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Review article

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Pharmacological and interventional treatment of phantom pain

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Phantom limb pain (PLP) is a common and debilitating form of neuropathic pain that occurs after limb amputation significantly impairing patients' quality of life.

The aim of this review is to summarize and analyze current data on pharmacological and interventional treatments for PLP, focusing on practical aspects of therapy to improve patients' quality of life and optimize treatment strategies for this complex condition.

A review of recent studies and clinical guidelines on PLP management was conducted, including pharmacological approaches (antidepressants, anticonvulsants, gabapentinoids, opioids, and NMDA receptor antagonists) and interventional methods (nerve blocks, radiofrequency procedures, neuromodulation).

Pharmacological treatment of PLP has shown variable outcomes. Gabapentinoids, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors have demonstrated moderate efficacy in reducing pain intensity. Opioids may be used only in severe cases due to the risk of dependency and side effects. Interventional methods such as peripheral nerve blocks, radiofrequency ablation, and neuromodulation techniques (spinal cord stimulation, transcranial magnetic stimulation) provide long-term pain relief in refractory PLP cases with minimal side effects.

A personalized approach combining pharmacological and interventional methods appears to be the most effective in managing PLP. Further randomized controlled trials are needed to optimize therapeutic strategies. Given the increasing number of amputees due to military actions in Ukraine, the standardization of PLP treatment has become a priority for the medical community.

Keywords: *phantom limb pain; personalized approach; treatment methods; pharmacotherapy; interventional treatment*

Introduction

Phantom limb pain (PLP) is a complex and debilitating pathological condition that arises after limb amputation and is characterized by pain sensation in the missing body part. This phenomenon is a form of neuropathic pain and remains a significant challenge for both patients and healthcare professionals due to its high prevalence and the complexity of treatment.

Current approaches to PLP management include both pharmacological methods (antidepressants, anticonvulsants, gabapentinoids, etc.) and interventional procedures (nerve blocks, radiofrequency techniques, neuromodulation). However, the effectiveness of many of these treatments remains controversial due to the limited number of high-quality clinical studies.

The aim of this review is to summarize and analyze contemporary data on pharmacological and interventional treatments for PLP, with a focus on practical therapeutic aspects to improve patients' quality of life and optimize treatment strategies for this complex condition.

Epidemiology of phantom limb pain

The prevalence of PLP varies significantly across studies, ranging from 64% to 87% among amputees, depending on the study sample and assessment methods [1, 2]. Phantom pain occurs in both civilian and military populations, but its frequency and severity are disproportionately higher among military personnel due to the traumatic nature of their amputations. Globally, approximately 356 million limb amputations are performed annually, with the highest burden observed in low- and middle-income countries due to trauma and infections [3]. In the United States, approximately 185,000 amputations are performed each year, with the leading causes being vascular diseases (82.0%), trauma (16.4%), oncological conditions (0.9%), and congenital anomalies (0.8%) [4]. Among amputees, PLP is a persistent and often debilitating condition. The lifetime prevalence of PLP ranges from 64% to 87% [2]. A systematic review and meta-analysis conducted by Limakatso et al. (2020) [1] found that the prevalence of PLP is significantly higher in developed

countries (66.55%) compared to developing countries (53.98%), suggesting that access to medical care, surgical techniques, and postoperative management may influence PLP development. Approximately 82% of amputees experience PLP within the first year after amputation, and a substantial proportion continue to suffer from pain for years, indicating the chronic nature of the condition [3].

Several preoperative, perioperative, and postoperative risk factors contribute to the development of PLP.

Preoperative risk factors

1. Pre-amputation pain. Persistent pain prior to amputation is a strong predictor of PLP, as it may lead to central sensitization and maladaptive neuroplasticity [5].

2. Psychological factors. Anxiety, depression, and catastrophizing are associated with an increased likelihood of developing PLP [6].

3. Age and sex. Older age is linked to a higher risk of PLP, while sex-related differences remain inconclusive [3].

Perioperative risk factors

1. Surgical technique. Traditional traction neurectomy, in which the nerve is cut under tension, causing it to retract, may lead to neuroma formation, increasing the risk of PLP [7].

2. Advanced surgical techniques. Techniques such as targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI) have been shown to significantly reduce PLP incidence by improving nerve regeneration and minimizing neuroma formation [8].

Postoperative risk factors

1. Residual limb pain (stump pain). This strongly correlates with PLP, suggesting shared pathophysiological mechanisms [9].

2. Prosthesis use. Advanced prostheses with sensory feedback may alleviate PLP, whereas poorly fitted or purely cosmetic prostheses may exacerbate symptoms [10].

3. Acute postoperative pain. Uncontrolled pain persisting for weeks after surgery significantly increases the risk of chronic PLP [3].

Phantom limb pain in military personnel

Phantom limb pain (PLP) is a relevant issue in wartime conditions due to the high incidence of traumatic limb loss among military personnel. Studies have shown that amputee veterans experience more severe and persistent PLP compared to civilian amputees [11]. This can be attributed to several factors:

1. Nature of amputation: Combat-related amputations are often caused by high-energy blast or gunshot wounds, leading to more severe nerve damage and an increased risk of PLP [12].

2. Psychological stress factors: Military amputees exhibit higher rates of post-traumatic stress disorder (PTSD) and depression, both of which are closely linked to increased PLP severity [13].

3. Rehabilitation challenges: Delayed or inadequate rehabilitation, including limited access to specialized prosthetics and pain management programs, may exacerbate PLP in veterans [14].

Pathophysiology of phantom limb pain

Despite extensive research, the precise pathophysiological mechanisms underlying PLP remain incompletely understood. This chronic pathological condition is believed to result from a complex interplay of morphological, physiological, and chemical alterations within the peripheral and central nervous systems. Understanding the peripheral, spinal, and supraspinal mechanisms contributing to PLP is crucial for developing effective preventive and therapeutic strategies.

Peripheral mechanisms. PLP often arises due to the transection of peripheral nerves during amputation, leading to maladaptive changes in neurons. Key peripheral mechanisms include:

1. Neuroma formation – following nerve transection, damaged axons attempt to regenerate, frequently resulting in neuroma formation. Neuromas exhibit spontaneous ectopic activity and heightened excitability, leading to persistent pain [15, 16].

2. Ectopic discharges – hyperexcitability of injured nerve endings and dorsal root ganglia leads to spontaneous pain signals, which are interpreted as originating from the missing limb [3].

3. Inflammatory responses – post-amputation inflammation and immune cell activation may enhance nociceptive signal transmission, increasing peripheral nerve sensitization [15].

Spinal mechanisms. The spinal cord plays a pivotal role in amplifying and modulating pain signals following amputation. Several key processes are involved:

1. Central sensitization – increased excitability of dorsal horn neurons results in heightened pain transmission, causing persistent pain even in the absence of peripheral input [15, 16].

2. Disinhibition of pain pathways – reduced inhibitory neurotransmission, such as diminished GABAergic and glycinergic activity, enhances nociceptive signaling from the residual limb [1].

3. Neuroplastic changes – the loss of afferent input from the amputated limb leads to maladaptive plasticity in the dorsal horn, intensifying pain perception despite the absence of ongoing nociceptive stimuli [15].

Supraspinal mechanisms. The brain undergoes significant structural and functional changes following limb amputation, contributing to the development of PLP. These changes include:

1. Cortical reorganization – functional magnetic resonance imaging (fMRI) studies indicate that somatosensory cortical areas representing the amputated limb are taken over by adjacent body part representations. This remapping is associated with the perception of pain in the missing limb [1, 3].

2. Thalamic dysfunction – the thalamus, which processes sensory information, exhibits hyperactivity in PLP patients, likely due to the loss of afferent regulation [15].

3. Altered descending pain modulation – dysfunction of descending pain modulation pathways originating from the brainstem and limbic system contributes to persistent pain sensations [16].

Pharmacological therapy of phantom pain

Various pharmacological treatment strategies for PLP have been proposed; however, the administration of different classes of medications demonstrates variable outcomes. This review focuses on the efficacy of tricyclic antidepressants (TCAs), serotonin-norepinephrine

reuptake inhibitors (SNRIs), gabapentinoids (pregabalin and gabapentin), anticonvulsants (carbamazepine, oxcarbazepine, topiramate), opioids (tramadol, morphine, oxycodone), and additional pharmacological approaches, including NMDA receptor antagonists (ketamine) and botulinum neurotoxin.

Tricyclic antidepressants. Amitriptyline, a widely used TCA, has been investigated for its effectiveness in treating PLP. It is believed to exert its effects by enhancing serotonin and norepinephrine transmission in the central nervous system, thereby modulating pain perception. However, studies on its efficacy for PLP have yielded conflicting results. L.R. Robinson et al. (2004) conducted a randomized controlled trial comparing amitriptyline with placebo in patients with PLP and found no significant difference in pain reduction between the two groups [17]. Additionally, adverse effects of amitriptyline, such as sedation, dry mouth, and dizziness, may limit its use [18].

Serotonin-norepinephrine reuptake inhibitors. Duloxetine, the most well-known agent in this class, is recommended for the treatment of neuropathic pain, including painful diabetic neuropathy and fibromyalgia, based on findings from randomized placebo-controlled clinical trials. However, its potential in treating PLP has been less extensively studied, as large-scale trials evaluating duloxetine for this condition are lacking. Nevertheless, a meta-analysis of SNRIs for neuropathic pain management revealed that duloxetine significantly reduces pain scores in conditions similar to PLP [19]. Given the low prevalence of PLP in contemporary Western countries and the consequently lower number of randomized controlled trials on this condition compared to other neuropathic pain disorders, the standard practice is to apply general pharmacotherapy guidelines for neuropathic pain [20]. Notably, duloxetine's favorable side effect profile compared to TCAs makes it a promising option for patients intolerant to other medications [18].

The initial dose of duloxetine is 30 mg once daily, preferably in the morning. If tolerated, the dose may be increased to 60 mg after one week. In the management of pain disorders, this dosage is typically considered the maximum, as no clinical benefit has been observed from further titration up to 120 mg [21].

Gabapentinoids. Gabapentinoids, including gabapentin and pregabalin, are widely used for neuropathic pain disorders due to their ability to modulate calcium channels in the central nervous system. Studies have demonstrated that gabapentin reduces the intensity of phantom limb pain (PLP). In a randomized controlled trial conducted by D.G. Smith et al. (2005) [22], patients receiving gabapentin reported a significant pain relief. The daily dosage of gabapentin was gradually increased from 300 mg to 3600 mg. More than half of the patients experienced substantial pain relief with this medication, compared to one-fifth of participants in the control group. In another randomized, double-blind, placebo-controlled study [23], patients with post-amputation PLP were administered gabapentin, starting at a dose of 300 mg/day, which was gradually increased to 2400 mg or the maximum tolerated dose. After six weeks of monotherapy, patients receiving gabapentin reported a statistically significant reduction in pain intensity. However, other studies have yielded less favorable results in terms of pain reduction compared to placebo [19].

The initial dose of gabapentin is 100–300 mg, taken either at bedtime or divided into three doses throughout the day. The dosage is then gradually increased by 300–900 mg per day, depending on efficacy and tolerability. The maximum dose may reach 3600 mg.

Pregabalin is a structural analog of γ -aminobutyric acid (GABA). As a more potent gabapentinoid than gabapentin, pregabalin has demonstrated efficacy in various neuropathic pain disorders, including PLP treatment. Pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing the release of excitatory neurotransmitters such as glutamate, substance P, and norepinephrine. This mechanism underlies its efficacy in treating neuropathic pain disorders such as diabetic neuropathy and postherpetic neuralgia. Studies have confirmed the efficacy and safety of pregabalin administration. Given that PLP shares pathophysiological mechanisms with other neuropathic pain syndromes, pregabalin is considered an effective treatment for PLP [24].

Numerous studies have demonstrated the efficacy of pregabalin in patients with various types of neuropathic pain at daily doses of 300, 450, and 600 mg. A dose of 150 mg/day was largely ineffective [25]. Treatment is recommended to begin with 150 mg/day, divided into 2–3 doses. After one week, the daily dose should be increased to 300 mg. If necessary, further dose escalation to 450–600 mg may be considered after 2–3 weeks [21]. A flexible dosing regimen of pregabalin, allowing individualized dose adjustment within the range of 150–600 mg/day based on efficacy and tolerability, effectively alleviates pain and reduces the likelihood of treatment discontinuation [26].

There have been numerous reports on the successful use of pregabalin in PLP treatment [27–29]. However, a review of pharmacological therapy for PLP [30] noted that the number of high-quality studies on pregabalin for PLP is lower compared to other neuropathic disorders. In our opinion, this may be explained by the lower prevalence of PLP in developed countries compared to other chronic neuropathic pain conditions in peacetime, as well as its significantly lower prevalence relative to domestic data from wartime. Nonetheless, the authors of the aforementioned review consider the use of gabapentinoids, along with tricyclic antidepressants (TCAs), duloxetine, and opioids, to be justified for PLP management.

The predominant side effects of gabapentinoids include dizziness and drowsiness, as well as weight gain, which may limit their long-term use [31]. Dizziness and drowsiness typically occur within the first week of pregabalin administration, gradually diminishing over time and regressing in most cases within one month of treatment initiation [32]. There are simple recommendations that can significantly help to prevent the development of gabapentinoid-related adverse effects, particularly those of pregabalin. It is recommended to initiate pregabalin treatment with

an evening dose. Although the drug's instructions indicate that it can be taken with or without food, the initial dose is best administered during dinner (in the evening). In some cases, a single evening dose of 150 mg can effectively reduce pain and improve sleep quality with minimal adverse reactions. If morning pregabalin administration is associated with significant drowsiness and/or dizziness, asymmetric dosing—taking a higher dose in the evening—may be considered. This approach is also supported by pathophysiological reasoning, as there is an interdependence between sleep quality and chronic pain severity. Improved sleep following evening administration of higher pregabalin doses may reduce the need for significant daytime dosing. Numerous studies on the efficacy of pregabalin in chronic neuropathic pain have demonstrated that sleep improvement significantly contributes to pain intensity reduction [32, 33].

Due to patients' concerns and apprehensions regarding potential side effects of gabapentinoids, physicians may prescribe low, subtherapeutic doses, or patients may fail to adhere to the prescribed treatment regimen. Patient education regarding the necessity of adequate time for pain control and the potential for minimizing side effects through adherence to the aforementioned recommendations can help prevent suboptimal treatment outcomes. Over time, these adverse effects may regress [33, 34].

Since PLP is a debilitating pain disorder that, in some cases, responds poorly to treatment, the possibility of combination therapy with antineuropathic agents should be considered. D.R. Spiegel et al. [35] reported that combined administration of duloxetine once daily and pregabalin two to three times daily significantly reduced PLP intensity and gradually (within two weeks) allowed discontinuation of previously prescribed morphine sulfate. The daily doses were 60 mg of duloxetine and 450 mg of pregabalin. The titration regimen was as follows: from day 1, 30 mg of duloxetine in the morning and 50 mg of pregabalin three times daily; from day 4, 60 mg of duloxetine in the morning and 100 mg of pregabalin three times daily; from day 8 onward, 150 mg of pregabalin in the morning and 300 mg in the evening. A multinational, double-blind, parallel-group COMBO-DN study [36], involving 804 patients, demonstrated that combination therapy with moderate doses of duloxetine (60 mg/day) and pregabalin (300 mg/day) yielded slightly better outcomes in the treatment of peripheral neuropathic pain compared to monotherapy with these agents at their maximum daily doses (120 mg and 600 mg/day, respectively). According to the authors, combination therapy with duloxetine and pregabalin is effective, safe, well-tolerated, and allows for the avoidance of drug-related side effects in cases where monotherapy would require the maximum permissible doses.

Anticonvulsants. Antiseizure medications help alleviate neuropathic pain by stabilizing hyperexcitable neuronal membranes.

Carbamazepine, traditionally used for trigeminal neuralgia, has demonstrated potential in the treatment of PLP. Case reports and small-scale studies suggest that it may reduce pain intensity by modulating sodium channels in hyperexcitable neurons. However, its side effect profile—including dizziness, fatigue, and hepatotoxicity—limits its clinical utility [21].

Oxcarbazepine, a structural derivative of carbamazepine, exhibits a similar mechanism of action but with a more favorable side effect profile. It has been evaluated for the treatment of neuropathic pain, with some studies indicating benefits in PLP. However, high-quality randomized controlled trials remain lacking [21, 37].

Topiramate is widely used for migraine prophylaxis and epilepsy management. It has also been investigated for the treatment of neuropathic pain, including PLP. Its mechanism of action involves modulation of sodium and calcium channels, as well as enhancement of GABAergic transmission. Some studies indicate a reduction in PLP severity, but significant adverse effects—such as cognitive impairment and weight loss—may limit its clinical application [38].

Opioids. The use of strong opioids for PLP remains controversial due to concerns regarding tolerability, dependence, and long-term efficacy. Oxycodone, a potent μ-opioid receptor agonist, has been studied for its potential benefits in PLP. A Cochrane review reported that opioids, including oxycodone, provided pain relief but were associated with adverse effects such as constipation, drowsiness, and respiratory depression [19]. Morphine efficacy has also been investigated, demonstrating short-term analgesic effects; however, its potential for dependence and variable tolerability present significant challenges. Opioids should be considered only in severe cases of PLP when other treatment modalities prove ineffective.

Tramadol is an atypical analgesic that exerts its effects through two primary mechanisms: 1) an opioid effect, acting as a weak μ-opioid receptor agonist to provide analgesia; 2) neurotransmitter modulation, inhibiting serotonin and norepinephrine reuptake, which enhances antinociceptive effects and reduces neuropathic pain intensity. Due to these mechanisms, tramadol is considered a promising agent for the treatment of PLP, as it not only alleviates pain but also influences neuroplastic changes underlying pathological pain transmission. N.B. Finnerup et al. [31] demonstrated that tramadol provides moderate pain relief in neuropathic pain conditions, including PLP. It is generally preferred over stronger opioids due to a lower risk of dependence and fewer adverse effects, such as nausea and dizziness.

Studies evaluating the efficacy of tramadol in PLP have yielded the following findings:

- pharmacological treatment reviews of PLP identify tramadol as potentially effective in a subset of patients, particularly those with mixed pain components (nociceptive and neuropathic) [19,39].
- some clinical trials suggest that tramadol may help reduce pain intensity, though its efficacy is less pronounced compared to traditional opioids (e.g., morphine) or NMDA receptor antagonists [19].
- the combination of tramadol with anticonvulsants (e.g., gabapentin) or antidepressants may offer superior efficacy compared to monotherapy [39].

The standard tramadol dosage for chronic pain management is 50–100 mg every 6–8 hours, with a maximum daily dose of 400 mg. In PLP patients, it is recommended to start with the lowest possible dose and gradually titrate to assess efficacy and tolerability.

Common side effects include nausea, dizziness, dry mouth, and sedation.

NMDA receptor antagonists (ketamine and memantine). NMDA receptor antagonists, such as ketamine and memantine, have been investigated as potential treatments for PLP due to the role of these receptors in central sensitization. Intravenous ketamine has demonstrated analgesic effects in PLP patients; however, its clinical application is limited by significant psychotomimetic side effects, including hallucinations and sedation [19,30,39,40]. Memantine, an NMDA receptor antagonist primarily used for Alzheimer's disease treatment, has shown limited efficacy in PLP, with no significant pain relief compared to placebo [19]. Further studies are required to determine the long-term benefits and safety of NMDA receptor antagonists in PLP management.

