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Constructing a Novel Multimodal Analgesic Strategy for OVCF: A Theoretical Framework for the Synergistic Action of Paravertebral Block, Celecoxib and Ozone

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Abstract: ***Osteoporotic vertebral compression fracture (OVCF) is a significant cause of chronic pain in elderly patients. Its complex pain mechanisms often render single-mode analgesia insufficiently effective. This study proposes a triple analgesic regimen based on paravertebral block (PVB), oral celecoxib, and medical ozone injection, exploring the synergistic mechanisms from a neurobiological perspective. Through theoretical modeling, we systematically analyzed the mechanical, inflammatory, and neuropathic pain mechanisms of OVCF, clarifying the distinct action targets of the three interventions at different levels: PVB blocks neural signal transmission, celecoxib inhibits the COX-2/PGE2 inflammatory pathway, and ozone remodels the local microenvironment. The study constructed a three-level synergistic model, using the inhibition of dorsal root ganglion (DRG) neuronal excitability as the core indicator, demonstrating that the triple analgesic regimen achieves maximal suppression of DRG neurons through multi-target synergy. This research provides new insights for OVCF analgesia and lays a theoretical foundation for subsequent studies.***

Keywords: Osteoporotic Vertebral Compression Fracture, Paravertebral Block, Celecoxib, Ozone, Multimodal Analgesia, Dorsal Root Ganglion**.**

1. Introduction

Osteoporotic vertebral compression fracture (OVCF) is a common and frequently occurring disease in the elderly population. The resulting severe acute and chronic pain, kyphotic deformity, and impaired mobility severely damage patients' quality of life and impose a heavy medical burden on society [1]. With the accelerating trend of global population aging, the incidence of OVCF continues to rise, making it a significant public health issue.

OVCF pain is not caused by a single mechanical stimulus but represents a complex pathological process involving mechanical, chemical, and neuropathic components. The fracture itself can cause local mechanical instability, stimulating the nerve-rich periosteum. More crucially, the "chemical inflammation" triggered by the release of large amounts of inflammatory mediators (such as prostaglandins, cytokines, etc.) post-fracture, and the subsequent increase in excitability of dorsal root ganglion (DRG) neurons, constitute the core pathogenesis for the maintenance and amplification of pain [2,3]. Recent studies have further revealed the association between intravertebral pressure changes and nerve ending sensitization, providing a new perspective for understanding OVCF pain mechanisms [4].

Confronted with this complex pain state, traditional single-mode analgesia, such as oral non-steroidal anti-inflammatory drugs (NSAIDs) or opioids alone, often fails to achieve satisfactory results due to limited efficacy or potential side effects. Paravertebral block (PVB), as a precise interventional analgesic technique, can effectively block pain signal transmission, providing a powerful tool for OVCF analgesia [5]. However, PVB itself, as a "nerve conduction blocker," while treating the "symptoms" by immediately interrupting pain signals, struggles to independently resolve the "root cause" – the local inflammatory microenvironment – leading to persistent neuronal sensitization.

In this context, the concept of "Multimodal Analgesia" has emerged. It aims to achieve synergistic effects and reduce side effects by combining analgesic drugs and techniques with different mechanisms of action. Based on this concept, we have observed in clinical practice that regimens based on PVB, combined with either the selective COX-2 inhibitor celecoxib or medical ozone injection, have shown potential superior to monotherapy [6,7]. Particularly thought-provoking is that preliminary theoretical and empirical evidence suggests a notable stepwise enhancement in analgesic efficacy among three regimens: PVB combined with celecoxib, PVB combined with ozone, and the triple combination of PVB, celecoxib, and ozone.

However, a unified theoretical explanation for the systematic neurobiological mechanisms behind this efficacy escalation, especially the synergistic role of celecoxib and ozone in enhancing PVB's inhibition of DRG neuronal excitability, is currently lacking. Therefore, this paper aims to construct a rigorous theoretical model to elucidate, progressively from molecular, cellular, and neural pathway levels, how these three combination regimens produce stepwise optimized analgesic effects. This endeavor aims to provide an innovative and theoretically solid strategic option for the clinical pain management of OVCF.

2. Theoretical Analysis of OVCF Pain Mechanisms and Intervention Targets

2.1 Complex Pain Mechanisms of OVCF

The pain associated with osteoporotic vertebral compression fracture (OVCF) involves the interaction of mechanical, chemical, and neuropathic components, which together constitute the pathological basis of chronic OVCF pain.

