrophic and destructive changes were observed in the knee joint on day 14. In the periarticular soft tissues, there was paralytic dilation of blood vessels accompanied by stasis, sludge formation, and mural thrombosis. The vascular walls were thickened and edematous, with focal necrotic alterations, loss of clear stratification, and leukocytic infiltration; the endothelium exhibited signs of dystrophy and necrosis. Numerous hemorrhages and leukocytic infiltrates were detected in perivascular regions. The lymphatic vessels were dilated, filled with lymph, and showed evidence of extravasation. In the muscle fibers, foci of dystrophy, necrosis, and fragmentation were identified; both perimysium and interstitium appeared edematous with focal necroses and infiltration by polymorphonuclear leukocytes.

The joint capsule was thickened, exhibiting mucoid and fibrinoid edema, focal necrosis, and leukocytic infiltration. In the inner layer, irreversible dystrophic and necrotic changes of synoviocytes were observed, with areas of denudation and fragmentation of the basement membrane. The synovial villi were enlarged, showing pronounced microcirculatory disturbances, edema, and leukocytic infiltration. The

articular cartilage lost its stratification, with indistinct boundaries between the zones; destructive and inflammatory changes predominated, including fibrillation and homogenization of the matrix, areas of mucoid and fibrinoid edema, and widespread fibrinoid necrosis (Fig. 1C, 1D).

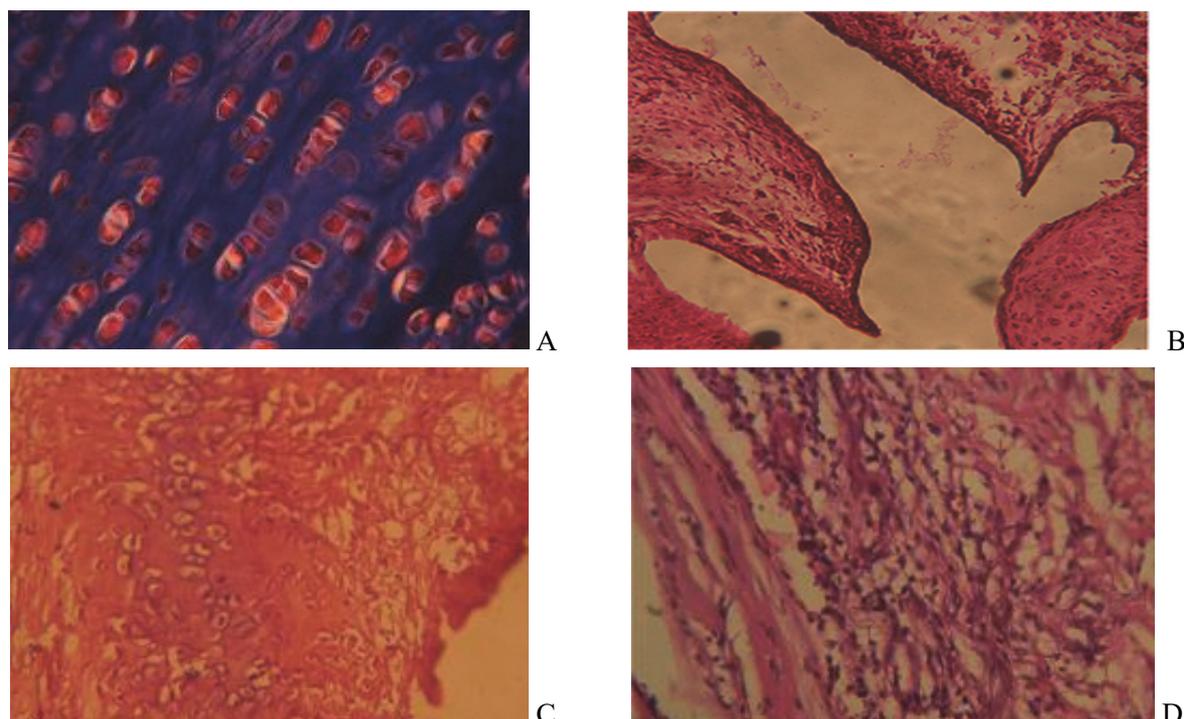


Fig. 1. Morphological structure of the rat knee joint under normal conditions and in osteoarthritis. Morphological structure of the rat knee joint in control groups. A – Columnar arrangement of chondrocytes in the intermediate zone of the articular cartilage. Staining: Masson's trichrome. Magnification $\times 400$. B – Synovial membrane with villous projections. Staining: hematoxylin Gill II and eosin. Magnification $\times 100$. C – necrotic changes in the superficial layer of the cartilage in osteoarthritis (day 14) (Hematoxylin Gill II and eosin, $\times 100$). D – degradation of collagen fibers in the matrix in osteoarthritis (day 14) (Hematoxylin Gill II and eosin, $\times 200$).