Botulinum neurotoxin type A (BoNT-A). A review of BoNT-A potential in neuropathic pain management can be found in the second edition of the monograph "Botulinum Toxin Treatment of Pain Disorders" by Yale University professor Bahman Jabbari [41], as well as in the recently submitted "Ukrainian national consensus statement on botulinum toxin therapy for neuropathic pain". Those interested in the pathophysiological basis of this method, indications, technical details, and dosing of BoNT-A in PLP may refer to these sources.

Interventional treatment of phantom limb pain

A wide range of interventional techniques is available for the management of PLP. These methods can be particularly beneficial when pharmacological treatment proves insufficiently effective or is associated with intolerable adverse effects.

In cases where myofascial trigger points are present in the stump, their injection may provide significant pain relief. The underlying rationale is that *trigger point injections* alleviate myofascial pain by reducing muscle spasms, increasing the range of motion, and improving circulation. The core principle of this approach is the interruption of the spasm–pain–spasm cycle within the muscles. A study involving 21 patients reported a significant reduction in pain intensity, as measured by the visual analog scale (VAS), following local anesthetic injections into stump trigger points over a five-week period in most patients with post-amputation pain [42].

Peripheral nerve blocks are widely used to provide temporary pain relief in PLP. These procedures involve the administration of local anesthetics, often in combination with adjuncts such as clonidine or steroids, to block nociceptive signal transmission. Regional blocks of the sciatic and femoral nerves have been shown to provide temporary relief; however, their effects are typically short-lived, necessitating repeated injections to achieve sustained pain control. Another approach for limb PLP management is continuous peripheral nerve block. A study demonstrated that a six-day perineural infusion of ropivacaine could reduce PLP for at least one month, with some patients experiencing relief for 6–12 months [43].

Several minimally invasive interventions targeting stump neuromas have been proposed for refractory cases of PLP. One such technique is *chemical neurolysis*, which involves the ultrasound-guided injection of alcohol or phenol into stump neuromas to induce nerve tissue degeneration and subsequent pain relief. X. Zhang et al. (2017) investigated this technique and reported that 54% of patients experienced significant pain reduction after 1–3 alcohol injections. In patients unresponsive to this treatment, pain relief was achieved through radiofrequency ablation of neuromas [44]. The use of ultrasound-guided phenol injections was prospectively evaluated in 82 patients, all of whom demonstrated noticeable improvement, with 12% achieving complete pain resolution after 1–3 procedures. A distinguishing feature of this treatment was the low complication rate (5% minor and 1.3% major complications) [45]. Although neurolysis is effective, nerve regeneration may occur over time, potentially leading to pain recurrence.

Radiofrequency Procedures. Radiofrequency ablation (RFA) is a widely used interventional technique that delivers thermal energy to neural tissue to modulate pain transmission. Although the efficacy of RFA in treating various pain syndromes has been well established, the procedure may be associated with adverse effects and complications, including incomplete denervation of the pain-generating region, sensory and motor dysfunction, symptom exacerbation due to chaotic nerve regeneration, neuroma formation, and the development of deafferentation pain [46]. These complications can be mitigated by employing pulsed radiofrequency (PRF) treatment, which is referred to as "пульсове радіочастотне лікування (ПРЛ)" in the domestic literature. Unlike conventional thermal RFA, which destroys nerve fibers, PRF delivers energy in controlled bursts without causing permanent tissue damage.

PRF represents an advancement over traditional RFA, offering reduced tissue destruction while maintaining therapeutic efficacy. This method applies radiofrequency current at 500 kHz to the tip of the cannula in a sequence of discrete electrical bursts lasting 5–20 ms, repeated at a frequency of 2–5 Hz. Under this mode, the cannula temperature does not exceed 42°C, preventing thermocoagulation of nerve fiber proteins while preserving motor function and sensory integrity. The analgesic effect of PRF is attributed to its selective action on unmyelinated and thinly myelinated fibers, particularly through the modulation of synaptic transmission and excitability of C fibers, which are responsible for temperature and pain sensitivity and are implicated in the pathophysiology of most neuropathic pain syndromes [47–49].

Two literature reviews [46,50] have summarized the findings of numerous studies on the therapeutic mechanisms of PRF. These mechanisms include: microscopic alterations, such as selective damage to nociceptive C and Aδ fibers, with endoneurial edema observed for up to one week post-treatment; molecular changes, including microglial deactivation in the dorsal horn of the spinal cord, reduced levels of pro-inflammatory cytokines, increased mRNA production of endogenous opioid precursors, modulation of calcitonin gene-related peptide (CGRP) activity, and changes in ion channel function, notably increased Na^+/

K^+ channel expression; neuronal activity modulation, involving activation of descending antinociceptive serotonergic, noradrenergic, and GABAergic pathways, as well as inhibition of afferent C-fibers excitability; sustained pain signal suppression, with the analgesic effects of PRF persisting for several months.

Publications indicate positive outcomes of PRF therapy in cases of phantom limb pain (PLP) resistant to pharmacological treatment. A clinical case report describes the successful application of PRF in a 63-year-old female patient with severe PLP and residual limb pain following a below-knee amputation, persisting for four years [51]. The pain intensity ranged from 6 to 8 on the Numeric Pain Rating Scale (NPRS). After unsuccessful pharmacological management with gabapentin, pregabalin, hydrocodone, methadone, and morphine, PRF was applied to the sciatic nerve (two cycles of 120 seconds at 42°C, with a pulse duration of 20 ms and frequency of 2 pulses per second). The patient experienced complete pain relief, enabling the discontinuation of opioid analgesics. However, due to pain recurrence after four months, the procedure was repeated.

M. West and N. Wu (2010) [52] reported successful PRF application in four patients, in whom a radiofrequency cannula was placed under local anesthesia at the most tender neuroma site identified through palpation prior to the intervention. Following the procedure, all patients experienced significant reduction in residual limb pain, with effects lasting for six months. Additionally, two patients demonstrated substantial improvement in PLP. Patients reported enhanced functional status, improved prosthesis tolerance, and reduced oral analgesic consumption.

A. Kumar et al. (2024) [53] published a case series of 10 patients with refractory PLP following upper limb amputation. After a diagnostic nerve block, PRF of the stellate ganglion was performed. Marked reductions in PLP and functional improvement were observed at 1 week, 1 month, and 3 months post-procedure, without any side effects.

In a pilot study by S. Pu et al. (2020) [54], the efficacy of ultrasound-guided PRF for residual limb neuromas was investigated. The study found that 82.4% of patients with residual limb pain and 69.2% with PLP experienced significant pain relief, with no serious complications.

These findings suggest that radiofrequency-based techniques may represent a promising therapeutic option for patients with PLP, particularly those unresponsive to pharmacological interventions.

Neuromodulation in the treatment of phantom limb pain

Neuromodulation techniques—including spinal cord stimulation, peripheral nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation — aim to modify neural activity at the spinal or cortical level to alleviate chronic pain.

Spinal cord stimulation (SCS) involves the implantation of electrodes in the epidural space to deliver electrical impulses to the dorsal columns of the spinal cord, modulating pain transmission. Studies have demonstrated that SCS can reduce PLP in certain patients. A systematic review by M. Corbett et al. (2018) [55] analyzed multiple studies on SCS and reported significant pain relief in patients with chronic PLP. The authors highlighted that the presence of residual limb pain is a strong predictor of SCS success, suggesting that SCS may be more effective in patients with both PLP and residual limb pain.

Peripheral nerve stimulation (PNS) is another promising approach, particularly for neuroma-related pain. This technique involves placing electrodes near the affected peripheral nerves to modulate pain perception. R. Pagan-Rosado et al. (2023) [56] demonstrated that PNS is a potentially effective neuromodulatory method for treating refractory chronic pain, including post-amputation pain.

Several studies have investigated both invasive and non-invasive brain stimulation techniques for PLP.

Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses magnetic pulses to modulate cortical excitability. A meta-analysis by K. Pacheco-Barrios et al. (2020) [57] found that continuous current TMS applied to the primary motor cortex significantly reduces PLP symptoms, with effects lasting up to one week post-stimulation.

Deep brain stimulation (DBS) targets deep brain structures, such as the thalamus and periaqueductal gray matter, to modulate pain perception. A literature review by M. Corbett et al. (2018) [55] reported that DBS provided long-term pain relief in 73% of patients. However, the invasive nature of the procedure limits its widespread application.

Motor cortex stimulation (MCS) involves implanting electrodes over the motor cortex to disrupt pain-related neural activity. Studies suggest that MCS is effective in patients with treatment-resistant PLP; however, further research is needed to optimize stimulation parameters [57].

The presented data indicate that interventional techniques and neuromodulation approaches significantly expand the treatment options for PLP, particularly in patients unresponsive to pharmacological therapy. Radiofrequency techniques, especially pulsed radiofrequency (PRF), have demonstrated efficacy in reducing both PLP and residual limb pain, providing long-term relief with minimal invasiveness. Neuromodulation techniques, including SCS, TMS, DBS show promise in modulating pain pathways at both the spinal and cortical levels. However, despite encouraging results, further research is needed to establish standardized treatment protocols and optimize patient selection criteria. Large-scale randomized controlled trials are essential to confirm the efficacy of these approaches and explore multimodal treatment strategies that integrate pharmacological therapy, advanced rehabilitation techniques, and interventional or neurosurgical procedures to improve clinical outcomes.

Conclusions

PLP remains one of the most challenging forms of neuropathic pain, significantly impairing the quality of life of individuals with limb amputations. Despite extensive research, the pathophysiological mechanisms

of PLP are not yet fully understood, making effective treatment selection difficult. Current data suggest that a comprehensive approach combining pharmacological and interventional therapies is the most promising strategy.

Among pharmacological treatments, gabapentinoids, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors have demonstrated moderate efficacy in reducing PLP intensity. Interventional techniques, such as peripheral nerve blocks, radiofrequency procedures, and neuromodulation, have shown high effectiveness in refractory pain cases, providing long-lasting relief with minimal side effects.

A personalized approach to PLP management, considering individual patient characteristics, pain patterns, and risk factors, is crucial to achieving optimal outcomes. Randomized controlled trials are needed to further elucidate the pathophysiology of PLP and determine the most effective treatment combinations.

Given the current reality and the increasing number of amputations due to military conflicts, the development of standardized PLP treatment protocols is a priority for the Ukrainian medical community. Conducting large-scale clinical studies and implementing innovative treatment approaches will significantly improve patients' quality of life and reduce the burden of this debilitating condition.

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Conflict of Interest

The authors declare no conflicts of interest.

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Review article

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Aspirin in Patients Undergoing Neurosurgery: A long time controversy

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Aspirin is frequently used to prevent ischemic episodes, either directly or indirectly. Long-term aspirin therapy can increase intraoperative blood loss and have an impact on blood clot development during surgery. This is particularly crucial for neurosurgery and other high-risk surgeries. There is currently no clinical evidence to support the European Society of Cardiology (ESC) recommendation that aspirin should be discontinued at least one week before neurosurgical intervention. In addition to summarizing current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumour surgery, cerebrovascular procedures, and spinal surgery, this narrative review presents evidence that casts doubt on the need for aspirin interruption in neurosurgical patients. It also discusses options for monitoring the effect of aspirin and the clinical implications of these methods.

Key words: *brain tumour; cerebrovascular surgery; spinal surgery; aspirin; neurosurgery; postoperative complications; bleeding risk*

Introduction

Due to its well-known ability to reduce platelet aggregation, aspirin (acetylsalicylic acid, ASA) is frequently used for either primary or secondary prevention of ischemic events [1]. Long-term aspirin therapy can also increase intraoperative blood loss and impact blood clot formation during surgery [2]. Because even mild haemostatic problems can result in serious postoperative consequences, such as acute cerebral bleeding, this is particularly significant for high-risk surgeries, including neurosurgery [3]. Historically, expert consensus—rather than clinical evidence—has determined recommendations for discontinuation of aspirin therapy before neurosurgical procedures [4]. The 2022 ESC guidelines continue to recommend stopping aspirin therapy at least 7 days before surgeries in patients with a high peri-operative bleeding risk (e.g., undergoing complex brain surgeries, spinal surgery or certain neurosurgical operations), have repeatedly reiterated this recommendation over the years [5]. Clinical evidence gathered from observational studies in patients who have had spinal and brain surgery, however, does not support the idea that preoperative long-term aspirin therapy increases the risk of postoperative haemorrhage. Instead, there is growing evidence of its benefits in mitigating postoperative thromboembolic events [6, 7].

Current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumour surgery, cerebrovascular procedures, and spinal surgery, are summarized in this narrative review along with evidence that casts doubt on the need for aspirin interruption in neurosurgical patients. It also discusses options for monitoring the effects of aspirin and the clinical implications of these methods.

Antiplatelet effect of aspirin

Aspirin's antiplatelet effect is achieved by suppressing the synthesis of thromboxane A2 (TXA2) after blocking the activity of cyclooxygenase (COX) within platelets [8]. Aspirin efficiently inhibits this method of platelet activation, and thromboxane A2 is a key player in the amplification of platelet aggregation [9]. Aspirin's antiplatelet effect has several clinically significant features, including its enhanced efficacy at low doses (75–325 mg/d). This effect is due to the lack of concurrent inhibition of prostacyclin in endothelial cells and irreversible COX inhibition, which distinguishes aspirin from other nonsteroidal anti-inflammatory drugs (NSAIDs). The duration of the antiplatelet effect of medications like ibuprofen, ketorolac, etc. correlates with the elimination time because they reversibly compete with the arachidonic acid substrate at the COX active site. Because aspirin irreversibly acetylates platelet COX, its antiplatelet action lasts for several days following a single dose [10]. After a single aspirin intake, the ability to produce TXA2 can only be restored with the generation of new platelets, which are regenerated by around 10% per day. Adenosine diphosphate, collagen, and thrombin are examples of non-TXA2-dependent activators of platelet aggregation that can circumvent the aspirin-dependent mechanism and produce effective coagulation. It makes aspirin a relatively weak antiplatelet agent because it only partially inhibits platelets [8]. Furthermore, up to 25% of patients may not respond to standard aspirin treatment [11].

Aspirin antiplatelet effect assessment

Increased bleeding time is the direct clinical effect of aspirin absorption on primary hemostasis [12]. Major attempts have been made in recent decades to

establish alternative and trustworthy assessments of the antiplatelet effect of aspirin due to the major challenges in standardizing this sort of test. In evaluating the aspirin effect, each of these suggested approaches showed considerable variation and a weak association with one another [13, 14]. More significantly, no trustworthy clinical evidence of any of these tests' predictive validity or association with clinically meaningful outcomes has been found to date [15]. It is important to note, that aspirin-associated hypocoagulation cannot be shown by non-specific viscoelastic tests such as thromboelastography or rotational thromboelastometry, which were created for an integrated evaluation of blood clot formation. This behaviour can also be viewed as the main risk factor for the formation of dense clots in the presence of aspirin [16].

Impact of aspirin on bleeding risk in non-neurosurgical patients

There is limited clinical evidence regarding the continuation or discontinuation of aspirin in surgical patients. However, interactions between aspirin, NSAIDs, and perioperative anticoagulants have raised concerns about the design and outcomes of related clinical trials. [17]. According to current guidelines on perioperative bleeding, "aspirin should not be withdrawn peri-operatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug," [18]. However, as previously said, neurosurgical patients require a distinct and individualized approach to care.

In Brain surgery and aspirin related studies, Rahman et al. [7] concluded that brain tumour surgeries were not associated with an increased haemorrhagic risk with patients who used low-dose aspirin before surgery. McGaul [19], mentioned perioperative aspirin related complications may increase risk in dental surgery but the results of this study cannot directly correlate with neurosurgical procedures outcome. Another case report by Kulikov et al. [20] identified that aspirin was not associated with increased bleeding risk. Another study found that haemorrhagic risk was the same in aspirin or non- aspirin groups [21]. Tonchev N, et al. [22], explained that "In patients with a high cardiovascular and cerebrovascular risk, low-dose ASA can be safely sustained after brain tumour surgery, and its perioperative use has not been linked to an increased rate of haemorrhagic complications after pituitary adenoma surgery". While Ma Y et al. [23] explained that antiplatelet therapy did not increase the risk of haemorrhage and improved outcomes after vascular revascularization procedures. Bianconi et al. [24] described intracranial haemorrhage after intracranial aneurysm clipping was more frequent in those patients who were using antiplatelet therapy. Dasenbrock et al. [25] explained in their study that the use of aspirin was not associated with an increased risk of postoperative haemorrhage in vascular surgery patients. Florez et al. [26] also presented the same finding and clearly explained that aspirin didn't increase the chance of bleeding in the intraoperative or preoperative period.

In spinal surgery patients, Zhang et al. [6] stated that there was no difference in perioperative complications between aspirin continuation and discontinuation. Similarly, Zian et al. [29] and Suk-Bong et al. [30] found that continued aspirin administration did not have an increased risk for bleeding. Meta-analysis ASA (Aspirin)-continuing group ASA-discontinuing group. Cuellar et al. [27] compared three groups—patients who never used aspirin, those who discontinued aspirin preoperatively, and those who continued aspirin therapy—and observed no differences in perioperative complications or clinical outcomes. In another study, Ju et al. [28] concluded that there was no association between low-dose ASA continuations with increased blood loss.

Balancing the risk

The clinical data presented reflect a lack of trustworthy evidence about clinical decision-making regarding the continuation or cessation of aspirin use during the perioperative phase in patients slated for elective neurosurgery procedures.

During surgery, the coagulation process gets triggered, (also known as blood clotting mechanism) which is a crucial mechanism that stops bleeding from incision site or dissection area automatically. The formation of a clot is created by various mechanisms including platelets, plasma proteins and various factors. Due to the involvement of various players in coagulation process, strength of aspirin's anticoagulation effect is unclear.

Variability in clinical practice is caused by inconsistent clinical data [31, 32]. Furthermore, there is inconsistency among the standards on this matter.

Guidelines on perioperative bleeding management from the European Society of Anaesthesiology and Intensive Care, for example, state that "intracranial surgery can be safely performed in the presence of low-dose aspirin." However, if aspirin withdrawal before surgery is taken into consideration, the time from the last medication intake to the intervention is three days. Nonetheless, a longer gap (5 – 7 days) can be taken into consideration for invasive treatments that have a high risk of bleeding [18]. Compared to the ambiguous ESC recommendations recommendation of at least 7 days of withdrawal, this period is substantially shorter [1].

A framework for such decision-making is not precisely defined. However, it is essential that multidisciplinary consultation among neurosurgeons, anaesthesiologists, cardiologists informs the choice to continue or discontinue taking aspirin in a given situation. It may include the estimated risk of blood loss consequences from prolonged bleeding, the risk of postoperative ischemia complications due to aspirin cessation, and the risk of delaying surgery. Non-specific variables including preoperative anaemia, renal dysfunction, chronic liver illness, metabolic disorders, etc., should also be considered when assessing a person's risk of bleeding [18]. Before having surgery, such defects should be fixed, if at all feasible.

It should be considered that the antiplatelet effect of aspirin may exacerbate high estimated blood loss. This is especially crucial in situations when neoplasms—tissues with aberrant vascular wall structure—will require surgical manipulation inside the tissues. For spinal and cerebrovascular surgery, this risk is generally lower.

However, in patients with high cardiac risk (history of myocardial infarction, coronary stenting, unstable angina, etc., which are among the most common indications for chronic aspirin use), the risk of thrombotic complications may exceed the risk of bleeding. In some situations, continuing aspirin therapy might yield better outcomes.