"Mechanical pain" is the initiating factor of OVCF pain. Vertebral compression fractures disrupt the normal biomechanical balance of the spine, causing intervertebral instability, abnormal facet joint loading, and persistent mechanical traction on the periosteum. The nerve-rich periosteum, under excessive stimulation, produces well-localized mechanical pain, typically characterized by worsening upon activity [8]. Recent research has further revealed the role of intravertebral pressure changes in pain; post-fracture bleeding and bone marrow edema within the vertebra can lead to a significant increase in pressure, directly compressing and stimulating nerve endings and causing pain. Imaging studies have also found that vertebral compression-induced narrowing of the intervertebral foramen and an increased ratio of injured vertebral body width are independent risk factors for flank pain and intercostal neuralgia in OVCF patients, providing objective imaging evidence for mechanical pain [9].

"Chemical Inflammatory Pain" plays a key role in OVCF pain. Fracture, as a traumatic event, immediately triggers a local "inflammatory cascade," activating platelets, mast cells, and others to release numerous inflammatory mediators, including prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), and the interleukin family [10,11]. These chemicals have a dual algogenic effect: they directly activate peripheral nociceptors as chemical irritants, and they significantly lower the activation threshold of nociceptors, leading to hyperalgesia and allodynia [10,11]. Clinical studies detecting elevated levels of algogenic factors such as neuropeptide Y (NPY), serotonin (5-HT), and substance P in the serum of OVCF patients confirm the crucial role of inflammatory mediators in pain maintenance [11].

The "Neuropathic Pain" component is the core link in the chronicity of OVCF pain. Persistent mechanical and chemical inflammatory stimuli collectively lead to functional and structural changes in the nervous system: on one hand, fracture fragments or hematomas may directly stimulate or compress the dorsal ramus of the spinal nerve; on the other hand, and more critically, persistent pathological afferent signals cause abnormally increased excitability of dorsal root ganglion (DRG) neurons. Studies show that DRG neurons undergo changes in ion channel expression (e.g., Nav1.8 channel dysfunction, HCN channel dysregulation), increased spontaneous ectopic discharge, and electrophysiological changes such as membrane lipid domain alterations, turning them into persistent pain signal generators [12]. These changes mean that pain persists even after the initial noxious stimulus has diminished, forming the neurobiological basis for the chronicity of OVCF pain.

2.2 Core Therapeutic Modalities and Their Target Theories

Targeting this complex pain network in OVCF, paravertebral block (PVB), celecoxib, and medical ozone act on different key targets, constituting a complementary analgesic strategy:

2.2.1 Paravertebral Block (PVB): The "Physical Blocker" of Pain Signals

PVB plays a key role in OVCF analgesia through a dual mechanism. First, as a "physical blocker," PVB involves the precise injection of local anesthetics around the target dorsal ramus of the spinal nerve, reversibly blocking voltage-gated sodium channels, thereby inhibiting the generation and conduction of nerve impulses [13]. This action rapidly interrupts the transmission of pain signals to the central nervous system, directly reducing the input load on the dorsal root ganglion (DRG), achieving immediate analgesia. Second, PVB also has a significant anti-inflammatory effect; by blocking pain signal transmission, it inhibits the release of pro-inflammatory neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) at the source, effectively reducing neurogenic inflammation and tissue edema [12].

2.2.2 Celecoxib: The "Precision Inhibitor" of the COX-2/PGE2 Pathway

Celecoxib, as a highly selective COX-2 inhibitor, plays a key role in OVCF analgesia by precisely regulating the inflammatory pathway. Locally at the OVCF site, tissue damage and inflammatory cells (e.g., macrophages) highly induce COX-2 expression, catalyzing the production of large amounts of prostaglandins (PGs), notably the potent algogenic and sensitizing substance PGE2. PGE2 directly sensitizes peripheral nociceptors, lowering their activation threshold. Celecoxib selectively inhibits COX-2, reducing the generation of PGE2 at its source, effectively alleviating peripheral sensitization [14].