Chondrocytes were distributed chaotically against the background of their overall reduction; vacuolar degeneration, karyopyknosis, and karyorrhexis were observed, along with empty lacunae devoid of cells.

In the subchondral plate, microcracks were observed with penetration of synovial fluid and the formation of cavities filled with eosinophilic proteinaceous masses. The bony trabeculae were thickened and heterogeneously stained, with areas of demineralized osteoid. The bone marrow exhibited signs of microcirculatory disturbances, while the lymphatic vessels showed dilation with extravasation.

On day 28 of observation, in the joints of animals with MIA-induced osteoarthritis, proliferative processes predominated over dystrophic-destructive changes. In the periarticular soft tissues, moderate edema was noted (less pronounced than on day 14), along with vessels exhibiting thickened, sclerotic walls and signs of sludge and thrombosis, as well as granulation tissue and focal lymphohistiocytic infiltration.

The synovial membrane was characterized by lymphohistiocytic infiltration with a predominance of macrophages. Locally, lymphocytes formed nodules resembling lymphoid follicles without reactive centers. Synoviocytes exhibited signs of proliferation, while foci of dystrophic and necrotic changes persisted. Blood vessels remained dilated with microcirculatory disturbances; perivascularly, connective tissue overgrowth with lymphocytic infiltration was observed. Synovial villi were hyperplastic and sclerotic, with granulation tissue and signs of neoangiogenesis. In some areas, the villi adhered to the cartilage surface, forming pannus with proteinaceous exudates (Fig. 2A, 2B).

In the intermediate zone of the cartilage, matrix disorganization and chondrocyte necrobiotic changes persisted, with areas of hyaline cartilage being replaced by coarse-fibrous and granulation tissue invading the subchondral bone. The superficial cartilage layer exhibited signs of sclerosis, dystrophy, and lymphohistiocytic infiltration, accompanied by ingrowth of granulation tissue into deeper layers. In the subchondral bone, demineralization and bone marrow edema were observed (Fig. 2C, 2D).

Thus, the morphological picture on day 14 was characterized by pronounced destructive and inflammatory changes, whereas by day 28 proliferative and sclerotic processes predominated, with the formation of pannus, granulation tissue, and invasion into the subchondral bone.

In animals subjected to correction of experimental osteoarthritis with diclofenac sodium or CO₂, by day 14 there were signs of positive dynamics in the restoration of the structural components of the joint

compared to the untreated group. In all treatment groups, a reduction in dystrophic and necrotic changes, as well as in the intensity of inflammatory reactions, was observed, with variations in the course of reparative processes depending on the applied therapy.