Additionally, treating patients who may suffer major repercussions from a delay in surgical intervention is often necessary in neurosurgical practice (e.g., seizures in patients with intracranial masses, increasing neurologic loss brought on by the mass effect and intracranial haemorrhage from a brain lesion, etc.). The risk-benefit ratio of stopping aspirin in these situations is still unknown. The ESC's suggestion to stop aspirin may understate the dangers and consequences of delaying surgery.

Conclusion

The discontinuation of aspirin before neurosurgical procedures remains a contentious clinical issue. Neurosurgical patients exhibit a wide range of bleeding risks during surgery, necessitating individualized risk assessments.

However, present neurosurgical treatment protocol, for the all preoperative patients, aspirin cessation is currently advised and followed. These protocols encourage doctors to make the same therapeutic choices regardless. Future research should focus on developing evidence-based guidelines to support logical and individualized clinical decision-making in this area.

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Conflict of interest

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Effects of valproic acid on rat C6 glioma cells proliferation and animals survival in the experiment

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Background. Treatment of glioblastoma is an extremely important problem of neuro-oncology. Despite the presence of modern medical and technological developments, there is no significant progress in solving it today. Valproic acid (VPA) is an antiepileptic drug with proven efficacy in epilepsy, and potential oncostatic effects of VPA in the treatment of brain tumors are considered. This study examined the effect of VPA on the growth of rat C6 glioma *in vivo*

Methods. After experimental glioma modeling in rats, valproic acid injections were performed intraperitoneally. Survival of rats was studied according to the Kaplan-Meier curve and tumors were examined histologically. Conclusions about proliferative activity were made based on the determination of the index of Ki67-positive cells

Results. Valproic acid significantly increased the median survival rate of rats with gliomas from 11 to 13 days (p=0,05) and significantly decreased the proliferative activity of glioma cells (3.53±0.96, Me=3.08 vs 2.17±0.38, Me=2.11, p=0,05)

Conclusions. These findings indicate that valproic acid inhibits the growth of glioma cells *in vivo*, which can be considered as a promising tool in the complex therapy of gliomas in clinical practice and is a perspective for further research

Key words: *rat C6 glioma; survival; valproic acid (VPA); proliferation*

Introduction

Glioblastoma is a tumor that originates from glial cells of the central nervous system, characterized by aggressive malignant growth, a high rate of recurrence and high mortality rate of patients [1].

Increasing the survival rates and improving the quality of life for patients with glioblastoma is an extremely urgent problem of neurosurgery, since the average life expectancy of such patients is 14.6 months, and the five-year survival rate in developed countries does not exceed 6.3%. Therefore, scientific research and optimization of both surgical techniques and adjuvant treatment methods remain highly relevant: over the last 25 years the life expectancy of patients has increased with glioblastoma by only 3.3 months [2, 3]. Survival rates are one of the most significant **criterium** in oncology. They are used for the most adequate evaluation of the effectiveness of various treatment methods in clinical studies, evaluation of the medical care organization effectiveness for the population in oncoepidemiological population studies [4] in experimental medical and biomedical research [5]

Kaplan-Meier (KM) **survival analysis** is a non-parametric estimate of the survival function that is commonly used to describe the survival of a study population and to compare two study populations [6]. This indicator is a reliable and convenient tool for comparing the life expectancy of patients (or experimental animals) when investigating new treatment methods compared to a control group (standard treatment). Thus, by comparing two or more survival curves, you can get a visual conclusion about the effectiveness of experimental treatment. The essence of such a comparison is to test null hypothesis - the assumption that survival in the two groups does not differ and the studied factor (treatment method) does not affect the studied value (survival rates). If there is a significant difference in the survival of the two studied groups, null hypothesis is rejected, which will indicate the effectiveness of a new or experimental method of treatment [7].

Animal models of tumors are valuable for studying the biological features of tumors and identifying agents with a potential oncostatic effect. The C6 glioma cell line was isolated from Wistar-Furthi rats, and is of astrocytic origin is both a well-characterized and most widely used glioma model, given its high malignancy and aggressiveness [5]. Rat glioma cells express a similar profile of human glioma markers (PDGFβ, IGF-1, EGFR,

Erb3/Her3) [8]. C6 glioma is a model of glioma cell proliferation and migration and is used to evaluate the potential antitumor growth of new drugs [5, 8].

The use of antiepileptic drugs in clinical practice (in the complex therapy of gliomas) is natural, since the frequency of symptomatic epilepsy can reach 100%, and in particular in glioblastoma - up to 60% [9]. Valproic acid, an antiepileptic drug from the valproate group, is primarily indicated for various forms of epilepsy, migraine management, bipolar disorders, etc. It also exhibits antipsychotic effects [10] and acts as a radiosensitizer in glioma treatment [11]. The realization of the clinical effects of VPA is carried out through its various mechanisms: blockade of sodium and calcium channels of cell membranes, as well as an increase in the concentration of GABA in brain tissues [12]. The oncostatic effect of VPA has been described in many types of tumors: gastric and breast cancers, etc., research data is still ongoing [13, 14], and is relatively new. Regarding glioblastoma, this effect of VPA has been known since the early 2000s, when the effect of histone deacetylase inhibition was discovered, which led to a decrease in mitotic activity in tumor cells and, as a result, to a decrease in its progression [6, 15, 16]. Data from experimental studies *in vivo* and *in vitro* on inhibition of glioblastoma growth under the influence of VPA show encouraging results [17, 18, 19], but the results of clinical use are quite contradictory and ambiguous: it is reported about a positive experience of using VPA in glioblastomas and anaplastic astrocytomas [11, 10], especially in children and young people, while it is completely ineffective for neuro-oncology patients [20].

Thus, the search for new treatment methods and the potential effect of VPA on glioma remains relevant. In this study we focused on investigating the effects of valproic acid on survival of laboratory animals using the well-characterized rat brain C6 glioma cell line, aiming to establish the potential impact of valproic acid on the proliferative activity of glioma cells *in vivo.*

Aim of the study: To determine the effect of valproic acid on the proliferative activity of C6 rat glioma cells based on the analysis of Ki67 indicators and the survival of animals with glioma. To determine the prospects and feasibility of further studies of the oncostatic effect of VPA in the treatment of glial tumors, based on the results of this experiment and literature data.

Materials and methods

C6 glioma model

White outbred male rats weighing 100±25 g, with an average age of 2 months, were selected for the study. The animals were kept in the vivarium under the conditions of a natural circadian light cycle. They were fed a combined balanced diet *ad libitum* and with free access to water. The control group was 10 animals and the experimental group was 14 animals. To transplant glioma cells from a sick animal, a tumor was removed from which a cell suspension was prepared. After counting the cells in the Horyaev chamber, all animals were implanted with C6 rat glioma cells (2×10^6 cells in 0.1 ml) in the right temporal area to a depth of 4 mm, as described [21].

This study was conducted in strict accordance with the recommendations of the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. The research protocol with animal experimentation was approved by the Scientific Ethics Committee (Protocol Number: 17/2022). All surgery was performed under general anesthesia and every effort was made to minimize suffering. The study was conducted on two groups of animals with glioma modeling: 1 – control; 2 - experimental, which was given VPA treatment.

Surgical procedure

Manipulations with animals were carried out under general anesthesia - intraperitoneal injection of thiopental sodium 50-60 mg/kg of animal weight. The injection site was previously disinfected with a 5% iodine solution.

All surgical procedures were carried out using sterile instruments in operation room. Prior to surgery, animals were fixed in stereotactic device. Skull operative area, was decontaminated by betadine solution with a cotton swab. Coronal suture was exposed through midline scalp incision. Cranial burrhole was made 4 mm to the right of midline and 1 mm anterior to the coronal suture by a mini-drill. A 26-gauge stainless steel guide cannula was stereotactically implanted through this hole to a depth of 4 mm and the suspension of C6 rat glioma cells was injected (2×10^6 cells in 0.1 ml) in the right temporal area. The skin was closed using 7–0 (ETICON) atraumatic sutures.

The animals were observed daily and their lifespan was recorded. On the 5th day, one animal in the control group and on the 6th day one animal in the experimental group dropped out due to death, neither death was related to the tumor; in addition, on the 10th day, 6 animals were removed from both groups to study and compare the morphological features of the tumor. These animals were not taken into account in the calculation of survival rates due to identical elimination dynamics in the groups. Thus, the number of animals in the control and experimental groups was 10 and 14, respectively ***(see Table 1)***.

The preparation of valproic acid in the form of a solution of 100 mg/ml was administered intraperitoneally at a dose of 300 mg/kg of the animal's body once daily throughout the experiment. This dose was selected based on its safety profile and its lack of undesirable biological reactions [22]. Animals were removed from the experiment by injecting a lethal dose of sodium thiopental intraperitoneally.

Table 1. Number of animals

Group	Animals, N
Control	10
Experimental	14
Overall	24

This article contains some figures that are displayed in color online but in black and white in the print edition

Histological examination

At 10th day of experiment, rat brains were fixed in a 10% formalin solution (pH 7.4, 4°C, 24 hours). Tumors were isolated from each brain, dehydrated in isopropanol and sealed in paraplast (Leica Surgipath Paraplast Regular). Sections with a thickness of 4 μm were obtained on a Thermo Microm HM 360 microtome. Sections after deparaffinization were stained with Sirius Red and Weigert's hematoxylin, hematoxylon and eosin to study tumor morphology. Proliferative activity was assessed by immunohistochemical method based on the analysis of immunopositive reactions to Ki67. (https://www.abcam.com/en-us/products/primary-antibodies/ki67-antibody-sp6-ab16667#tab=datasheet) A monoclonal antibody against Ki67 (Abcam, USA, Cat.number: ab 16667) was used. Primary antibodies were used at a dilution of 1:200. Reaction products were visualized using a diaminobenzidine-based detection system (EnVision FLEX; Dako, Glostrup, Denmark). Sections were incubated with antibodies at a temperature of +24°C (with primary and secondary antibodies for 20 and 10 min, respectively). Cell nuclei were stained with hematoxylin Gill I. The obtained micropreparations were examined in an Olympus BX51 microscope, magnification ×200, ×400. Proliferative activity was evaluated as the relative number of Ki67-positive cells in 10 fields of view for each tumor sample, as the number of Ki67 positive cells to the total number of cells in the region of interest.

Statistical analysis

Data processing was carried out using the statistical software package Statistica 10.0 (StatSoft Inc., USA). Survival rates were standardized, entered into the database and subjected to statistical processing using descriptive and non-parametric statistical methods. Survival analysis was performed using the Kaplan-Meier method. Pearson's χ2 test was used to determine the difference between the survival of animals in the study and control groups. When comparing survival in different groups, the risk ratio with a 95% confidence interval (CI) was used. The Mann-Whitney test was used to analyze the difference in the values of proliferative activity between groups. The results were considered statistically significant provided that the level of statistical significance (p) was <0.05. Spearman correlation coefficient was used to analyze the correlation between Ki-67 index and tumor mass. The results are given in the discussion.

Results

Survival analysis

In the control group, one animal died on the 6th day, two animals on the 8th day, three animals on the 11th day, and four animals on the 12th day. In the experimental group: on the 7th day – one animal, on the 8th day – three animals, on the 9th day – two animals, on the 13th day – one animal, on the 20th day – four animals, on the 21st day – one animal and on the 22nd day – two animals. Generalized data are shown in ***Fig. 1***. The results of statistical processing of the given data with survival rates are shown in ***Table 2***.

Thus, the median survival in the control group was 11 days, in the experimental group 13 days, which is demonstrated by the Kaplan-Meier curves in ***Fig. 1***.

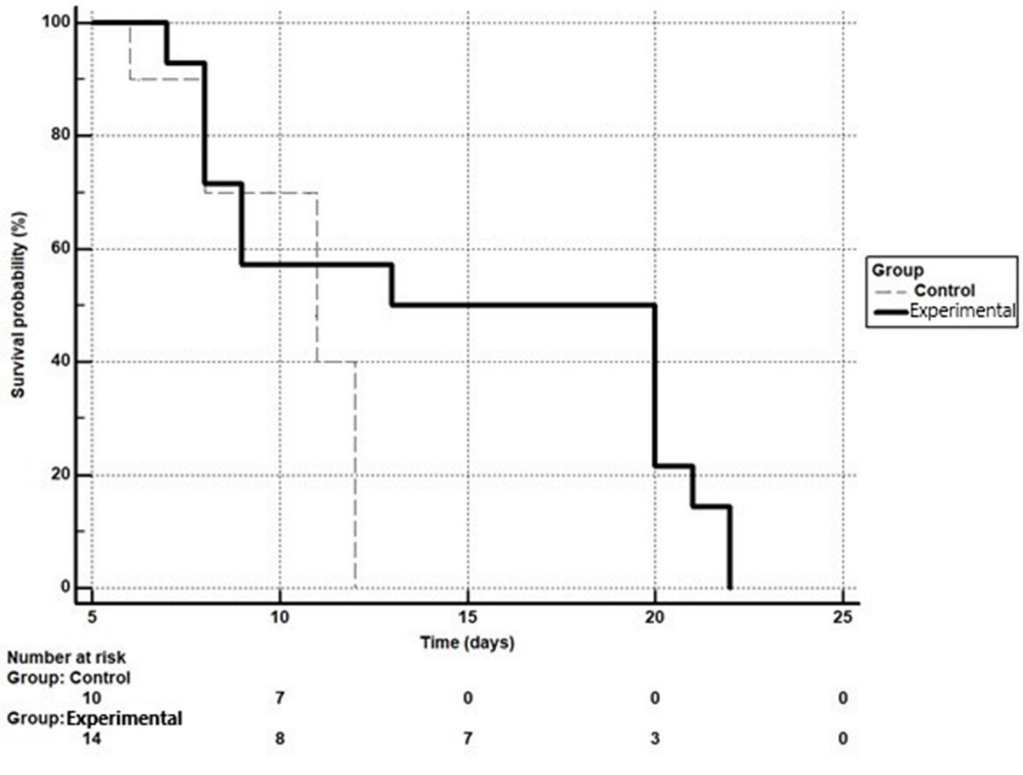

Fig. 1. Kaplan-Meier curve of survival of rats of the control and experimental groups. The difference between groups according to chi-square results is statistically significant (p=0.04)

Table 2. Survival rate of animals

Group	Mean survival (days)	SE	Confidence interval for the mean 95%	Median survival (days)	Confidence interval for the median 95%
Control	**10,300**	0,684	8,959 to 11,641	11,000	8,000 to 12,000
Experimental	**14,786**	1,691	11,472 to 18,100	13,000	8,000 to 20,000

For the experimental group versus the control group: hazard ratio (HR)=0.51 (0.21-1.26), p=0.0448 – relative risk reduced by 49%. It is defined as (1-0.51)*100. For the control group versus the experimental group: HR=1.96 (0.79-4.84), p=0.0448 – relative risk increased by 1.96 times.

The risk of death in the control group compared to the experimental group is 1.96 times higher (HR=1.96), but the risk of death in the experimental group compared to the control group is reduced by 49% (HR=0.51).

Tumor morphology

10 days after implantation of C6 glioma cells into the brain of rats, intracerebral tumors were detected. The tumors had a small volume and clear borders. This proved that the glioma model was successfully reproduced. The average weight of tumors was 254.1 ± 38.67 mg in the control group and 308.3 ± 55.8 in the experimental group (p>0.05). Glioma tissues in both the control and experimental groups were characterized by moderate nuclear atypia (nuclear pleomorphism) and not high mitotic activity. It was also found that a certain proportion of tumor cells in both groups had cytoplasmic vacuolation; this feature was slightly more prevalent in the experimental group. According to the results of staining with hematoxylin and eosin, Sirius Red, tumors grew intracerebral, glioma cells occasionally extended into the dura mater which is rich in collagen. The peripheral zone of the tumors had less vascularization than in the central part of the tumor. Areas of sparse necrosis were observed in the central part of the tumor contained only single Ki67-positive cells ***(Fig. 2)***. The Ki67 index in the control group was 3.5%, and in the experimental group it was 2.1% ***(Fig. 3, Table 4)***. According to the results of the assessment of the one-sided Mann-Whitney test, the difference was probable at p=0.01, and for two-sided p=0.02. Thus, the study results revealed a slight but statistically significant difference between the values of the proliferative activity index in the comparison groups. At the same time, a negative correlation was found between the mass of tumors and the average value of the proliferative index in the general sample of the experiment (r=-0.61, p=0.04), while for the control and experimental groups, the correlation analysis did not show a probable dependence (r =-0.71, p=0.11 vs r=-0.49, p=0.33)

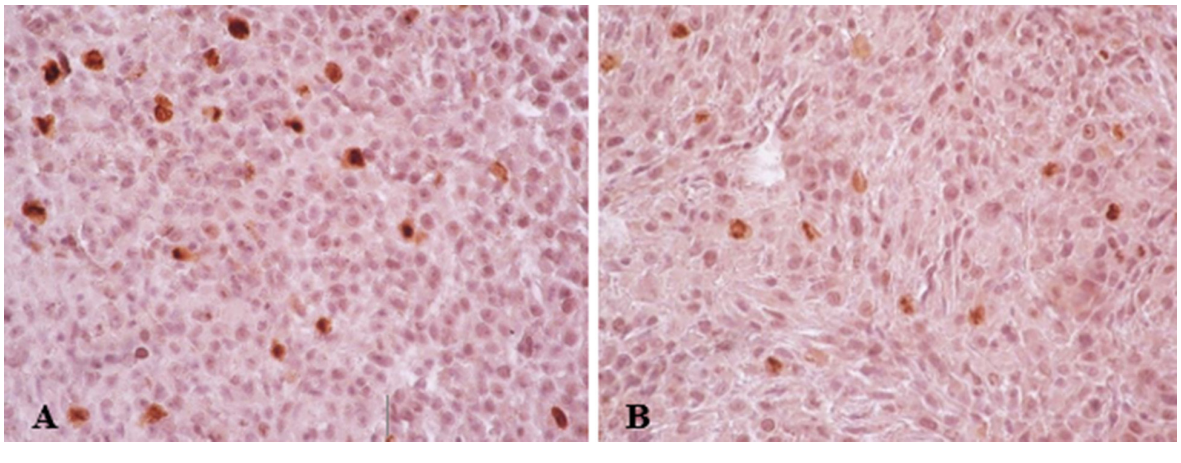

Fig. 2. Micrographs of C6 glioma tumor tissues, Ki67-positive cells (brown). Control group (A) and the experimental group with valproic acid (B). Immunohistochemical detection of Ki67. Rev. 40, approx. 10

Table 3. Hazard ratios of survival with 95% confidence interval

Group	Hazard ratio of survival (HR) and 95%CI
Experimental vs Control	0,51 (0,21 to 1,26)
Control vs Experimental	1,96 (0,79 to 4,84)

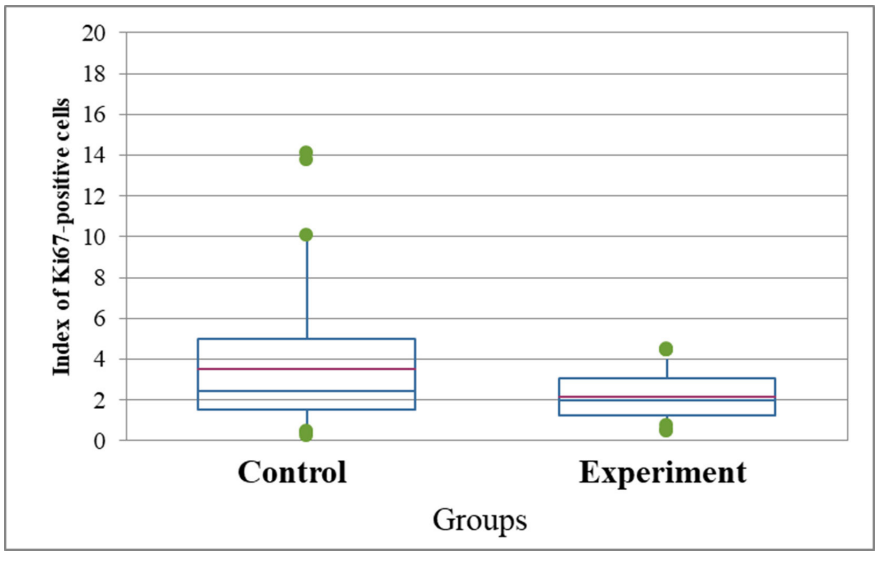

Fig. 3. Index of Ki67-positive C6 cells in glioma tumors according to the results of Ki67 immunohistochemical detection (%). For the one-sided Mann-Whitney test p=0.01, for two-sided p=0.02

Table 4. Index of Ki67-positive C6 cells in tumor tissues of control and experimental groups of rats on day 10 (n=24)

Group	Mean	SEM	Minimum	Q1	Median	Q3	Maximum
Control	3,53	0,96	1,29	1,45	3,08	5,51	6,48
Experimental	2,17	0,38	1,11	1,42	2,11	3,03	3,18

Notes. Mean - arithmetic mean value of the data in the group; Median - the average value from the main data array in the group; Q1 and Q3 are the interquartile range in the data set. All these indicators are used when conducting data analysis using the Mann-Whitney method, when the samples in both groups differ from the Gaussian distribution, making parametric methods inapplicable.