Furthermore, celecoxib has a central regulatory effect. Studies suggest that PGE2 can cross the blood-brain barrier and also affect neuronal excitability within the DRG, participating in the formation of central sensitization. By inhibiting systemic and local DRG PGE2 synthesis, celecoxib indirectly reduces the excitability of the central nervous system, thereby intervening in the pain chronicization process [15]. This dual mechanism of peripheral and central regulation allows celecoxib not only to relieve immediate pain but also to prevent its long-term maintenance, providing crucial pharmacological support for the immediate analgesic effect of PVB.

2.2.3 Medical Ozone: The "Broad-Spectrum Remodeler" of the Local Microenvironment

Medical ozone exerts a broad-spectrum remodeling effect on the OVCF pain microenvironment through multi-target mechanisms. Its potent anti-inflammatory action is primarily achieved by activating the Nrf2 pathway, upregulating the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase, effectively neutralizing excess reactive oxygen species (ROS) at the

fracture site, thereby reducing the release of key inflammatory factors (e.g., TNF-α, IL-1β, IL-6) driven by oxidative stress [16]. These inflammatory factors are important mediators causing peripheral sensitization and pain maintenance. Substance P, while stimulating the body to release endogenous analgesic substances such as endorphins, producing central analgesic effects by activating descending inhibitory pathways [17]. Additionally, ozone improves local blood circulation, effectively reducing tissue edema and hypoxia, creating a favorable environment for nerve repair and tissue regeneration.

This synergistic action of anti-inflammatory, analgesic, and microcirculation-improving mechanisms enables ozone to remodel the pathological microenvironment around DRG neurons at multiple levels, not only directly alleviating pain symptoms but also creating favorable conditions for tissue repair, demonstrating unique therapeutic value in OVCF pain management.

3. Construction of the Synergistic Theoretical Model and Analysis of Efficacy Escalation

The dorsal root ganglion (DRG), as the first relay station in the pain conduction pathway, holds a central position in the initiation and maintenance of chronic OVCF pain. The establishment of our theoretical model is precisely based on "inhibiting DRG neuronal hyperexcitability" as the ultimate biological indicator and common action hub for evaluating the synergistic effects of different analgesic regimens.

In the complex pain state of OVCF, DRG neurons undergo significant functional remodeling and excitability changes. Persistent noxious input drives a series of molecular and electrophysiological adaptations in DRG neurons: upregulation and enhanced function of voltage-gated sodium channels (especially the Nav1.8 subtype), inhibition of potassium channel currents, and sensitization of transient receptor potential (TRP) channels, collectively leading to a lowered neuronal activation threshold and increased spontaneous ectopic discharge [3,12]. The establishment of this peripheral sensitization state transforms the DRG from a passive signal transmitter to an active pain signal generator, becoming a key driver of OVCF pain chronicity.

The innovation of this theoretical model lies in unifying the mechanisms of the three intervention strategies within the common framework of "DRG neuronal excitability regulation" for analysis. PVB directly reduces the input load on the DRG by blocking voltage-gated sodium channels at the nerve trunk level; celecoxib reduces the chemical drive on DRG neurons by inhibiting the COX-2/PGE2 pathway; ozone comprehensively corrects the pathological basis causing neuronal sensitization by remodeling the DRG's surrounding microenvironment. The three therapies act on this key node of the pain pathway from three different dimensions: signal conduction, molecular drive, and microenvironment.

3.1 PVB + Celecoxib Group – "Nerve Conduction Block - Inflammatory Pathway Inhibition" Mode

This combination establishes an efficient synergistic mode of "nerve conduction block - inflammatory pathway inhibition." PVB provides rapid, potent afferent blockade through reversible sodium channel blockade, while simultaneously reducing neurogenic inflammation by inhibiting neuropeptide release [8]. Celecoxib, on the other hand, inhibits the generation and amplification of pain signals at the source by precisely inhibiting the core inflammatory pathway COX-2/PGE2 [14]. More importantly, significant mutual promotion exists between the two: PVB, by blocking pain signal input and reducing central sensitization, indirectly enhances celecoxib's regulation of peripheral inflammation; whereas celecoxib, by inhibiting systemic and local DRG PGE2 synthesis, improves the chemical environment around neurons, making PVB's blocking effect more durable and stable [15].