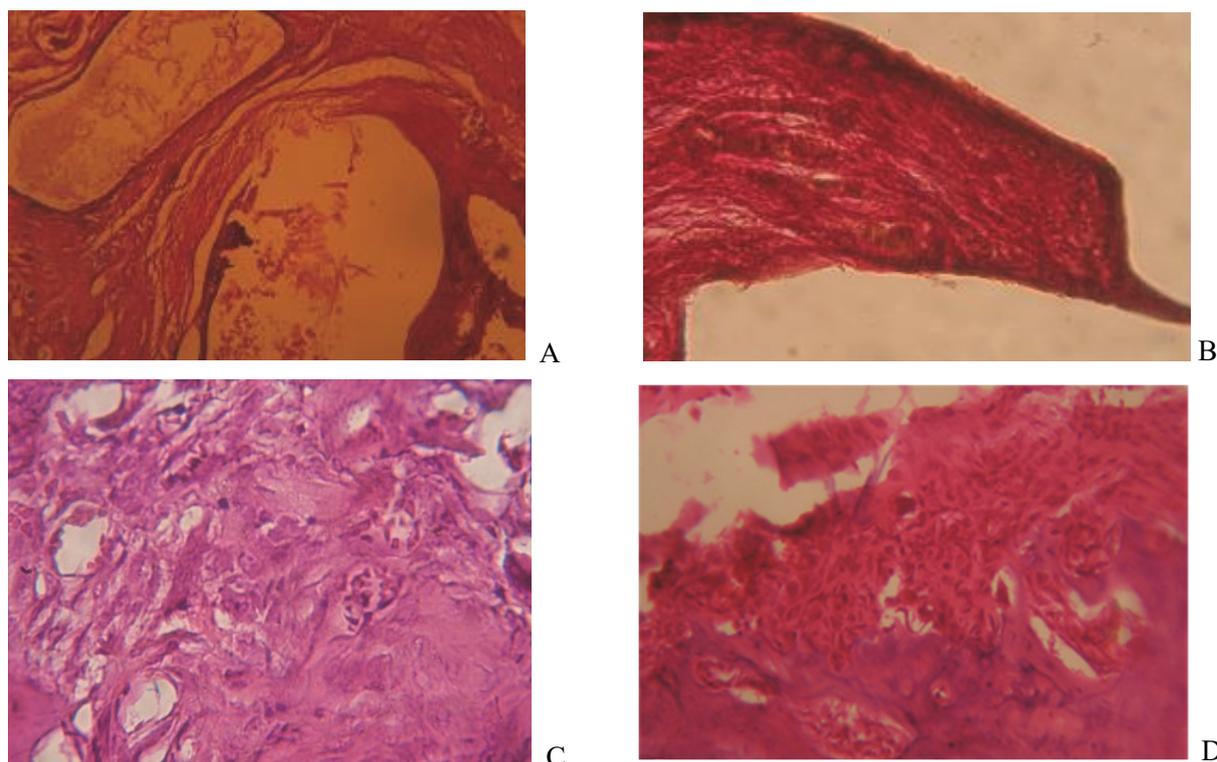


Fig. 2. Changes in the synovial membrane, articular cartilage, and subchondral bone in osteoarthritis (day 28). A – fusion of villi with proteinaceous exudates (Hematoxylin Gill II and eosin, $\times 50$). B – sclerosis of villous stroma (Van Gieson's picrofuchsin, $\times 200$). C – replacement of hyaline cartilage with granulation tissue (Gill II hematoxylin and eosin, $\times 200$). D – invasion of granulation tissue into the subchondral bone (Gill II hematoxylin and eosin, $\times 100$).

In animals treated with diclofenac, the morphological changes were characterized by moderate vascular congestion in the joint capsule without pronounced stasis phenomena, while infiltration of the periarticular tissues was limited. The synovial membrane preserved its architectural organization, showing only mild proliferation of synoviocytes and occasional foci of mucoid edema. The cartilaginous tissue maintained the typical columnar arrangement of chondrocytes in the intermediate zone, and the intercellular matrix showed no significant areas of disorganization. The subchondral bone exhibited no signs of destruction, with vascular congestion noted in the intertrabecular spaces (Fig. 3A).

In the CO₂-treated group, a reduction in dystrophic changes was observed; however, in comparison with the diclofenac group, isolated foci of necrosis persisted in the superficial layers of the cartilage. Areas of disorganization of the intercellular matrix were identified, although the columnar arrangement of chondrocytes in the intermediate zone was preserved. Some cells exhibited signs of vacuolar degeneration and pyknotic nuclei. In the synovial membrane, small foci of mucoid and fibrinoid edema were noted, along with occasional areas of basal membrane denudation and focal lymphocytic infiltrates (Fig. 3B).