Discussion

The rat C6 glioma model is widely used as an animal model in human glioblastoma research because it is similar in terms of growth and biological behavior to malignant brain gliomas [5, 23].

The results of *in vivo* research on the C6 glioma model in rats indicate a significant difference in both survival rates and **proliferative** activity (Ki67) **in glioma-bearing rats without treatment comparing to glioma-bearing rats with VPA treatment**, which correlates with literature data on this issue. In our opinion, a certain paradoxical situation has arisen regarding the effectiveness of VPA in the treatment of glial tumors: on the one hand, experimental data both *in vitro* and *in vivo* (and our own experience) convincingly testify to the oncostatic effect of valproic acid on glial tumors; on the other hand, there is no convincing clinical data on such effectiveness. This raises the question of prospects and possible directions of further research: possible ways to overcome the obvious difference between experimental data and clinical results can be implemented as follows:

1) increasing the dose of VPA to the maximum possible **level** for each specific patient [23] while exploring strategies to mitigate its toxic effect of VPA on the patient's body; for example, the use of various carbon nanomaterials (nanotubes, fullerenes, etc.) is promising for reducing toxicity [24];

2) combination with other medicinal products to potentiate their effect; for example, taking VPA in combination with temozolomide increased the median survival of patients with glioblastoma by 8 weeks, compared with the group where patients received temozlomide montherapy [10, 22];

3) combination with other treatment methods, such as radiosurgery, radiochemotherapy and others [25, 11];

4) development of VPA-based drugs: separate experimental studies demonstrate that various VPA derivatives have different anticonvulsant, antitumor and histone deacetylase inhibition properties compared to VPA itself [26, 27, 28];

5) advancing drug delivery methods to target cells, for example, the use of nanoparticles containing an oncostatic agent (doxorubicin) has demonstrated a 40% cure rate in laboratory animals [29].

Another unsolved question that arises from the results of this work is the absence of a positive correlation between tumor mass and Ki67 as an indicator of proliferative activity of tumor C6 cells. In other studies in the C6 rat model, such a strong relationship was demonstrated between Ki67 values and mean tumor size measured by spectral CT [30] and studying the mechanisms of tumor cell death.

This issue requires further analysis and research by other methods, in particular, the detection of cellular markers of cell death.

Therefore, further studies of the VPA action in neuro-oncology are essential. Evaluating the impact of VPA on malignant cells suggests several possible mechanisms for its oncostatic action: a direct effect on the mitotic cycle by inhibiting histone deacetylase and an indirect one - through the inhibition of angiogenesis, activation of aging mechanisms and death of tumor cells. Cell death is typically caused by apoptosis or necrosis. However, an alternative scenario may occur - autophagy. It is already known that VPA is able to initiate a moderate apoptotic response by preferential activation of the mitochondrial pathway in cancer cells [31] and induce cell death through the autophagy pathway [32]. Microscopic differences in autophagy in cells include the detection of large vacuoles in the cytoplasm and specifically in the presence of VPA. In our study, vacuolization was not quantified as the primary focus was mainly aimed at an integral assessment of the oncostatic effect - that is, overall survival. However, the weak signs of vacuoles in the cytoplasm of cells in the VPA group suggests that autophagic cell death induced by VPA may be involved in the tumor growth inhibition. VPA was also found to disrupt blood vessel formation by reducing eNOS expression [33]. In general, given the diversity of VPA effects on biological systems, at the level of macromolecules, cells, tumor tissue, and the organism as a whole, the molecular mechanisms of the oncostatic action of VPA require further research.

Conclusions

1. A significant increase in survival rates and median survival was revealed under the influence of VPA in C6 rat glioma models (Mean control 10,3 vs Mean VPA 14,8; Median control 11,0 vs Median VPA 13,0, days). It is noteworthy that the maximum life expectancy in the study group was 22 days, while in the control group it did not exceed 12 days

2. The Ki-67 proliferative index in the group where the VPA drug was used is significantly lower compared to the control group (2.17±0.38, Median=2.11 vs 3.53±0.96, Median=3, 08)

3. Further studies of the oncostatic effect of VPA on glial tumors should be considered promising

Disclosure

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Conflicts of interest/Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Availability of data and material

Not applicable

Code availability

Not applicable

Ethics approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. The work was approved by the Bioethics Committee No. 43 dated 04.24.23

Consent to participate

Not applicable

Consent for publication

Not applicable

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Aseptic Vertebral Body Necrosis in Unstable Traumatic Injuries of the Thoracolumbar Spine

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Instability from traumatic spinal injuries is a major indication for urgent stabilizing surgery to prevent adverse consequences of pathological mobility in the injured spinal segment. However, the staged evacuation of injured individuals from active combat zones and the need for urgent life-saving interventions often delay stabilization, leading to an increase in cases of delayed stabilization for unstable spinal injuries. Clinical analysis of such cases has revealed specific features that are underrepresented in the literature. One of these is post-traumatic aseptic necrosis in unstable injuries, which differs in several respects from Kummel disease and requires detailed characterization.

Objective: To characterize and conduct a preliminary analysis of clinical cases of post-traumatic aseptic necrosis of the vertebral body in unstable thoracolumbar spinal injuries.

Materials and Methods: A retrospective analysis was conducted on a patient database of those receiving inpatient treatment at the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine, between 2021 and 2024, as well as patients consulted in Kyiv healthcare institutions, either in person or via telemedicine. The primary inclusion criterion was a verified unstable traumatic injury of the thoracolumbar spine, where surgical stabilization was not performed within two weeks post-injury.

Results: Nineteen cases of delayed stabilization for unstable thoracolumbar injuries were identified through medical documentation and imaging data. Six (31.6%) of these cases exhibited signs of aseptic post-traumatic vertebral necrosis. Clinical examples of patients with and without developed spondylonecrosis are presented. The groups were compared based on demographic and trauma-specific characteristics; however, statistically significant predictors for spondylonecrosis development were not identified. Additionally, the presence of chronic septic processes was not found to contribute to this phenomenon. Follow-up data indicated that delayed stabilization contributed to halting bone tissue lysis. Relevant literature on spondylonecrosis and a cascade of pathological processes potentially leading to this condition are discussed.

Conclusions: This publication is among the first to describe post-traumatic aseptic vertebral body necrosis in unstable thoracolumbar spinal injuries. The data and proposed pathogenic mechanisms emphasize the importance of early stabilization for unstable injuries from both neurological and orthopedic perspectives.

Keywords: *thoracolumbar spine; traumatic injury; instability; aseptic vertebral body necrosis; delayed stabilization*

Introduction

The stability of traumatic spinal injury is one of the fundamental criteria determining not only the general strategy and individualized tactics of patient management but also, in some cases, the prognosis for the restoration of functional activity. According to the classic concept proposed by M. Panjabi et al., spinal stability refers to the spine's ability, under physiological loads, to maintain intervertebral relationships that prevent both initial injury and subsequent irritation of the spinal cord or nerve roots, as well as the development of deformity or pain [1].

Spinal stability relies on the interaction of three systems: the passive system (comprising bony structures, intervertebral discs, and ligamentous apparatus, which mechanically limit mobility), the

active system (the muscular corset, which provides dynamic stabilization), and the control system (the nervous system, which regulates and coordinates activity to maintain stability). Disruption of one (as in neurologically uncomplicated trauma) or several (in cases with neurological impairments) of these systems leads to functional spinal instability [2].

The zones of functional activity within the spinal motion segment (SMS) are an objective criterion in classical spinal biomechanics that define a specific injury. The neutral zone is characterized by the range of motion where the SMS experiences minimal resistance from passive structures, with minimal load on stabilizing elements. The elastic zone lies beyond the neutral zone, where resistance from passive structures increases, and the SMS begins to encounter significant resistance to limit overmobility. The overload zone is defined by the failure of compensatory mechanisms, leading to primary (describing the immediate trauma mechanism) or secondary (describing an already injured SMS) damage to both osteo-ligamentous and neural structures [3, 4].

This brief description of the mechanics of an injured SMS indicates that the concept of stability or instability is, to some extent, relative. Most often, an injured SMS, in the absence of mechanical load, remains in a state of relative stability. The transition from an expanded neutral zone through a shortened elastic zone to the overload zone depends on the intensity of the applied force [5]. In some cases, the mechanical integrity of the injured SMS is sufficient to maintain an upright posture but inadequate to perform everyday functional activities [6, 7].

The term "conditionally unstable injuries," previously widely used to describe such conditions, has been removed from clinical practice, complicating the description of functional impairments in these patients [2].

Spinal instability is a primary indication for stabilization surgery, aimed at mitigating the adverse effects of instability. These include preventing the onset or progression of neurological deficits, creating optimal conditions for resolving neurological dysfunction when present due to trauma, halting the progression of deformities through structural support provided by implants, facilitating consolidation, reducing pain intensity, and consequently improving the quality of life for patients while enabling more effective rehabilitation [8]. Evidently, the timing of surgical correction for unstable spinal injuries is largely determined by the risk of neurological deterioration, and to a lesser extent, orthopedic complications [9]. Notably, 15% of neurological deficits in spinal trauma cases do not manifest immediately but develop later, likely due to instability [10]. The progression of the deformity increases the extent of intraoperative correction required, which in turn complicates and prolongs the surgical procedure.

The escalation of the Russian Federation's aggression against Ukraine into active hostilities in 2022 led to a significant rise in injuries among both military personnel and civilians. This increase included a notable rise in spinal trauma cases, predominantly closed injuries, reflecting the nature of combat operations. A similar trend was observed in other conflicts, such as in Iraq and Afghanistan, where the primary causes of injuries were blast waves and mechanical forces [11, 12].

Modern protective gear, such as body armor and helmets, significantly reduces the risk of penetrating wounds but does not fully protect against closed injuries caused by blast waves, severe mechanical impacts, or falls [13]. The use of high-powered ammunition in contemporary armed conflicts generates shock waves that can cause severe spinal injuries upon impact. Additionally, these blast waves are often accompanied by extensive structural collapse, resulting in secondary injuries from falling debris [14].

The significant strain on the healthcare system, the staged process of medical evacuation, and the large number of polytrauma patients have led to an increase in delayed stabilization of unstable spinal injuries. This approach primarily applies to neurologically intact patients, where dynamic observation minimizes the risk of dysfunction, or to patients presenting with complete spinal cord injury. Such a strategy is a necessity under wartime conditions and is not typically employed in peacetime. The analysis of clinical cases involving delayed stabilization of unstable spinal injuries has revealed aspects that are underrepresented in the literature. One of these is post-traumatic aseptic necrosis of an unstable injury, which is the focus of this article. The only previously documented form of post-traumatic aseptic necrosis of the vertebral body (ANVB) is Kummell's disease, described by the German surgeon in 1891 [15]. However, the cases we have documented demonstrate fundamental (in totality of features) differences from Kummell's disease requiring a detailed description and analysis.

Objective: To characterize and conduct a preliminary analysis of clinical cases of aseptic post-traumatic vertebral body necrosis in unstable thoracolumbar spinal injuries.

Materials and Methods:

Study Design: retrospective observational study.

A retrospective analysis was conducted on a patient database from the Romodanov Institute of Neurosurgery, National Academy of Medical Sciences of Ukraine, covering the period from 2021 to 2024. This included patients who received inpatient care or were consulted either in person or via telemedicine at healthcare institutions in Kyiv, to identify cases of the specified pathology.

Inclusion Criteria:

- Presence of a verified unstable traumatic injury of the thoracolumbar spine, with no surgical correction performed within 2 weeks post-injury.
- Availability of high-quality computed tomography (CT) scans taken within the first 3 days post-injury and follow-up scans obtained 2 weeks or later.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Exclusion Criteria:

- Presence of penetrating spinal injuries and/or bullet or shrapnel injuries in the paravertebral region, regardless of fracture zone.

- Clinical and/or laboratory signs of septic spondylitis/spondylodiscitis.

- History of spinal trauma of any severity and/or prior spinal surgeries.

The analyzed variables included gender, age, and the mechanism of injury. Neurological deficits were assessed using the American Spinal Injury Association (ASIA) criteria [16]. The injury pattern was evaluated using the AOSpine Thoracolumbar Spine Injury Classification System (TLSICS) [17], while injury severity was graded according to the Thoracolumbar Injury Classification and Severity Score (TLICS) [18]. Imaging data, including spondylography, magnetic resonance imaging (MRI), and spiral computed tomography (CT), were analyzed using the RadiAnt DICOM Viewer software (Medixant, Poland, Version 2023.1, License No. 1860F047).

Statistical Analysis

Data processing was performed using R (version 4.0.5, R Foundation for Statistical Computing) in the RStudio development environment (version 1.4.1106).

Results

The available medical records were analyzed, as well as the results of examinations of the affected individuals provided for remote consultation. Nineteen clinical cases meeting the inclusion criteria were identified ***(Table 1)***. Post-traumatic ANVB phenomena were verified in 6 (31.58%) of the affected individuals. Several clinical cases are presented as examples.

Table 1. Brief Characteristics of Patients

Parameter	Value
Sex:	
male	12 (63,16%)
female	7 (36,84%)
Age, years:	
median (95% confidence interval)	40 (24–48)
range	18–61
Injury circumstances:	
road traffic accident	5 (26,32%)
fall from height	8 (42,11%)
fall on a flat surface	6 (31,58%)
Injury level:	
thoracic	5 (26,32%)
thoracolumbar junction	9 (47,37%)
lumbar	5 (26,32%)
Type of injury (AOSpine):	
B2	9 (47,37%)
B3	1 (5,26%)
C	9 (47,37%)
Neurological deficit (ASIA):	
A	12 (63,16%)
B	3 (15,79%)
E	4 (21,05%)
TLICS, points	
5	3 (15,79%)
6	2 (10,53%)
7	3 (15,79%)
8	9 (47,37%)
9	3 (15,79%)

Clinical case No.1

Patient N., a 50-year-old military serviceman, sustained injuries as a result of a road traffic accident (RTA) while driving. During initial hospitalisation at a military hospital, CT scans of the cervical, thoracic, and lumbar spine were performed. Diagnosed injuries included an incomplete burst fracture of the vertebral body and a comminuted fracture of the vertebral arch at Th3 (type B2), a compression fracture of Th4 (type A1), and a fracture of the spinous process of Th2 ***(Fig. 1A)***. The neurological status of the patient corresponded to ASIA E. Given the preserved neurological functions and certain technical challenges associated with performing stabilisation surgery, the patient was evacuated in stages and subsequently admitted to the Romodanov Institute of Neurosurgery, NAMS of Ukraine. CT scans conducted at each hospital allowed monitoring of the dynamic changes in the bony structures at the injury site. Two weeks post-injury ***(Fig. 1B)***, initial signs of lysis in the anterior sections of the Th3 vertebral body and erosion of the Th4 vertebral endplate were observed.

After one month ***(Fig. 1C)***, the anterior half of the Th3 vertebral body was fragmented into separate bone pieces, and pathological changes extended to the posterior part of the body. Negative changes were also noted in the Th4 vertebral body, though these were less pronounced.An analysis of the provided medical documentation revealed that C-reactive protein (CRP) levels post-injury did not exceed 4.8 mg/L, and peripheral blood leukocytes remained at 7.6×10^{12}/L, ruling out a septic nature for the observed changes [19–21].

Clinical case No.2

Patient T., a 41-year-old military serviceman, sustained injuries due to a fall on a flat surface caused by a blast wave, accompanied by a brief loss of consciousness. During the initial examination at the hospital, lower paraplegia and anesthesia of all types of sensation below the Th12–L1 level were detected. On the day of hospitalisation, a brain CT scan was performed, resulting in resection craniotomy and removal of an acute subdural hematoma in the left parietal region.

On the second day post-injury, CT scans of the cervical, thoracic, and lumbar spine were conducted. Diagnosed injuries included a compression fracture of the L1 vertebral body, fractures of the superior facet joints of L1, and the inferior facet joints of Th12, with the fracture line extending to the spinous process of Th12. Significant compression of spinal canal structures was identified due to anterolisthesis of the Th12 vertebral body, with an 11 mm forward displacement, corresponding to type C injuries ***(Fig. 2A)***.

On the seventh day of hospitalization, decompressive-stabilization surgery was planned but was not performed due to acute cardiac dysfunction during anesthetic management. The patient remained in the intensive care and resuscitation unit and later in the trauma department. After 1.5 months post-injury, the patient demonstrated recovery of proprioceptive elements in the lower limbs.

At the request of the patient's relatives, he was transferred to the Romodanov Institute of Neurosurgery, NAMS of Ukraine, for surgical intervention. During preparation for the transfer, a follow-up CT scan of the thoracolumbar spine was performed at the hospital, revealing significant lysis of the anterior two-thirds of the L1 vertebral body ***(Fig. 2B)***. Upon admission to the Romodanov Institute of Neurosurgery (2 months post-injury), a CT scan revealed almost complete lysis of the L1 vertebral body: the anterior sections were not visualized, and the posterior sections consisted of isolated bone fragments. Additionally, the process extended to the endplates of the adjacent vertebrae, Th11 and L2. At the time of admission, the leukocyte count was 8.8×10^{9}/L, and the C-reactive protein (CRP) level was 3.1 mg/L. Bacteriological analysis of intraoperatively obtained samples (three specimens from the lysis zone of the L1 vertebral body) showed no microbial growth.