In promoting bone metabolism, this combination shows unique advantages. The effective analgesia provided by PVB enables patients to engage in early functional activities, and moderate mechanical load promotes osteoblast activation via the Wnt/β-catenin signaling pathway [7]. Simultaneously, celecoxib, as a selective COX-2 inhibitor, minimizes interference with bone healing while controlling inflammation, creating a favorable pharmacological environment for bone repair [14]. The synergistic action of both effectively relieves pain and provides a good biological basis for fracture healing.

3.2 PVB + Ozone Group – "Conduction Block - Microenvironment Remodeling" Mode

This combination represents a significant advancement in treatment strategy beyond the primary synergy. PVB continues to provide signal conduction blockade and neurogenic inflammation control [8], while ozone achieves a "three-dimensional remodeling" of the pathological microenvironment around the DRG through its unique multi-target action [16]. The mutual promotion between the two is reflected at multiple levels: ozone enhances the distribution and retention time of PVB local anesthetics in the lesion area by improving local blood supply and oxygenation; simultaneously, after PVB blocks pain signals, it reduces sympathetic nerve tension, further improving local blood circulation, creating a better environment for ozone to exert its effects [17].

In terms of bone metabolism promotion, this combination forms a more powerful synergistic effect. Ozone promotes osteogenic differentiation by activating the Nrf2/HO-1 pathway, exerting antioxidant effects, and upregulating BMP-2 expression [16]. Meanwhile, the improved microcirculation by ozone provides ample nutrients and oxygen for bone repair [18]. Early activity ensured by PVB reinforces this process through mechanical stimulation, together building a microenvironment conducive to bone regeneration [7]. Studies indicate that this combination can significantly increase angiogenesis and callus mineralization speed at the fracture site [16].

3.3 PVB + Celecoxib + Ozone Group – Formation of a "Multi-target Three-dimensional Intervention Network"

The triple therapy achieves the maximization of therapeutic effects by constructing a multi-level, multi-target

three-dimensional intervention system. The three treatment modalities form an organic whole with deep complementarity and mutual promotion: ozone-improved local microcirculation promotes the enrichment of celecoxib at the callus site, while its alleviated oxidative stress state inhibits COX-2 expression by downregulating the NF-κB signaling pathway, enhancing the inhibitory efficiency of celecoxib [16]; the sustained systemic anti-inflammatory provided by celecoxib ensures no inflammatory rebound during ozone treatment intervals [14]; PVB provides a time window for the action of the former two through effective analgesia and enhances the overall efficacy by blocking the pain-inflammation vicious cycle [8].

In promoting bone metabolism, the triple regimen demonstrates unique synergistic advantages. Celecoxib precisely controls inflammation levels, avoiding excessive inflammation's inhibition of bone healing [14]; ozone promotes angiogenesis and osteogenic differentiation through multiple mechanisms [16]; PVB-guaranteed early activity provides necessary mechanical stimulation [7]. More importantly, a positive feedback loop forms among the three: the improved local environment by PVB and ozone enhances the distribution and efficacy of celecoxib; the inflammation controlled by celecoxib creates optimal conditions for ozone to promote bone regeneration; and the early functional activity [15] ensured by PVB reinforces the biological effects of the former two through mechanical stimulation. This "drug distribution-molecular egulation-mechanical environment" three-dimensional network comprehensively optimizes the molecular biological environment for fracture healing, significantly accelerating the bone regeneration process [7].

3.4 Beyond Analgesia: Synergistic Promotion Mechanism for Bone Metabolism and Fracture Healing

The triple therapy demonstrates a unique system-level synergistic effect in promoting bone metabolism and fracture healing [1]. At the molecular level, this regimen establishes a molecular environment favorable for bone formation by coordinately regulating multiple signaling pathways, including BMP-2/Smad, Wnt/β-catenin, and RANKL/OPG [7]. Celecoxib maintains an appropriate bone remodeling balance by precisely controlling PGE2 levels [14]; ozone synchronously promotes angiogenesis and osteogenic differentiation by upregulating VEGF and BMP-2 expression [16]; PVB activates mechanosensitive ion channels and integrin signaling pathways by ensuring early activity [8].

At the cellular level, the triple therapy coordinately regulates the biological behaviors of various bone tissue cells, including osteoblasts, osteoclasts, and osteocytes. Celecoxib inhibits excessive osteoclast activation while maintaining normal osteoblast function; ozone reduces oxidative stress damage to osteoblasts by clearing excess ROS and creates a favorable healing environment by regulating immune cell function [18]; PVB indirectly optimizes the systemic environment for bone healing by improving the patient's overall condition [8].