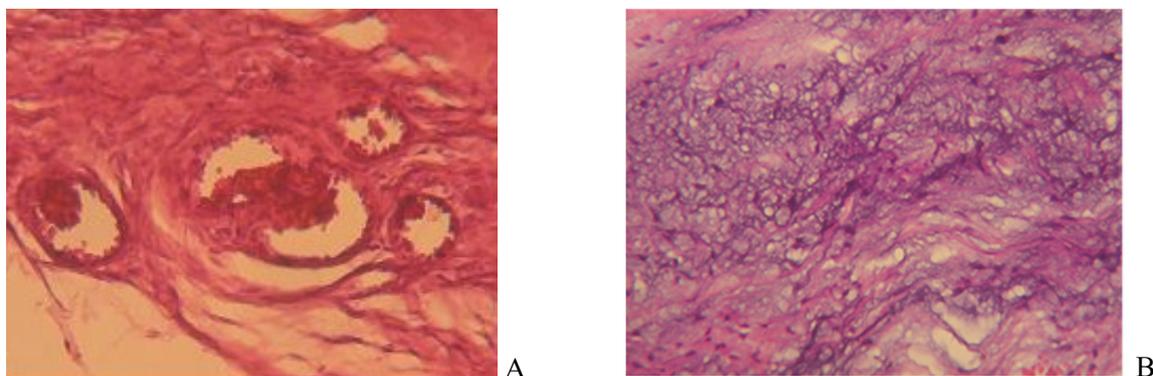


Fig. 3. Morphological structure of the rat knee joint under correction with diclofenac or CO₂ on day 14 of observation. A – Vascular congestion with signs of stasis and sludge formation in the periarticular tissues after chondroitin administration. Hematoxylin Gill II and eosin. $\times 100$. B – Moderate mucoid and fibrinoid edema in the synovial membrane after diclofenac administration. Hematoxylin Gill II and eosin. $\times 200$.

Thus, diclofenac and CO₂ contributed to a reduction in the intensity of dystrophic–necrotic alterations and inflammatory responses. In animals that received combined therapy with diclofenac and CO₂, a significant decrease in the severity of inflammatory and degenerative changes was observed compared both with the untreated group and with the monotherapy groups.

In the periarticular tissues, only occasional small foci of lymphohistiocytic infiltration were detected; blood vessels maintained patency, and no signs of stasis were present. The synovial membrane exhibited minor areas of edema and synoviocyte proliferation, with thin and sparse adhesions between villi. The articular cartilage retained its zonal organization; in the superficial zone, only small areas of fibrous remodeling of the matrix were noted, while the intermediate and deep zones preserved their normal histoarchitecture (Fig. 4A, 4B).

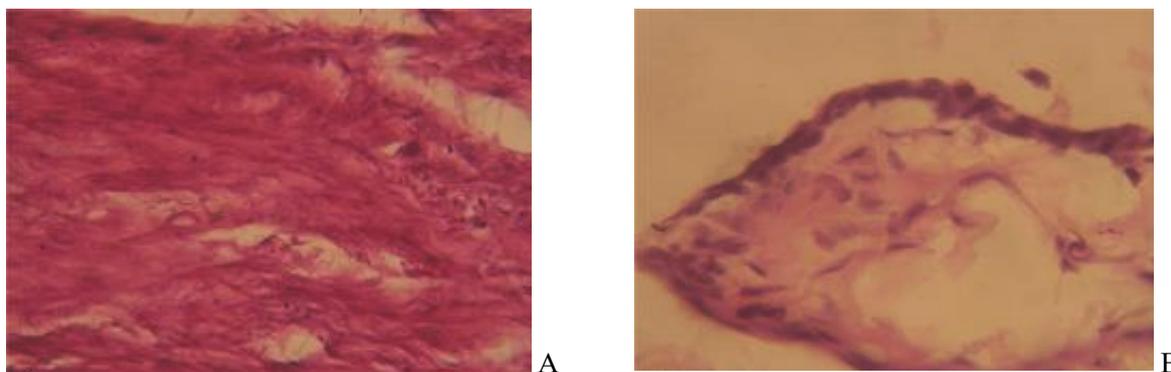


Fig. 4. Small foci of connective tissue in the periarticular muscles under combined therapy with diclofenac + CO₂ on day 14. Staining: hematoxylin Gill II and eosin. Magnification $\times 100$. A – Synovial villus with minor focal edema under combined therapy with diclofenac + CO₂ on day 14. Staining: hematoxylin Gill II and eosin. Magnification $\times 200$. B – Preserved zonal organization of cartilage layers under diclofenac + CO₂ therapy on day 14. Staining: hematoxylin Gill II and eosin. Magnification $\times 400$.