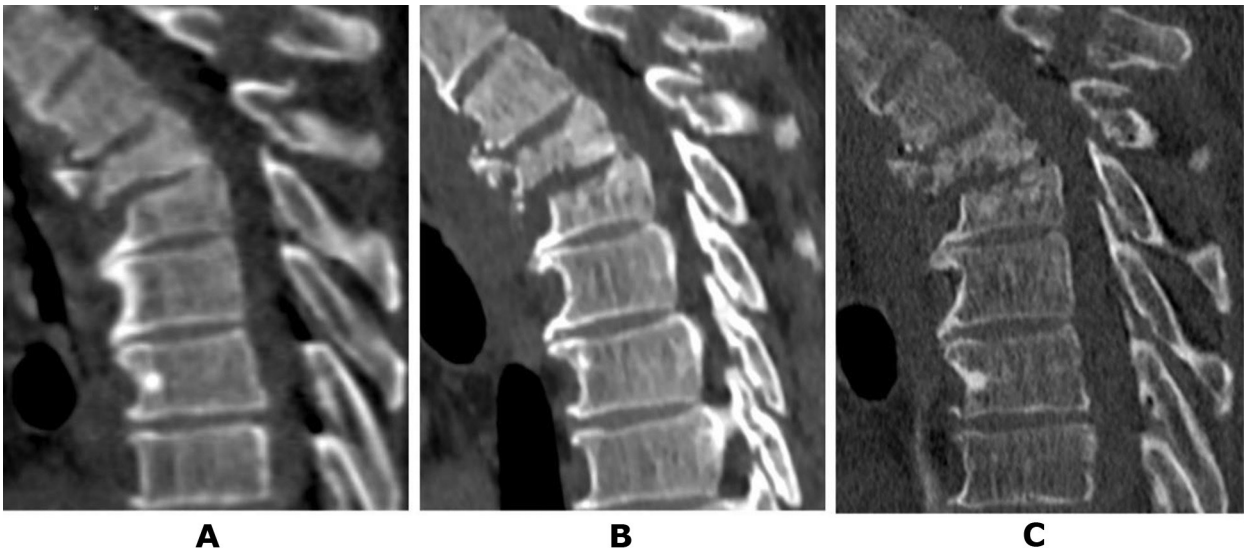

Fig. 1. Patient N., 50 years old. CT scans of the thoracic spine: A – on the day of the injury; B – after 2 weeks; C – after 1 month (details in the text)

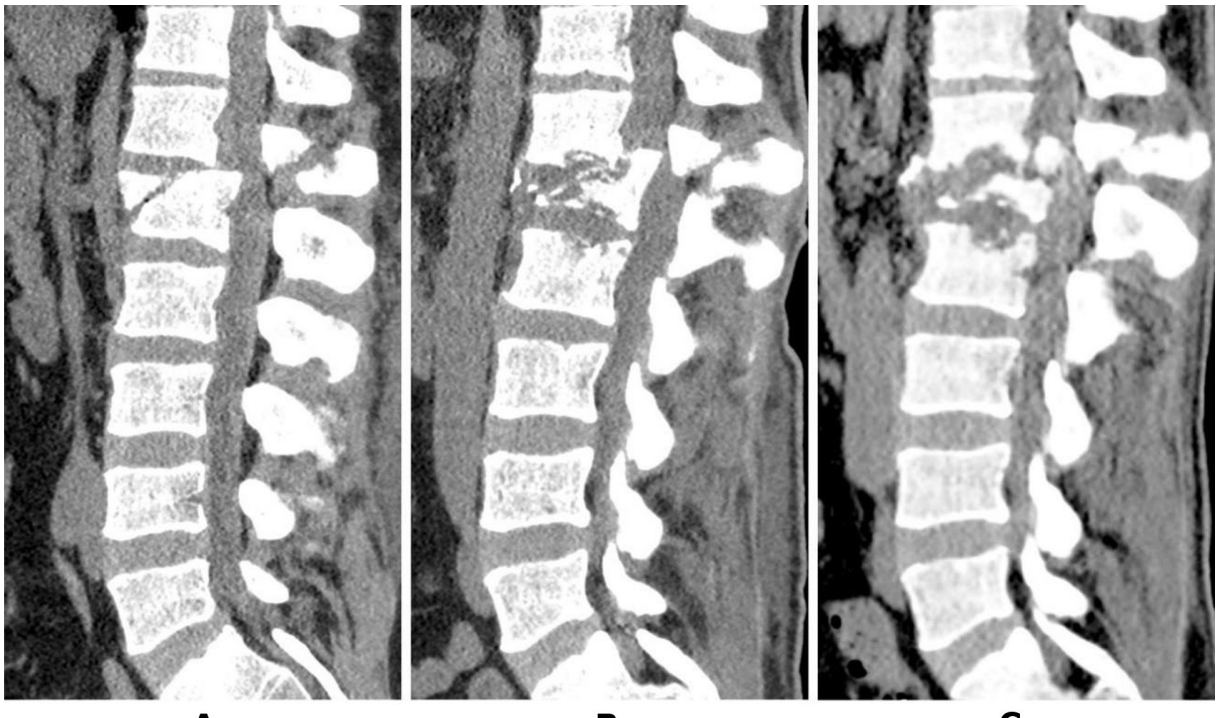

Fig. 2. Patient T., 41 years old. CT scans of the lumbar spine: A – the day after the injury; B – after 1.5 months; C – after 2 months post-injury (details in the text)

An analysis of the available clinical material did not support radiologically established instability as the primary predictor of aseptic spondylolysis. As an example, we present two cases where this pathology was not observed despite significant bone-destructive changes.

Clinical case No.3

Patient P., a 37-year-old woman, was injured in a road traffic accident as a passenger. Upon hospitalisation at a central district hospital, CT scans were performed, revealing a fracture of the Th7 vertebral body with significant destruction and fragment displacement into the spinal canal, as well as fractures of the arches and spinous processes of Th6 and Th7 vertebrae ***(Fig. 3A)***. Additionally, multiple rib fractures and hemopneumothorax were diagnosed. The neurological status was classified as ASIA A.

The patient remained in the intensive care unit for 3 weeks, followed by 2 weeks in the trauma department after stabilization of vital functions. She was then transferred to the Romodanov Institute of Neurosurgery, NAMS of Ukraine, for surgical treatment. At the time of transfer, the level of neurological deficit remained ASIA A. A CT scan performed during hospitalisation revealed progression of the deformity ***(Fig. 3B)***. The patient also presented with a sacral pressure ulcer measuring up to 10 cm (grade 2, proliferative stage). The leukocytosis count at the time of admission was 10.8 × 10^9/L.

Clinical Case No. 4

Patient V., a 58-year-old woman, was injured in a road traffic accident as a pedestrian. She was hospitalised in the local trauma department and diagnosed with fractures of both femurs and the right tibia. Neurological status at admission corresponded to ASIA E. Skeletal traction was applied. Due to complaints of back pain on the day following the injury, a CT scan of the thoracic spine was performed, revealing a distraction fracture in the Th7-Th8 segment against the background of localized thoracic ossification of the anterior longitudinal ligament ***(Fig. 3C)***. Given the minor displacement, preserved neurological functions, and the anticipated prolonged immobilisation period, stabilisation of the injury was not performed. The patient remained in the trauma department for 2 months and reported gradual reduction in back and lower limb pain. However, a scheduled neurological examination confirmed lower paraplegia and anesthesia at the Th8 level. She was transferred to the Romodanov Institute of Neurosurgery, NAMS of Ukraine, for surgical treatment. At the time of hospitalisation, CT scans showed no significant negative radiological changes compared to previous findings. Neurological status corresponded to ASIA A. Examination revealed a large sacral pressure ulcer exceeding 20 cm in diameter (grade 4 with necrotic areas). Peripheral blood leukocyte count at admission was 16.3 × 10^9/L.

These clinical cases clearly demonstrate that the presence of chronic septic processes in patients is not a predictive factor for the development of post-traumatic ANVB. Furthermore, a retrospective analysis of medical records did not identify potential predictors for this pathological condition. ***Table 2*** provides a comparative characterization of the group of patients with post-traumatic ANVB and the comparison group in which such changes were not observed despite unstable injuries.

It is noteworthy that stabilization surgery in all patients with post-traumatic necrosis associated with unstable spinal injuries completely prevented further progression of destructive processes. None of the

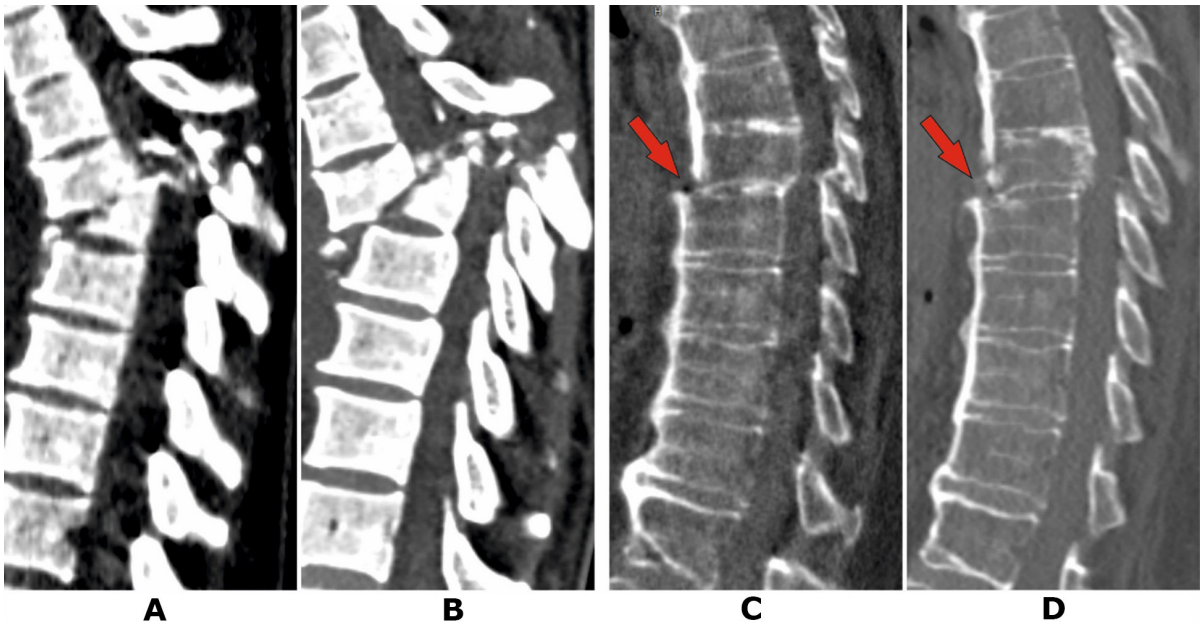

Fig. 3. Patient P., 37 years old. CT scans of the thoracic spine: A – on the day of the injury; B – after 5 weeks. Patient V., 58 years old: C – 2 days post-injury; D – after 2 months (details in the text)

Table 2. Comparison of key clinical parameters between the group of patients with aseptic post-traumatic vertebral body necrosis and the comparison group

Indicator	Group with Spondylolysis	Comparison Group	P
Sex:			0,99Δ
men	66,67%	61,54%	
women	33,33%	38,46%	
Age, years:			0,5*
median (95 % confidence interval)	43,5 (25,25–58,08	40 (26,9–45,78)	
Injury Level:			0,3Δ
thoracic	33,33%	23,08%	
Thoracolumbar junction		38,46%	
lumbar	0%	38,46%	
AOSpine injury type:			0,99Δ
B2	50%	46,15%	
B3	0%	7,69%	
C	50%	46,15%	
TLICS, score			0,7*
median (95 % confidence interval)	8 (6,05–8,95)	8(6,38–7,93)	
Neurological deficit (ASIA):			0,4Δ
A	50,0%	69,23%	
B	33,33%	7,69%	
E	16,67%	23,08%	
Presence of neurotrophic changes	16,67%	61,54	0,1Δ
Peripheral blood leukocytes, 10^9/L			0,01†
mean (95% confidence interval)	8,47 (5,79–11,14)	13,04 (10,3–15,78)	
C-Reactive Protein (CRP), mg/L			–
mean (95% confidence interval)	2,45 (0,96–3,94)	–	

Note: Δ – Fisher's exact test; * – Fisher-Pitman permutation test for two samples; † – Welch's t-test.

presented clinical cases involved the use of osteotropic antibacterial therapy, underscoring the aseptic nature of the condition. For example, consider the follow-up data of patient T. (Case No. 2). Amid total lysis of the L1 vertebral body, rapid destruction of the endplates of the adjacent vertebrae was observed ***(see Figures 2B, 2C)***. However, following decompressive-stabilization surgery—including removal of L1 vertebral body fragments, placement of a body-replacement implant via a posterior approach, and subsequent transpedicular stabilization of the Th11-Th12-L2-L3 vertebrae—the process was fully arrested ***(Fig. 4A)***. Follow-up studies conducted 2 and 6 months after surgery demonstrated stable fixation and no signs of progressive osteolysis ***(Figures 4B, 4C)***.

Discussion

Aseptic necrosis of vertebral bodies remains a subject of active study. The literature contains conflicting data regarding its pathogenesis and actual prevalence. As noted above, in most cases, references to aseptic necrosis of the vertebral bodies (ANVB) pertain to Kummell's disease. However, the diagnostic criteria for this rare pathological condition have been significantly expanded, often unjustifiably, leading to a blurred clinical picture and complicating the understanding of its course and the development of optimal treatment methods [22]. According to some authors, the prevalence of Kummell's disease is approximately 37% among all osteoporotic fractures in the elderly population, which suggests overdiagnosis [23].

Traditionally, Kummell's disease is interpreted as a post-traumatic vertebral fracture that is asymptomatic and radiologically undetectable at initial stages but eventually leads to vertebral body collapse [24].

In 1951, H. Steel provided a detailed description of the stages of Kummell's disease progression [25]. First stage: Initial trauma, which can vary in severity and mechanism, while the radiologically examined vertebra remains intact. Second stage: Post-traumatic phase, where patients may experience mild back pain without significant functional limitations. Third (latent) stage: May last from several weeks to months, often asymptomatic. Fourth stage (recurrence phase): Persistent and progressive back pain localized at the site of the forming compression fracture. Terminal stage: Gradual development of kyphotic deformity with potential spinal cord compression.

The presented data highlight the fundamental differences between the pathology discussed in this publication and Kummell's disease. Given the similarity of pathological processes, specifically ANVB, and the lack of literature describing the pathological condition we observed, we explore the currently known potential mechanisms of aseptic spondylonecrosis pathogenesis.

There are numerous hypotheses explaining the development of aseptic necrosis of vertebral bodies (ANVB): avascular osteonecrosis [26–28], impaired consolidation due to atrophy [29], microfractures [24], tissue nourishment disorders [25], pseudoarthrosis [26], and stress fractures [30]. Identified risk factors include prolonged glucocorticoid therapy, venous stasis, diabetes, alcoholism, pancreatitis, radiation therapy, oncopathology, and chronic infections [31, 32]. Despite extensive studies of post-traumatic ANVB

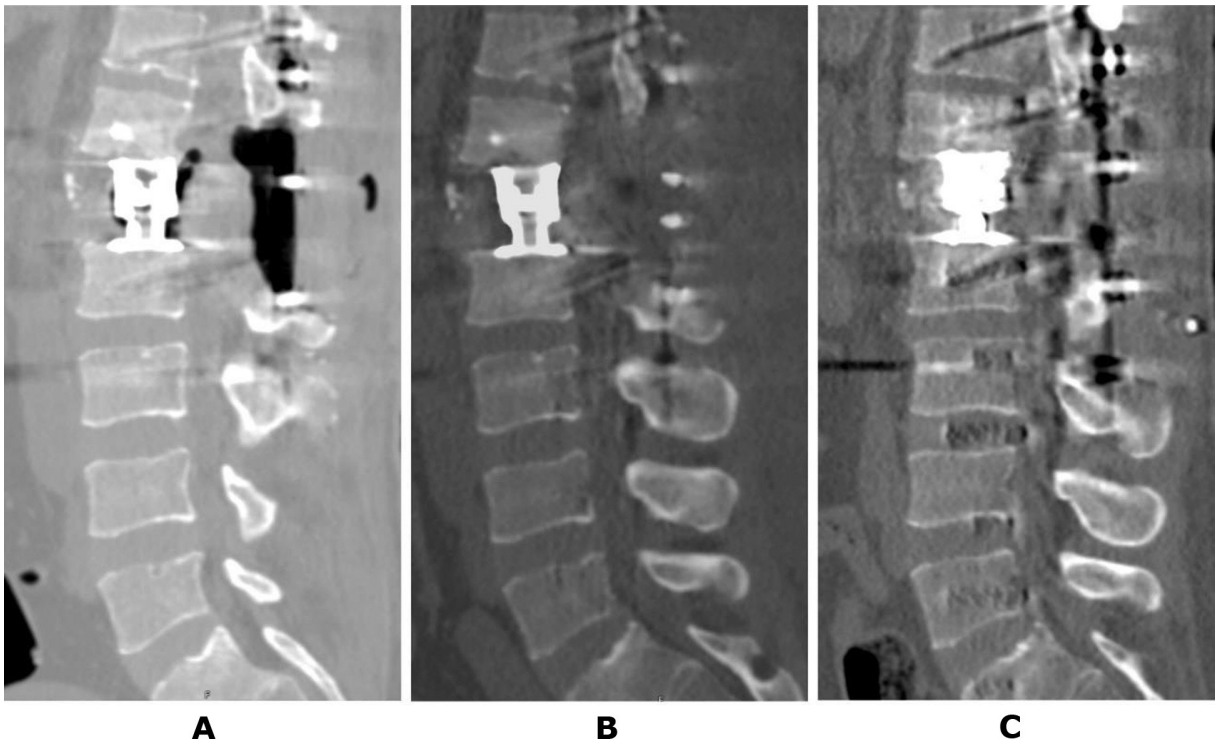

Fig. 4. Patient T., 41 years old. CT scan of the lumbar spine: A – 3 days after surgery; B – 2 months later; C – 6 months later (details provided in the text)

in general, and Kummell's disease in particular, the cascade of pathological processes leading to vertebral body lysis remains unknown. Ischemia of the vertebral body is considered the most probable cause of ANVB development. Some authors suggest that avascular osteonecrosis of the vertebral body and Kummell's disease are synonymous. According to current theories, ischemia may result from blood vessel rupture due to trauma, intravascular occlusion, or extravascular compression caused by increased interstitial pressure [33].

The nature of **the initial traumatic injury to vertebral body blood vessels** is closely related to the specifics of its blood supply. A review of the literature reveals limited research on blood flow in bony structures, as the most detailed publications on this topic date back to the 1960s–1980s. More recent studies predominantly focus on spinal cord blood supply, which understandably holds greater practical significance. Moreover, the lack of a clear nomenclature for small-caliber arteries further complicates comprehension [34]. Below is a fundamental description of the blood supply scheme necessary for understanding the theory of avascular spondylonecrosis.

It is known that the primary source of blood supply to the vertebral bodies of the mid-to-lower thoracic and lumbar regions is the segmental arteries, which include posterior intercostal arteries (*aa. intercostales posteriores*) and lumbar arteries (*aa. lumbales*), originating from the thoracic and abdominal sections of the aorta, respectively. In the thoracic region, the right segmental arteries are longer than the left due to the aorta's position along the anterolateral left surface of the spine at the arch, transitioning to a nearly central location in the abdominal section. As the segmental arteries curve around the vertebral body, they give rise to small branches—anterior and lateral vertebral branches—that perforate the cortical layer and contribute to forming the vertebral body vascular plexus. There are no reports suggesting direct blood supply to vertebral bodies from the aorta. On the lateral surface of the vertebral body, anastomoses link homonymous vessels located cranially and caudally, which also give rise to lateral vertebral branches. At both thoracic and lumbar levels, the segmental arteries give off a large dorsal branch (*r. dorsalis = a. dorsospinalis*) critical for the vascularization of bony and neural structures. The dorsal branch divides into *r. retrovertebralis, r. spinalis, and r. muscularis.* The retrovertebral branch, passing through the intervertebral foramen, encircles the vertebral body on its posterior surface, often forming anastomoses with the contralateral branch. Small vessels branching from it penetrate the cortical layer and participate in forming the vascular plexus of the vertebral body. Some authors consider the retrovertebral branch the primary source of vertebral body blood supply [35]. *R. spinalis* also courses dorsomedially, dividing into anterior and posterior radiculomedullary arteries (*aa. radiculomedullaris ant. et post*.), which supply the spinal canal's neural structures. *R. muscularis*, extending dorsally, supplies structures of the posterior supporting complex and the deep muscles of the back. Some authors distinguish medial, intermediate, and lateral branches of the *r. muscularis* [36].