This multi-level, multi-target synergistic effect ultimately manifests as a significant improvement in fracture healing quality [7]. Preclinical studies show that triple therapy promotes faster callus maturation and better trabecular bone structure reconstruction, reflected in the simultaneous improvement of bone mineral density, bone volume fraction, and biomechanical properties [8]. This integrated strategy of "analgesia-anti-inflammation-promoting healing" not only effectively controls OVCF-related pain but also creates the optimal biological environment for fracture healing through system-level regulation, representing a major advancement in the OVCF treatment paradigm [7].

4. Discussion and Prospects

By constructing a "three-level synergy" theoretical model, this study systematically elucidates the neurobiological mechanisms behind the stepwise enhancement of analgesic efficacy of paravertebral block (PVB), celecoxib, and medical ozone in osteoporotic vertebral compression fracture (OVCF). This progressive effect not only embodies the essence of the multimodal analgesia concept but also demonstrates the evolution of treatment strategy from single-target intervention to multi-target system regulation.

Regarding the mechanism of efficacy escalation, the three-level synergy model proposed in this study shows distinct hierarchical characteristics. Primary synergy (PVB + celecoxib) establishes a basic mode of "conduction block - upstream inhibition," where PVB rapidly interrupts pain signal conduction by blocking voltage-gated sodium channels [8], and celecoxib reduces algogenic mediators at the source by inhibiting the COX-2/PGE2 pathway [14], forming an effective linear complement. Intermediate synergy (PVB + ozone) achieves a significant upgrade in treatment strategy; ozone, through multiple mechanisms like activating the Nrf2 pathway and improving microcirculation [14], performs three-dimensional remodeling of the pathological environment around the DRG, its scope of action surpassing the single-pathway inhibition of celecoxib, showing advantages in both intervention depth and breadth. The triple therapy constructs a complete three-dimensional intervention network, achieving full coverage of the pain pathological chain and, through unique mutual promotion mechanisms – such as ozone-improved local microcirculation promoting the distribution and enrichment of celecoxib in the lesion area, and the sustained anti-inflammatory provided by celecoxib ensuring no inflammatory rebound during ozone treatment intervals [15,16,17] – produces a "1+1+1>3" synergistic effect.

It is noteworthy that this efficacy escalation phenomenon has a solid foundation in clinical practice. Multiple clinical observational studies have shown that analgesic effects indeed present a stepwise enhancement trend from PVB combined with celecoxib, to PVB combined with ozone, and further to the triple combination [1,6]. This study explains the biological mechanism behind this phenomenon at the theoretical level, providing a scientific basis for clinical practice.

However, as a theoretical exploration, this study has several limitations. First, the validation of the theoretical model still requires rigorous experimental research, especially concerning the specific mechanisms of DRG neuronal excitability changes and bone metabolism regulation. Second, the standardization of ozone treatment technical parameters remains a challenge for clinical application; more research is

needed to determine the optimal concentration, dosage, and treatment frequency [17]. Furthermore, the mechanism of individual differences affecting treatment efficacy is not yet clear, and reliable predictive biomarkers for efficacy are lacking, which limits the implementation of precision medicine to some extent.

Based on the above analysis, future research should focus on the following directions: First, basic experiments are needed to verify the specific action pathways of each treatment modality in the three-level synergy model, especially elucidating the nature of the mutual promotion mechanism at the molecular level. Second, multicenter, large-sample randomized controlled trials should be conducted to directly compare the efficacy differences of the three combination regimens, providing high-level evidence-based medical evidence for clinical decision-making. Additionally, exploring individualized treatment plans based on biomarkers such as inflammatory factor profiles and gene expression characteristics will help achieve the goal of precision medicine. Finally, in-depth research on the impact mechanism of the triple therapy on bone metabolism, especially the specific pathways in promoting osteogenic differentiation and accelerating fracture healing, will provide more sufficient theoretical support for the integrated strategy of "analgesia-promoting healing."

In conclusion, the three-level synergy theoretical model proposed in this study not only provides new treatment ideas for OVCF analgesia but also offers a new theoretical framework for multimodal analgesia mechanism research. With the deepening of future research and the accumulation of clinical practice, this innovative strategy is expected to bring a better treatment experience and clinical outcomes for OVCF patients.

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