On day 28 of the experiment, animals in the combined diclofenac + CO₂ therapy group demonstrated almost complete restoration of the morphological structure of the knee joint. The synovial membrane appeared intact, without signs of inflammation or proliferation. The cartilage retained clear zonal organization: the superficial layer contained only minimal areas of fibrosis, while the intermediate and deep layers preserved normal columnar arrangement and intercellular matrix structure. The subchondral plate and bone marrow showed no pathological changes.

Combined therapy with CO₂ contributed to the attenuation of inflammation, partial restoration of cartilaginous tissue, and exhibited a pronounced chondroprotective effect. This was confirmed by the preservation of an intact subchondral plate and only minimal residual dystrophic alterations.

Thus, the combined administration of CO₂ enhanced the effect of diclofenac and demonstrated a more pronounced chondroprotective action on the articular cartilage and subchondral bone, indicating its potential as an optimal scheme for pharmacological correction of experimental osteoarthritis.

The study established that both monotherapy and combined diclofenac + CO₂ treatment exerted significant therapeutic effects in the osteoarthritis model. The most substantial outcomes were observed with the combination of CO₂ and diclofenac, confirming the rationale for a multifactorial approach in the management of OA.

Diclofenac demonstrated efficacy in the correction of OA, which is consistent with data on prostaglandin inhibition through cyclooxygenase blockade [15]. This was manifested by reduced leukocyte infiltration and preservation of cartilage zonal organization. CO₂ monotherapy also exerted a beneficial effect. Similar outcomes were reported in [12], where CO₂ attenuated NF- κ B activation and stimulated antioxidant defense via the HO-1/Nrf2 pathway, confirming the anti-inflammatory action of CO₂ previously established [11].

The combination of CO₂ with diclofenac resulted in nearly complete morphological restoration of joint structure, normalization of the cytokine profile, and absence of necrotic changes. This effect is likely attributable to the synergistic mechanisms of NSAID-mediated anti-inflammatory action together with the vasodilatory, antioxidant, and immunomodulatory properties of CO₂. A similar approach has previously been supported [5], emphasizing the advantages of combined therapeutic strategies. Moreover, [14] reported that induction of the M2 phenotype is associated with reduced pain sensitization and decreased NGF production, further highlighting the importance of immunomodulatory mechanisms in the pathogenesis of OA.

Particular attention should be paid to the study [14], in which CO₂, when combined with pharmacological agents, reduced TNF- α and IL-6 levels while increasing TGF- β 1, thereby promoting cartilage repair. This finding is consistent with our results and underscores the potential of CO₂ as an adjuvant therapeutic approach.

Current evidence confirms that CO₂ exerts anti-inflammatory, antioxidant, and immunomodulatory effects through several key mechanisms. First, it regulates MAPK signaling pathways (ERK1/2, JNK, p38) and modulates NF-κB activity, leading to decreased expression of Toll-like receptors and suppression of TNF-α, IL-1β, and IL-6 production [4]. Second, CO₂ activates antioxidant mechanisms, particularly the HO-1/Nrf2-dependent cascade, which reduces the generation of reactive oxygen species and limits oxidative stress [11]. Third, CO₂ has been shown to restore TGF-β1 production, which possesses regenerative potential, promotes extracellular matrix remodeling, and enhances cartilage and synovial repair [11].

Thus, the available evidence indicates that CO₂ not only enhances the effects of conventional anti-inflammatory agents but also exerts its own multifactorial action by reducing inflammation and oxidative stress while simultaneously stimulating reparative processes. This makes it a promising adjuvant in the treatment of degenerative and inflammatory joint diseases, particularly osteoarthritis, with the potential to optimize therapeutic outcomes and reduce the risks associated with long-term drug administration and possible adverse effects.

Conclusions

1. In the experimental osteoarthritis model, local administration of CO₂, diclofenac, and their combination on day 14 of therapy reduced the severity of inflammatory-destructive processes in the cartilage and subchondral bone; however, the most pronounced anti-inflammatory and chondroprotective effect was observed in the group receiving combined diclofenac and CO₂ treatment.

2. By day 28 of the experiment, the proposed therapeutic correction attenuated necrotic-degenerative changes and promoted the restoration of the morphological structure of the articular cartilage and subchondral bone.

3. Combined administration of CO₂ and diclofenac demonstrated a more pronounced protective effect compared to monotherapy with either agent alone, highlighting the rationale for considering this therapeutic approach in osteoarthritis management.

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Стаття надійшла 18.06.2024 р.