Within the vertebral body, the vascular plexus—centered at the anatomical core of the vertebral body—is formed by arteries penetrating the cortical layer from the sources described earlier. Radiating outward in all directions, the vessels of the plexus anastomose with branches of penetrating arteries, creating both centrifugal and centripetal blood flow. The densest arterial network is visualized in the posterolateral regions of the vertebral body and its center [35, 37]. These features result in the formation of a watershed zone—a region of reduced blood supply located in the anterior third of the vertebral body. On sagittal sections, this watershed zone has a wedge shape directed from the center to the anterior surface of the vertebral body and is characterized by exclusively centrifugal blood flow, as penetrating arteries are virtually absent on the anterior surface [38]. Expectedly, this phenomenon becomes more pronounced the closer the aorta is to the central line—at the level of the arch, the thoracolumbar transition, and the lumbar region down to the bifurcation into the common iliac arteries.

The presented data demonstrate that, overall, the blood supply to the vertebral body has significant compensatory potential due to numerous anastomoses. Clinical observations indicate that even substantial damage and fragmentation of vertebral bodies rarely result in pronounced ischemia. However, the specifics of blood flow and vascularization in traumatically injured vertebrae have not been thoroughly studied. Consequently, blood flow disturbances resulting from traumatic injury or compression of adjacent vessels, either in isolation or combined with other factors, are considered potential causes of ANVB.

Blood flow disruption within the vertebral body may also occur due to **intravascular occlusion**. Cases of non-traumatic ANVB have been described in the literature in association with vaso-occlusive sickle cell crisis or decompression sickness [38,39]. It has been noted that pancreatitis is also a risk factor for ANVB development, as elevated levels of lipolytic enzymes in the blood lead to the breakdown of intramedullary fat structures and vascular obstruction by fat droplets. Additionally, instances of pancreatic enzyme release into the abdominal cavity following cyst rupture, leading to subsequent ANVB development, have been documented [40–42]. Arterial anomalies, dyslipidemia, leukemia, and lymphoma have also been linked to the development of spondylonecrosis [43, 44]. Regarding post-traumatic osteonecrosis, intravascular occlusion is likely a heightened risk factor for the group of patients under consideration [33].

Some authors consider **extravascular obliteration** caused by increased interstitial pressure as one of the links in the pathogenesis of ANVB [45]. Chronic glucocorticoid therapy and alcohol consumption, which lead to fat embolism, lipid deposition, and adipocyte hypertrophy, are also significant risk factors as noted in the literature [46–48]. Regarding the pathology we analyzed, it can be hypothesized that extravascular obliteration may contribute to the progression of spondylonecrosis. Specifically, primary traumatic damage to the vertebral body and the resulting disruption of blood flow due to vascular injury in the spongy bone leads to the formation of an ischemic zone. The

situation is exacerbated by instability at the injury site, which causes increased fragment mobility and hinders neoangiogenesis. Bone tissue lysis is accompanied by the release of a significant amount of low-molecular-weight compounds into the interstitial space, negatively affecting the patency of intact vessels and leading to the gradual spread of pathological changes to unaffected areas of the body. Overall, the avascular theory of post-traumatic ANVB development aligns well with the clinical picture. In all documented cases, the lysis process began in the anterior parts of the vertebral body and gradually extended to the central and posterior regions. However, regarding Kummell's disease, the avascular mechanism is questioned by several researchers. The pathological cascade described struggles to explain the development of avascular osteonecrosis in patients 2–3 months after trauma, with no clinical manifestations or radiological changes at the onset [15, 49].

When considering the phenomenon of ANVB, it is important to mention the "vacuum effect," which has been increasingly recognized as a practically pathognomonic symptom of Kummell's disease in recent decades. Gas formation is attributed to tissue breakdown and the release of gas as a result of necrotic processes. The decomposition of proteins, lipids, and other components of necrotic tissues releases gases such as nitrogen, oxygen, and carbon dioxide, which then accumulate in the vertebra or disc region. T. Armingeat et al. analyzed the composition of the gas responsible for the vacuum effect and found that 90–92% of it is nitrogen [50]. On the other hand, some authors note that tissue necrosis leads to changes in intravertebral pressure, causing gas diffusion from the blood into bone structures [46]. However, this excludes the possible influence of increased interstitial pressure on the development of ANVB.

An analysis of the literature on the vacuum effect revealed that its occurrence is inversely proportional to the bone density of the affected vertebra [32]. Since in the last decade there has been a tendency to consider osteoporotic fractures as Kummell's disease, the presence of gas in the vertebral body or intervertebral disc has been given excessive diagnostic significance. It is known that the presence of gas in a compression fracture can be a radiological finding and does not necessarily indicate progressive bone tissue destruction [51, 52]. The vacuum phenomenon is often observed in degenerative spinal diseases [53–56]. In our group of patients with documented ANVB phenomena, the vacuum phenomenon was not observed in any case.

As noted above, the role of injury instability in the development of ANVB has not been adequately studied. However, concerning traumatic injuries in other parts of the skeleton, this issue has been much better addressed. Several publications demonstrate a clear relationship between instability, the timing of its resolution, and the frequency of osteonecrosis [57–59], which to some extent supports the validity of our assumptions. The data we have presented on the possible pathophysiological mechanisms underlying this phenomenon allow differentiation from Kummell's disease and highlight areas for further research and prevention of this significant complication.

A notable limitation of this study is its retrospective nature and the small number of patients, which prevented us from identifying precise predictors of ANVB development in cases of unstable vertebral injury. Furthermore, the interpretation and subsequent formation of a comparison group are complicated by the definition of instability. While often effective in the context of overall functional activity, this definition does not fully characterize the biomechanical state of the damaged spinal motion segment (SMS). This can be illustrated by the example of the cervical spine, where a complete locked dislocation is, by definition, unstable but simultaneously rigidly fixed in terms of the range of motion in the damaged SMS. A similar situation is sometimes observed in the thoracolumbar spine and is well known to practicing surgeons: despite a significant degree of injury, fragmented structures of the posterior supporting complex, due to fragment interlocking, may hinder further displacement and even completely immobilize the segment. This factor should also be considered in future research.

Conclusions

This article is one of the first dedicated to describing the practically unexplored phenomenon of post-traumatic ANVB in unstable injuries of the thoracolumbar spine. The presented data, along with the consideration of possible pathogenetic mechanisms, clearly highlight the importance of early stabilization of unstable injuries not only from a neurological perspective but also from an orthopedic standpoint. This information may be valuable for practicing neurosurgeons or orthopedic trauma specialists, especially given the high incidence of traumatic injuries in the population.

Disclosure

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

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Coccygodynia combined with lumbosacral pain syndromes. A case series and clinical recommendations

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Coccygodynia (CD) is characterized by pain in the coccyx area, but in some cases the pain radiates to the sacrum, perineum, anus, genitals, gluteal area, sacroiliac joint, lower lumbar spine and thighs. The association of CD with other pain syndromes can lead to complicated diagnosis and non-targeted treatment, which will not improve the patient's condition.

Objective: To investigate the frequency of the combination of low back pain in patients with CD who underwent spinal surgery and to evaluate the effectiveness of their treatment.

Materials and methods: An analysis of the results of 62 interventions on Ganglion Impar (GI) in 54 patients was performed. Interventions were performed in the three medical centers in Kyiv, Ukraine in the period from 2017 to 2024: Main Medical Clinical Center of the Ministry of Internal Affairs of Ukraine, Romodanov Neurosurgery Institute and MedClinic Medical Center.

Results. 14.8% of all study participants had post-traumatic CD (history of falling on the coccyx), in one case CD was caused by pelvic cancer, the vast majority of 83.3% had idiopathic CD. 21 (38.9%) of the study participants were male and 33 (61.1%) were female aged 23 to 84 years (mean age 48.0±15.4 years). In our series, 16 (29.6%) patients had lumbar or sciatic syndrome. Following treatment for CD, all patients noted a significant reduction of low back pain. In 4 (7.4%) observations, the intervention on GI was performed after lumbosacral spine stabilization surgery.

Conclusions: Surgical treatment of spinal pathology in patients with CD partially reduced the intensity of the pain syndrome. The execution of the GI steroid block ensured the achievement of a stable analgesic effect during the six-month follow-up. Patients presenting with CD accompanied by lumbago or radiating pain require an integrated approach to ensure accurate differential diagnosis and optimal treatment outcomes.

Key words*: coccygodynia; low back pain; lumbalgia; lumbago;* sciatica; *pelvic pain; ganglion impar; ganglion of Walther; coccyx; spine; spinal stabilization; ganglion impar block*

Introduction

Coccygodynia (CD) is pain in the coccygeal region that intensifies when sitting on hard surfaces. This pain is also provoked by leaning backward while seated. The coccyx is the terminal segment of the spine, forming a triangular bone composed of three to five fused segments (vertebrae), with the largest segment articulating with the lower sacral segment. Despite its small size, the coccyx performs several important functions: it serves as an attachment site for multiple muscles, ligaments, and tendons, and, along with the ischial tuberosities, acts as one of the "tripod" supports that bear body weight in a sitting position. Leaning backward while sitting increases pressure on the coccyx. Additionally, the coccyx plays a role in positional support of the anal region.

Idiopathic CD is the most prevalent among etiological factors [1–5]. It is believed to be associated with abnormal hypermobility of the coccygeal region—hypermobility of the coccyx and the sacrococcygeal joint—leading to chronic inflammation [1, 5, 6]. Trauma to the coccygeal area, such as from falls or childbirth, and coccygeal dislocation are the second most common causes of CD, while other etiological factors (infection, tumor, osteophyte, etc.) are significantly rarer [3, 4]. Obesity and female sex are associated with an increased risk of CD [4]. Women are more susceptible to CD due to anatomical and physiological characteristics of the pelvis, including a larger coccyx, more posterior sacral positioning, and the pressure exerted on the sacrococcygeal region during pregnancy and childbirth [7, 8].

Pain in CD may radiate to adjacent anatomical regions, including the sacrum, perineum, anus, genital organs, buttocks, sacroiliac joint, thighs, and lower lumbar spine, which can obscure the primary source of pain. This is attributed to the significant innervation of this anatomical region. On the anterior surface of the coccyx lies the ganglion impar (GI), the caudal termination of the sympathetic trunk, which provides sympathetic and nociceptive innervation to the perineum, coccyx, distal rectum, anus, distal urethra, vulva, vagina, and penis. Visceral afferents from these anatomical structures converge at the GI [9]. Postganglionic sympathetic fibers from the sympathetic trunk pass through gray communicating rami to the GI, providing sympathetic innervation to the pelvic viscera [10]. Additionally, the ventral branches of the sacral nerves pass near the GI [11].

According to the literature, CD accounts for 1–3% of cases of lower back pain, although its exact prevalence remains unknown [12]. In a study of 50 CD patients undergoing osteopathic manipulative treatment, 27 (54%) also experienced lower back pain or radicular pain syndrome [13]. The association of CD with other pain syndromes may complicate diagnosis and lead to inappropriate treatment, which does not contribute to patient recovery.

Objective: To investigate the frequency of : low back pain in patients with coccygodynia undergoing spinal surgery and to evaluate the effectiveness of their treatment.

Materials and Methods

Study Participants

A sample of patients with CD (n=54) who underwent 62 interventions on GI was analyzed. Written informed consent was obtained from all patients after a detailed explanation of the procedure.

Inclusion Criteria:

Presence of coccygeal pain for ≥3 months, patients of both sexes, age between 23 and 84 years, lack of response to analgesics, anti-inflammatory drugs, and other conservative treatment methods.

Exclusion Criteria:

Age below 16 years, presence of a local skin infection at the injection site or systemic infection,allergy to anesthetics or contrast agents, sacrococcygeal fusion due to any pathology, history of coccygectomy, coagulation profile disorders, pregnancy, psychiatric disorders, including those under psychiatric dispensary supervision, inability to continue participation in the study during the follow-up period.

Group Characteristics

Among the patients, 33 (61.1%) were female and 21 (38.9%) were male. The mean patient age was 48.0±15.4 years.

Minimally invasive GI interventions were performed using five different techniques. Ganglion impar block (GIB) was conducted in 44 patients, while alternative GI interventions were applied in cases of resistant CD following prior steroid injections. These included GI neurolysis with ethanol (n=2) or phenol (n=2), GI radiofrequency modulation (n=4), and GI radiofrequency ablation (n=10).

Study design

A prospective interventional study was conducted on the basis of three medical institutions in Kyiv, Ukraine: the Main Medical Clinical Center of the Ministry of Internal Affairs of Ukraine, the Romodanov Institute of Neurosurgery of the National Academy of Medical Sciences of Ukraine, and the «Medclinic» Medical Center, over the period from 2017 to 2024.

The study adhered to the principles of bioethics in accordance with the Declaration of Helsinki on Human Rights (1975) and its subsequent revisions (1996–2013), the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine. The study protocol was approved by the Ethics and Bioethics Committee of the Romodanov Institute of Neurosurgery, National Academy of Medical Sciences of Ukraine (Minutes No. 3, dated December 16, 2020). The study did not pose an increased risk to participants and was conducted in compliance with bioethical norms and scientific standards for clinical research involving patients.

Patient data were analyzed based on clinical assessments, including a preliminary survey using the Visual Analog Scale (VAS) for pain (0 cm – no pain, 10 cm – unbearable pain). The functional status of patients was assessed before and after the procedure using the Karnofsky Performance Scale (KPS), ranging from 0% to 100%. Patients were followed up for six months, with evaluations conducted at one week, one month, three months, and six months post-procedure.

Statistical analysis

The collected data were processed using the statistical software package MedCalc V 22.016. Quantitative variables (age, VAS, and KPS scores) were presented as mean values with standard deviations. To determine differences following the interventions, the paired Student's t-test was used for normally distributed data, while the Wilcoxon signed-rank test was applied for non-normally distributed data. A significance level of 0.05 was considered statistically significant.

Results

Characteristics of the study material

Idiopathic CD was diagnosed in the majority of patients (83.3%) ***(Table 1)***. One female patient (1.9%) had CD due to oncological involvement of the pelvic organs and had undergone surgical intervention for this condition. Another female patient (1.9%) developed CD following the excision of a coccygeal cyst. In these cases, GIB resulted in significant pain reduction.

In our series, 16 patients (29.6%) presented with lumbalgia or sciatic syndrome. Following treatment for CD, all patients reported significant pain relief in the lower back.

In four cases (7.4%), the intervention on the GI was performed after a stabilization surgery in the lumbosacral spine.

Clinical case analysis

Four patients (two males and two females) aged 51 to 70 years sought medical attention due to pain in

This article contains some figures that are displayed in color online but in black and white in the print edition.

the lumbosacral spine and coccyx ***(Tables 2 and 3)***. The duration of pain ranged from three months to one year. None of the patients had a history of direct coccygeal trauma. Before surgery, all patients underwent magnetic resonance imaging (MRI) of the lumbosacral spine, including the coccyx, and functional radiography of the lumbosacral spine. Based on their complaints and the findings of neurological and neuro-orthopedic examinations, surgical treatment was deemed necessary.

Prior to surgery, none of the patients exhibited a significant response to conservative pharmacological therapy or physiotherapeutic treatment methods. In three cases, transpedicular fixation of the spine was performed at the L5/S1 level, while in one case, it was conducted at the L4/L5 level. The surgical interventions were carried out without complications, and all patients were discharged in satisfactory condition, reporting a reduction in radicular pain in the lower extremities. However, the intensity of pain in the coccyx, sacrum, and lower lumbarsacral spine remained largely unchanged. The persistence of this pain syndrome, along with the presence of postoperative discomfort, hindered rapid and full recovery in patients and adversely affected their functional status. Consequently, GIB was performed, leading to a sustained reduction in pain intensity over a six-month follow-up period ***(Tables 4 and 5)***. All interventions were successfully executed on the first attempt. No difficulties arose during the procedure, and there were no cases of rectal or pelvic structure perforation. Additionally, no complications were recorded post-procedure.

Table 1. Characteristics of the overall study population with coccydynia (n=54)

Parameter	Number	
	Abs.	%
Sex:		
male	21	38,9
female	33	61,1
Age, years	48,0±15,4 (23–84)	
Etiology of pain:		
idiopathic coccydynia	45	83,3
trauma	8	14,8
oncology	1	1,9

Table 2. Characteristics of patients with coccydynia who underwent surgical intervention on the lumbosacral spine (n=4)

№	Sex	Age, years	Etiology of coccydynia	Comorbid pathology	Pain duration
1	M	51	Idiopathic	LS osteochondrosis *	6 months
2	F	68	Idiopathic	LS osteochondrosis, HTN **	6 months
3	M	70	Idiopathic	LS osteochondrosis, HTN	1 year
4	F	54	Idiopathic	LS osteochondrosis	3 months

Note: *LS osteochondrosis; ** HTN - hypertension.

Table 3. Pain localization (n=4)

Pain localization										
								Radicular (root) symptoms		
№	Coccyx	LS spine*	Sacrum	SI joint**	Perineum	AR***	GO****	Buttock	Thigh	Lower leg
1	+	+	+	-	+	+	+	+	+	-
2	+	+	+	-	-	-	-	+	+	+
3	+	+	+	-	-	-	-	+	+	+
4	+	+	-	-	-	-	-	+	+	+

Note. *LS spine – Lumbosacral spine; **Sacroiliac joint; ***Anal region; ****Genital organs.

Table 4. Pain syndrome intensity assessment using VAS (cm) at different follow-up periods (n=4)

№	Preoperative	Postoperative	Post-GI intervention			
			1 week	1 month	3 months	6 months
1	8	8	3	2	1	2
2	9	5	2	0	0	1
3	9	7	1	1	2	2
4	8	6	0	1	0	0

Table 5. Functional status assessment using the KS (%) at different follow-up periods (n=4)

№	Preoperative	Postoperative	Post-GI intervention			
			1 week	1 month	3 months	6 months
1	70	70	80	90	90	100
2	80	70	90	100	100	100
3	70	70	80	80	90	90
4	70	70	90	90	100	100

Clinical case

Patient B., a 70-year-old male, was hospitalized with complaints of intense pain in the lumbosacral spine, radiating to the sacrococcygeal region, the right gluteal area, and the right thigh along its posterolateral surface. The pain intensity, assessed using the Visual Analog Scale (VAS), was 9 cm. Examination revealed a herniated intervertebral disc at the L4/L5 level, compressing the right L5 spinal nerve root. Functional radiography of the lumbosacral spine confirmed instability at the L4/L5 level.

The patient underwent surgical intervention, including transpedicular fixation of the spine at the L4/L5 level and removal of the herniated intervertebral disc at L4/L5 ***(Fig. 1)***. In the postoperative period, the patient reported a reduction in pain in the right thigh; however, pain persisted in the sacrococcygeal region and the lower lumbar spine. Postoperative pain assessment using VAS was recorded at 7 cm.

Two weeks after the surgical intervention, the patient underwent GIB using the following technique [14]. After antiseptic preparation of the skin, the target intergluteal area was covered with sterile surgical drapes. Injections were performed under fluoroscopic guidance using a C-arm. In this case, the «Cios Select with FD» device (Siemens, Germany) was used. A total of 2 mL of 2% lidocaine was administered into the subcutaneous tissue of the upper intergluteal fold as a local anesthetic, followed by the insertion of a 23G (0.6 × 30 mm) needle into the sacrococcygeal disc. The needle was advanced to the point of loss of resistance, indicating its placement anterior to the ventral sacrococcygeal ligament. Once the needle was positioned along the sacrococcygeal disc line, 1 mL of a radiopaque dye, «Tomogexol 350» (Farmak,

Ukraine), diluted in saline at a 1:2–1:3 ratio, was injected. The needle position was confirmed by the appearance of a "comma" or "crescent" sign in the retroperitoneal space on lateral fluoroscopic imaging ***(Fig. 2)***. The spread of contrast within the sacrococcygeal disc indicated the need for further needle advancement. The presence of the contrast agent in the lumen of the rectum suggested posterior wall perforation and excessive needle advancement, which is an undesirable outcome. Following a negative aspiration test, confirming the absence of blood or cerebrospinal fluid, 2–3 mL of 0.5% bupivacaine and 1 mL of «Depo-Medrol®» (methylprednisolone, Pfizer, USA) were administered. One week after the GIB, the patient's VAS score was recorded at 1 cm. The patient reported high satisfaction and was able to fully undergo the prescribed postoperative rehabilitation course.

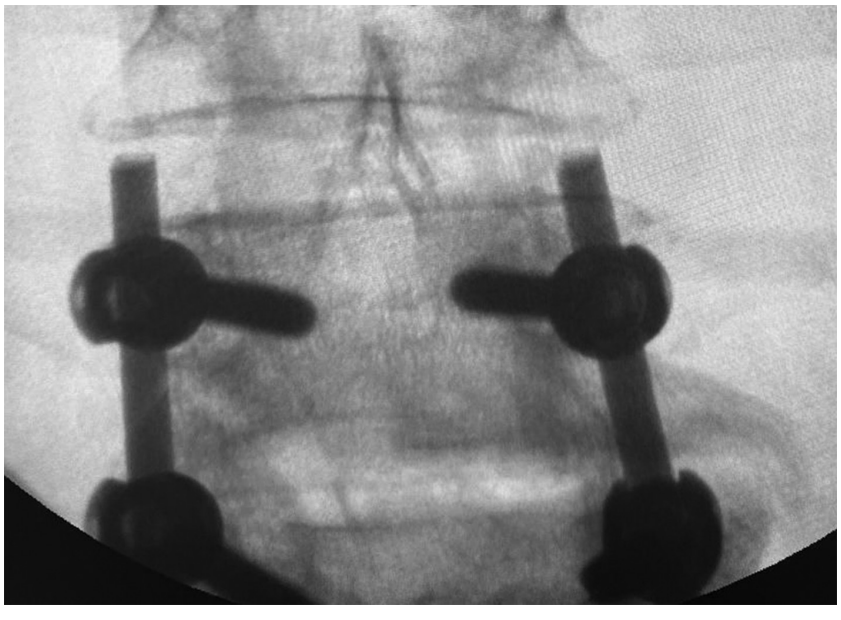

Fig. 1. Intraoperative radiographic control image of the lumbar spine in the anteroposterior view. The transpedicular fixation system is installed at the L4/L5 level

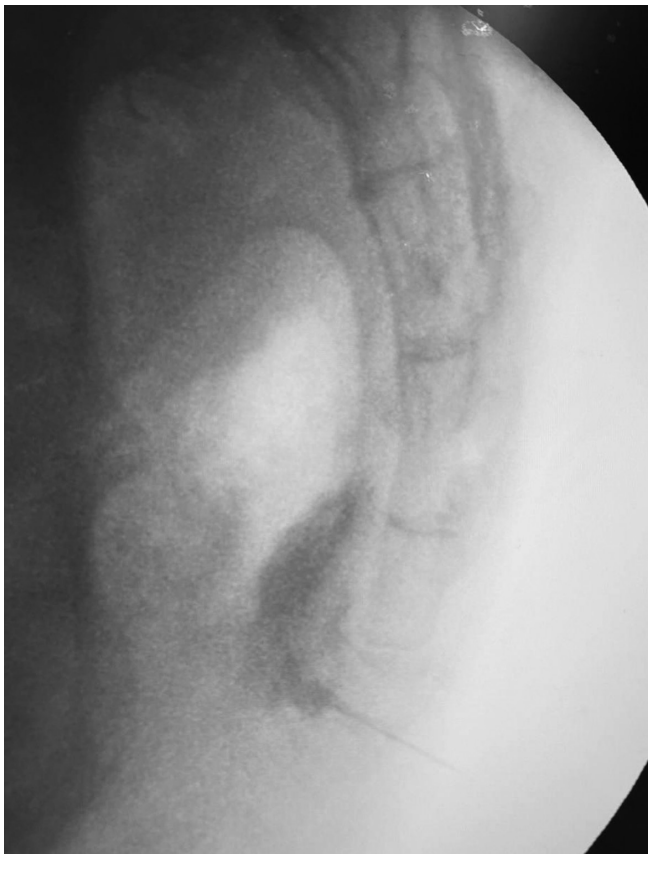

Fig. 2. GIB under X-ray control using a trans-sacrococcygeal approach, lateral projection. The needle is visualized passing through the sacrococcygeal disc, with contrast staining of the ganglion impar

Discussion

Cases of an association between low back pain and CD have been described in the literature. In the presented series of four patients with CD, two cases were accompanied by lower back pain of secondary origin due to CD. Following CD treatment with GIB, pain in both the coccyx and lower back fully regressed [5].

In another case, a 51-year-old woman sought medical attention due to lifelong persistent low back pain. Clinical examination raised suspicion of CD, and functional radiographic assessment revealed a hypermobile coccyx with dorsal angulation. The patient underwent total coccygectomy, after which the pain syndrome completely resolved, as confirmed during a follow-up examination one year postoperatively [15].

We did not find documented cases of CD occurring after similar spinal surgical interventions. Therefore, we hope this article will be valuable to the medical community. The purpose of this publication is to highlight lesser-known pain syndromes encountered in clinical practice (e.g., CD, sacroiliitis, pudendal neuralgia, Roth's syndrome) that can mimic the common presentation of low back pain.

The concepts of pain association and radiation are often conflated. However, association refers to the coexistence of different types of pain, such as the presence of multiple pain sources in a single patient (e.g., CD and lower back pain), each requiring separate treatment. In contrast, radiation describes the spread of pain from its origin (the directly affected structure or organ) to a distant location. For example, in CD, pain may radiate from the coccyx to the sacroiliac joint or the lower lumbar spine. In our series, some patients exhibited radicular symptoms triggered by degenerative spinal changes. Although surgical intervention improved their condition, complete pain regression was only observed following GIB. This suggests that the primary pain source had associated radiation, which masked the symptoms of another underlying pathology.

Currently, there are no well-defined diagnostic criteria for CD [1, 12]. Diagnosis is based on patient complaints, thorough history-taking, physical examination, and diagnostic imaging. Patients typically identify a well-localized painful area over the coccyx or report tenderness on palpation. Common symptoms include sharp coccygeal pain while sitting—especially on hard surfaces—or in a reclined position that exerts direct pressure on the coccyx. Many patients report pain when transitioning from sitting to standing, dyspareunia (pain during sexual intercourse in women), and pain during defecation. Symptoms often improve when leaning forward or shifting weight frequently between the buttocks [16].

A thorough inspection and palpation of the coccygeal region allow for the assessment of mobility, fluctuation, localized tenderness, and coccyx formation. The presence of tenderness, erythema, and swelling may indicate inflammatory processes such as cellulitis or osteomyelitis. Rash, discharge, and fistula formation may suggest a pilonidal cyst, while point tenderness at the distal tip of the coccyx may indicate degenerative osteophytes (bone spurs) [16].Rectal examination, performed by grasping the coccyx between the index finger and thumb, enables the evaluation of local sensitivity, hypomobility, and hypermobility of the sacrococcygeal joint [6]. Other potential causes of coccygeal pain include internal hemorrhoids, perineal abscesses, rectal masses, and prostate hypertrophy [17]. During a physical examination, it is essential to assess the lumbar spine for pain related to facet joint arthritis, L5-S1 intervertebral disc degeneration, and sacroiliac joint dysfunction [12]. When CD coexists with or mimics pain associated with degenerative changes in the lumbosacral spine, diagnostic challenges increase significantly.

The coccyx is not typically included in standard radiographic protocols for the lumbar spine or pelvis; therefore, the radiologist should be informed about the need to include the coccygeal region in the examination. The most critical imaging study is a lateral radiograph of the coccyx taken in both standing and seated (weight-bearing) positions [16]. The optimal protocol involves capturing standing radiographs after the patient has been upright for 5–10 minutes to ensure the coccyx is in a neutral position [18]. Seated images should be acquired while the patient is sitting on a firm surface with a slightly extended spine, applying pressure on the coccyx at an angle that provokes pain. Ideally, the patient should remain seated on a firm surface for one minute before imaging [18]. These dynamic radiographs facilitate the assessment of fractures, dislocations, hypermobility, and hypomobility. Hypermobility is defined as an inter-coccygeal angle change of >25° between sitting and standing images, while hypomobility is characterized by a change of <5° [12]. In cases where dynamic functional imaging is challenging due to pain, the recommended standing and sitting duration may be reduced. If severe or intolerable pain is present, weight-bearing projections should be avoided, and lateral projections in the supine position should be performed instead [12].

Additional radiographs, including anteroposterior and lateral views of the lumbar spine and pelvis, may be required to detect coccygeal pathology. If spondylolisthesis or other instability is observed on standard lumbar radiographs, further assessment with flexion-extension functional imaging is warranted [12].

Computed tomography (CT) of the coccyx is indicated when a fracture is suspected following direct trauma or when a more detailed evaluation of bone anatomy is needed after radiography. Magnetic resonance imaging (MRI) of the coccyx, with or without contrast, is recommended when tumors (e.g., chordoma, teratoma), abscesses, infections, or other pathological conditions are suspected [12,16]. In Ukraine, MRI of the coccyx is not mandatory when performing MRI of the lumbosacral spine; however, the coccygeal region is often included in the scan. For a more targeted assessment of pathological changes, dedicated coccygeal MRI may be prescribed.

Clinical recommendations

1. When assessing complaints, medical history, and conducting a physical examination in patients with spinal pathology and pain syndrome, it is essential to consider the possibility of pain originating from other sources. Such pain may radiate in a pattern resembling low back pain and obscure the primary source of pain.

2. Special attention should be given to patients with atypical pain characteristics for lumbalgia or sciatica,

particularly when it is associated with pain in the coccyx, sacrum, perineum, anal region, or genital organs.

3. In cases of suspected CD, a rectal examination and palpation of the coccygeal region should be performed to assess local sensitivity, hypomobility or hypermobility of the coccyx, and sacrococcygeal joint dysfunction.

4. If CD is suspected in conjunction with clinical manifestations of spinal instability, imaging should include not only functional radiography of the lumbosacral spine but also functional lateral radiography of the coccyx in both standing and seated (weight-bearing) positions.

5. In cases where CD and low back pain syndromes coexist, the effectiveness of a minimally invasive treatment— GIB —should be evaluated first, followed by consideration of additional interventions if necessary.

6. GIB significantly reduces pain intensity in CD patients who have undergone spinal surgery, facilitating a quicker and more comprehensive postoperative rehabilitation.

Conclusions

1. Among 54 patients with CD, 16 (29.6%) presented with lumbalgic or *sciatic* syndromes, and 4 (7.4%) had undergone spinal stabilization surgery in the lumbosacral spine.

2. Surgical treatment of spinal pathology in CD patients resulted in partial pain reduction. However, GIB provided a sustained analgesic effect for up to six months of follow-up.

3. Patients with clinical manifestations of CD associated with lumbalgia or radiating pain require a comprehensive diagnostic approach for more accurate differential diagnosis, ensuring optimal treatment outcomes.

Disclosures

Conflict of Interest

The authors declare no conflicts of interest.

Ethical Standards

All procedures performed on patients in this study complied with the ethical standards of institutional and national ethics committees, as well as the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards.

The study was approved by the Ethics and Bioethics Committee of the Romodanov Institute of Neurosurgery, National Academy of Medical Sciences of Ukraine (Minutes No. 3, December 16, 2020).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Original article

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Functional and morphological indicators of the sciatic nerve condition in rats in the long-term period after injury: A correlation analysis

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Peripheral nerve injury (PNI) is a common pathology during wartime, significantly complicating the course and treatment of limb damage. Restorative treatment of PNI requires substantial improvement, which is impossible outside the methodology of experimental neurosurgery. The most frequently used PNI model involves transection of the rat sciatic nerve, followed by observation over 9–12 weeks and verification of results using functional-anatomical, electroneuromyographic, and morphometric methods. A key pathophysiological question—whether there is a correlation between the results of these three classes of research methods—remains a topic of ongoing debate.

Objective: to determine the correlation between individual values of the sciatic functional index (SFI), the amplitude and latency of the M-response, as well as the density of nerve fibers in the injured sciatic nerve 12 weeks after its transection and neurorrhaphy.

Materials and Methods. This study was conducted on adult male white outbred rats, selected from groups analyzed in a previous publication, which underwent electroneuromyographic and morphological examinations. In the sham-operated group (Sham; n=6), a surgical approach to the sciatic nerve was performed without nerve injury. In the Sect group (n=7), the sciatic nerve was transected in its middle third. In the Raph group (n=6), the stumps of the transected sciatic nerve were immediately sutured in an end-to-end way using several interrupted stitches. Twelve weeks post-surgery, SFI was calculated using the Bain–Mackinnon–Hunter formula. Additionally, the amplitude and latency of the M-response and specially calculated density of nerve fibers in three main sections of the sciatic nerve (proximal, central, and distal parts) were determined using longitudinal sections impregnated with silver nitrate (Sham — n=4, Sect — n=7, Raph — n=6). Quantitative data processing and statistical correlation analysis were performed using mathematical statistics tools.

Results. Against the background of significant differences in the mean SFI values across all samples, a statistically significant difference was also found in the M-response amplitude for three pairs of sample comparisons, in the M-response latency (when comparing the values of the Sham and Sect groups, as well as the Sham and Raph groups), and in the density of nerve fibers (for the proximal part, central part or neuroma, and distal part of the nerve in three pairs of comparisons). Within each group, a statistically significant (strong negative) correlation was observed only between the M-response latency and the nerve fiber density in the distal section of the nerve in the Raph group. When combining the results from all groups into one cohort, significant correlations were found between individual values of the M-response amplitude and latency, SFI and M-response amplitude, SFI and M-response latency, SFI and nerve fiber density across all three nerve sections, M-response amplitude and nerve fiber density in all sections, and M-response latency and nerve fiber density in the central section of the nerve or neuroma.

Conclusions. There is a correlation between the sciatic functional index, M-response amplitude and latency, and the density of sciatic nerve fibers. The statistical significance of these correlations becomes evident only with a sufficient number of observations and a broad range of individual values for the mentioned parameters.

Keywords: *peripheral nerve injury; neurorrhaphy; sciatic functional index; M-response amplitude; M-response latency; nerve fiber density; correlation.*

Introduction

Peripheral nerve injury (PNI) is generally considered the simplest and most prognostically favorable type of nervous system trauma for obvious reasons. However, it is also characterized by long-term, often lifelong impairments in motor function, sensory deficits, and chronic pain [1–5]. In peacetime, the incidence of this pathology remains relatively low [6–9]. However, during armed conflicts, its frequency is likely to increase due to the high occurrence of combat-related limb injuries [10, 11], where PNI is often associated with damage to major blood vessels and tubular bones [12–16]. In such cases, several factors significantly worsen the outcomes of PNI treatment [10, 17, 18].

Several factors contribute to the substantial socioeconomic impact of PNI: 1) the majority of those affected are men of prime working age [6–9, 19, 13]; 2) the most frequently injured nerves are those of the upper limbs, particularly in the wrist and hand regions [6–8, 13, 19, 20]; 3) the primary treatment for PNI is predominantly surgical [3–5, 7–9, 21]; 4) these patients typically require prolonged rehabilitation therapy afterwards [5]. These aspects contribute to significant financial costs [6, 20, 22–24].

Despite the nervous system's considerable capacity for self-repair following PNI and notable advances in treatment approaches [4, 21, 25–30], therapeutic efficacy remains limited [4, 31]. This limitation is due to several factors: the lack of satisfactory conditions for nerve fiber growth through the injury site [28], the death of neurons whose axons were damaged during the PNI — particularly brain neurons [32–34], restricted compensatory plasticity of brain neural networks [35–37], and rapid atrophy of muscles deprived of innervation as a result of PNI [31, 38–40]. Therefore, improving PNI treatment outcomes could be achieved by optimizing conditions for nerve fiber regeneration at the injury site [28, 41], maintaining the viability of injured neurons [32–34], stimulating the plasticity of their networks [35–37], and limiting the atrophy of denervated muscles [31, 40].

The development of any of these approaches is impossible outside the methodology of experimental neurosurgery. The optimal design for PNI research typically involves modeling the transection of a rat's sciatic nerve with immediate suture connection, followed by observation over 9–12 weeks and verification of results through clinical-functional tests, electroneuromyography, and morphometric analysis [42]. Arguably, the most widely used comprehensive tool for evaluating motor function and the macroscopic morphology of a paretic limb is the sciatic functional index (SFI) [43]. Currently, data on the correlation of results from these three assessment methods in sciatic nerve injury under experimental conditions remain inconsistent [44–48].

Objective: to determine the correlation between individual SFI values, the M-response amplitude and latency, and the density of nerve fibers in the injured sciatic nerve 12 weeks after its transection and neurorrhaphy.

Materials and Methods

Experimental animals and groups

The study was conducted on 19 white outbred male rats aged 4–6 months, weighing 280–380 g, obtained from the vivarium of the A.P. Romodanov Institute of Neurosurgery of the National Academy of Medical Sciences (NAMS) of Ukraine. The animals were kept under standard laboratory conditions. The study design was approved by the Bioethical Expertise and Scientific Research Ethics Committee of the Bogomolets National Medical University (Minutes No. 155 dated January 31, 2022) and the Bioethics Committee of the Romodanov Neurosurgery Institute of the NAMS of Ukraine (Minutes No. 39 dated May 18, 2022). The animals were selected from a general population (n=42), the SFI study results of which were presented in a previous publication [49].

Three experimental groups were formed: 1) Sham-operated animals which underwent surgical access to the sciatic nerve (Sham; n=6), 2) animals, which underwent complete sciatic nerve transection (sectio) in the middle third (Sect; n=7), 3) animals which immediately after complete sciatic nerve transection, underwent neurorrhaphy (neurorrhaphia, or neurorraphia) of the stumps (Raph; n=6).

Peripheral nerve injury model

The surgical techniques used in the experimental groups were described in detail in a previous study [49]. All procedures were performed under general anesthesia and deep muscle relaxation, achieved through intraperitoneal administration of a mixture of xylazine hydrochloride (15 mg/kg, "Biowet", Poland) and ketamine hydrochloride (75 mg/kg, "Farmak", Ukraine) under mild aseptic conditions. The animals were placed in a prone position, and surgical access to the sciatic nerve was achieved through a linear skin incision along the outer surface of the femur, followed by cutting the tendon of the short head of the biceps femoris muscle. After isolating the sciatic nerve trunk, the procedure was completed in the Sham group without further intervention. In the Sect and Raph groups, the nerve was completely transected. In the Raph group, the nerve stumps were reconnected using an end-to-end epineural suture technique with 3–6 monofilament stitches (8.0–10.0; "Ethicon", USA) under 14x magnification. In all groups, the surgical wound was closed with two layers of interrupted sutures, and the skin incision was treated with povidone-iodine solution (Betadine, "EGIS", Hungary). For systemic pain management and anti-inflammatory therapy, bicillin-5 ("Arterium", Ukraine) was administered subcutaneously in the posterior cervical region at a dose of 1 million IU/kg body weight, while dexamethasone ("KRKA", Slovenia) was injected intraperitoneally at a dose of 6 mg/kg body weight. Until satisfactory behavioral activity was restored, the rats were kept at an elevated ambient air temperature, after which they were housed in groups of 3–6 animals per cage.

Exclusion Criteria

No animals in the study population exhibited signs of purulent-inflammatory complications, trophic ulcers of the paretic limb or adjacent areas, or autophagy. For

This article contains some figures that are displayed in color online but in black and white in the print edition.

reasons not specifically investigated, two animals from the Sect sample died during the observation period; their deaths occurred within the first week but more than 48 hours post-intervention. These animals were not included in the declared study population (n=19), and data obtained from them were excluded from analysis.

Assessment of Sciatic Functional Index

The SFI was determined using a standard methodology [45, 50, 51] with proprietary technical modifications [49] in all experimental groups and samples 12 weeks after peripheral nerve injury (PNI) modeling ***(Fig. 1)***. Variations in the actual testing periods among the experimental animals did not exceed 5% of the corresponding observation periods and concerned five animals from the Raph sample. Footprints were obtained on a paper strip covering the floor of a tunneled horizontal walkway, and SFI was calculated using footprint measurements based on the Bain–Mackinnon–Hunter formula [45]:

$$SFI = -38{,}3 \times \frac{EPL-NPL}{NPL} + 109{,}5 \times \frac{ETS-NTS}{NTS} + 13{,}3 \times \frac{EIT-NIT}{NIT} - 8{,}8, \quad (1)$$

where SFI represents the sciatic functional index;

E denotes the injured limb, and N denotes the intact limb;

PL is the distance between the heel print and the longest toe print;

TS is the distance between the first and fifth toe prints;

and IT is the distance between the second and fourth toe prints.

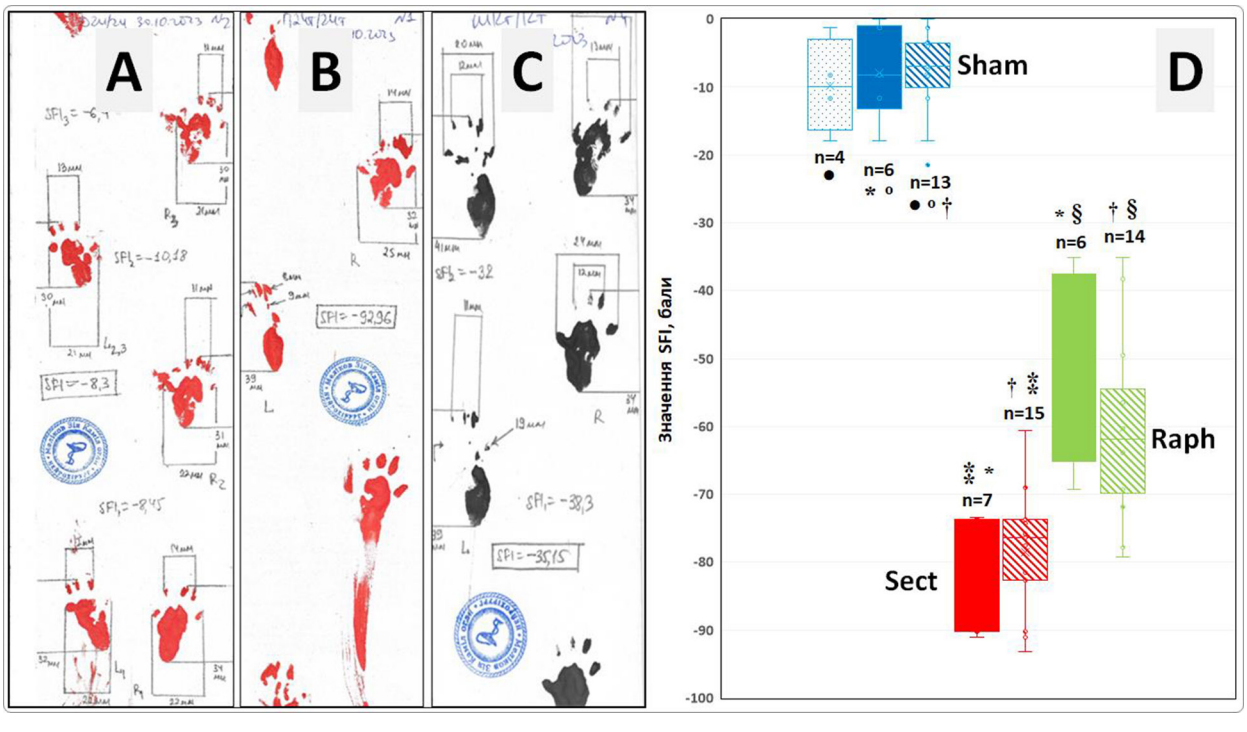

Fig. 1. Examples of footprints and the measurement of their geometric parameters for calculating the sciatic functional index (SFI) in animals from the Sham (A), Sect (B), and Raph (C) groups and subgroups. D - actual SFI values (points), their medians (horizontal lines within the rectangles), interquartile range boundaries (lower and upper sections of the rectangles corresponding to the first and third quartiles, respectively), mean values (x), standard deviations (distance between the mean value marker and the lower or upper edge of each rectangle), and dispersion beyond the upper and lower quartiles (horizontal bars of the vertical whiskers) in the subgroups analyzed in this study (Sham – n = 6 and n = 4; Sect – n = 7; Raph – n = 6), as well as in the corresponding overall groups (Sham – n = 13; Sect – n = 15; Raph – n = 14) investigated in the previous study [49].

Notes:

* Statistically significant differences in SFI values in pairwise subgroup comparisons ($p < 0.001$, ANOVA test and Tukey's post-hoc comparisons).;

† Statistically significant differences in SFI values when comparing overall groups ($p < 0.001$, Kruskal–Wallis test and Steel–Dwass post-hoc comparisons);

°, •, ‡, § – Differences in SFI values in comparisons between an overall group and its corresponding subgroup are statistically non-significant ($p > 0.05$, Student's t-test for independent samples).

Electroneuromyographic Examination

Electroneuromyographic (ENMG) assessment was performed on all animals from all study groups 12 weeks after injury modeling, immediately after obtaining data for determining the SFI. Anesthesia was induced via intraperitoneal injection of 1% thiopental sodium solution (10 mg/mL) ("Kyivmedpreparat", Ukraine), with additional intraperitoneal administration of ketamine and xylazine when necessary (as previously described) due to premature reduction of anesthesia depth. The sciatic nerve was freed from scar tissue through the same surgical approach. A grounding electrode, moistened with 0.9% sodium chloride solution, was placed under the animal's abdomen. Proximally to the injury site, the nerve was enclosed between two contacts of a custom-made stimulating electrode ***(Fig. 2A, B)***, avoiding contact with surrounding tissues. Each contact was made from a 5-mL syringe needle with an external diameter of 0.7 mm, a length of 38 mm, and an electrical resistance of up to 0.1 Ohm ***(Fig. 2A)***. Stimulation current was generated using a four-channel electromyograph "M-Test" (LLC SPE "DX-SYSTEMS", Kharkiv) in packets of 10 impulses, each lasting 0.2 ms at a magnitude of 6 mA, with a pulse frequency of 1 Hz per packet. A registration electrode, constructed similarly to the stimulation electrode, was inserted into the gastrocnemius muscle (*m. triceps surae*), compressed between the experimenter's thumb and index finger, parallel to the main axis of the tibia at the thickest muscle region ***(Fig. 2B)***. The distance between the stimulation and registration electrodes was approximately 25 mm. Impulses were recorded and processed using the electromyograph with the "M-Test" software package (LLC SPE "DX-SYSTEMS", Kharkiv).

Two parameters were evaluated: 1) amplitude of the M-response (mV) – the absolute difference between the peak negative and peak positive values of the recorded electrical potential (M-response) during gastrocnemius muscle excitation induced by sciatic nerve stimulation; 2) latency period of the M-response (ms) – the time from the moment of sciatic nerve electrical stimulation to the initial negative deviation of the recorded electrical potential in the gastrocnemius muscle.

In Vivo Fixation of biological material, withdrawal of animals from the experiment, and subsequent material fixation

Immediately after the completion of electroneuromyography, the animal, under deep anesthesia, was secured in a supine position on the operating table. The thoracic cavity was widely opened to expose the heart apex, which was perforated with a needle connected to a reservoir containing cooled physiological saline. The reservoir was positioned at a height sufficient to create the necessary infusion pressure. Blood was expelled from the circulatory

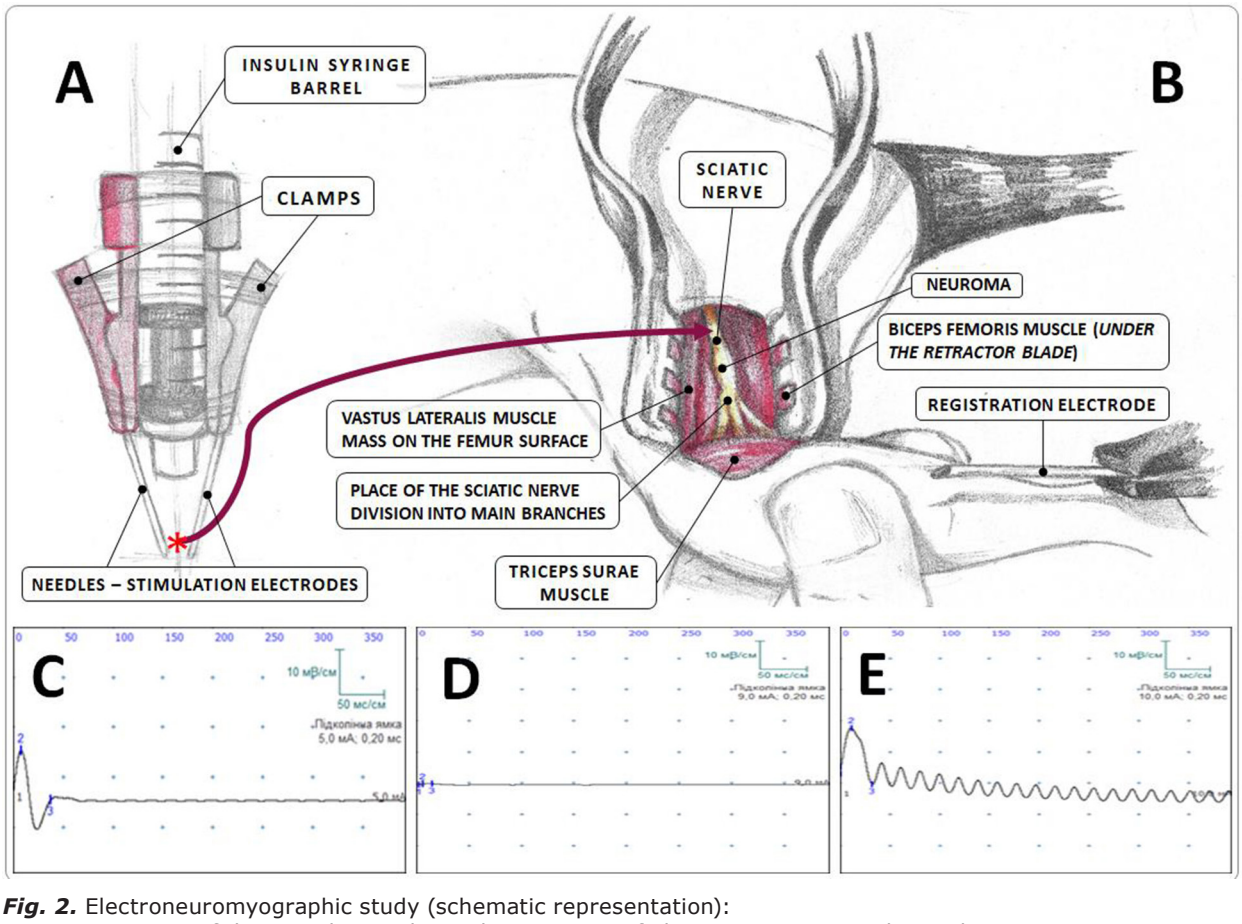

Fig. 2. Electroneuromyographic study (schematic representation):
A — construction of the stimulation electrode; B — area of electroneuromyography implementation;
C–E — examples of electroneuromyograms in the Sham (C), Sect (D), and Raph (E) groups;
* the site of sciatic nerve trunk capture by the needle of the stimulation electrode.

system through a perforation in the right atrial wall. While the heart was still beating, the circulatory system was perfused with cooled physiological saline (~50 mL), followed by a 4% paraformaldehyde solution (~50 mL), until fibrillation of the limb, trunk, and tail muscles was observed. The paraformaldehyde solution was freshly prepared (ex tempore) from a 37% formalin solution ("Inter-Synthesis", Ukraine) and distilled water in the required volume.

In animals whose tissues were pre-fixed using this method, the sciatic nerve, including the injury site (for rats in the Sham and Raph groups), or segments of both nerve stumps, each 0.5–1.0 cm in length (for the Sect group), was excised. The distal segment in the Sect group exhibited severe atrophy, appearing semi-transparent and often containing multiple closely adjacent nerve trunks. The excised samples were placed in a 4% paraformaldehyde solution for 5–7 days, followed by washing in phosphate-buffered saline for 1–2 days. After removal of residual surrounding tissues, the nerve samples were transferred to a 10% neutral paraformaldehyde solution for histopathological examination. The phosphate-buffered saline was prepared by dissolving one tablet of a concentrated dried reagent of a similar chemical composition (Phosphate buffered saline; Sigma-Aldrich, USA) in 200 mL of distilled water. Throughout the post-excision and primary fixation period, all samples were stored at a temperature of 0 to +5 °C.

Pathomorphological examination of the sciatic nerve was conducted on 4 animals from the Sham group, 7 from the Sect group, and 6 from the Raph group. Sciatic nerve samples obtained from the Sect and Raph groups were acutely segmented into three fragments: central (Sect group) or regenerative neuroma (Raph group), proximal, and distal (Sect and Raph groups). In the Sham group, the fixed nerve trunk was not divided into fragments for obvious reasons. Typically, the proximal fragment in the Sect and Raph groups represented an intact trunk, while the distal fragment contained the initial sections of the common peroneal and tibial nerves, which were closely positioned. In the Sect group, the central fragment exhibited poor development, leading to the presence of a diastasis between the proximal and distal segments.

Not all fixed samples were selected for further analysis (see below). During histological processing, the material was placed on the surface of the metal working block of a microtome-cryostat (MK-25, USSR), frozen to approximately –20 °C, and sectioned into longitudinal slices with a thickness of 20 μm. These sections were then immersed in room-temperature tap water. The selected sections were carefully transferred using a glass hook into a 1% acidic formalin solution for storage. After approximately 24 hours, the sections were placed in an organic solvent (pyridine) for one day, followed by three washes in tap water (~10 min each) and three additional washes in distilled water (~5 min each). Subsequently, the sections were transferred into a 30% silver nitrate solution for 24 hours. The next day, the sections were briefly (less than 1 min) immersed in distilled water, then subjected to three washes (~4 min each) in a 1% acidic formalin solution. This was followed by ~2 min immersion in a freshly prepared ammoniacal silver solution. The sections were then placed in a 1% acidic formalin solution until they developed a brown coloration, after which they were treated for 15–20 s in a 0.5% acidic formalin solution containing ~1–2% glucose, followed by ~30 s in a weak ammonia solution and ~10–15 min in distilled water. Subsequently, the sections were immersed in a 99.8% isopropyl alcohol solution for several minutes and then mounted onto glass slides. After drying, 1–2 drops of Canada balsam were applied, and the sections were covered with a thin cover glass. Photodocumentation was performed no earlier than 24 hours post-processing using an Olympus BX51 microscope equipped with an Olympus C3040ZOOM digital camera and Olympus DP-Soft 3.2 software (Olympus, Tokyo, Japan). The micrographs, captured at 200× magnification, had a calculated height of 440 μm with a digital resolution of 2272×1704 pixels. For each of the three nerve segments, at least six micrographs were obtained, typically from different longitudinal sections of the same segment. The digital image height was measured using ImageJ software (Wayne Rasband, USA). A perpendicular line was drawn across the main nerve axis, and the number of nerve fibers intersecting this line was counted. This procedure was repeated multiple times, shifting the line along the nerve's main axis within the micrograph. In the neuroma region, the number of measurements was increased to 5–6 for greater accuracy. The obtained fiber count values from each measurement were used to construct variability series for statistical analysis. The results were expressed as the nerve fiber density – the number of fibers calculated per 440 microns of actual length of the aforementioned imaginary line perpendicular to the main nerve axis.

Statistical data analysis

Statistical analysis of the quantitative data was performed using the EZR (R-STATISTICS) software package. If the distribution of the studied parameter in the samples did not deviate from normality, the mean level was presented as M±SD, where M represents the arithmetic mean and SD denotes the standard deviation. In cases where the distribution deviated from normality, the median and interquartile range were reported as Me (Q_I-Q_{III}), where Me is the median, and Q_I-Q_{III} represent the first and third quartiles, respectively. The Shapiro–Wilk test was used to assess the normality of the data distribution. If at least one of the compared samples exhibited a non-normal distribution of individual values, the Kruskal–Wallis test was applied to determine the significance of differences between groups, with post hoc comparisons conducted using the Steel–Dwass test. If the data were normally distributed, the homogeneity (equality) of variances among the samples was assessed using Bartlett's test. If variance distributions deviated from normality, comparisons were made using the Kruskal–Wallis test combined with the Steel–Dwass test for post hoc analysis. In cases where variance distribution was normal, analysis of variance (ANOVA) was employed, followed by Tukey's test for post hoc comparisons.

To determine the significance of differences in SFI values between the analyzed samples and overall groups at the corresponding observation time points [49], Student's t-test for independent samples was used.

The significance of correlation between individual SFI values, amplitude and the latency of M-response and

nerve fiber density across all groups was evaluated using Spearman's rank correlation test (if the distribution of values for both studied variables differed from normal) or using Pearson's criterion (if at least one of the variables followed a normal distribution).

In all cases, the assumptions regarding the statistical significance of the obtained result were considered correct if the probability of the opposite assumption was less than 0.05 ($p<0.05$).

Results

Sciatic Functional Index (SFI)

According to previous data [49], the mean SFI value at 12 weeks post-injury was –7.6±6.3 points in the overall Sham group (n=13), –78.5±8.6 points in the overall Sect group (n=15), and –60.4±13.0 points in the overall Raph group. Statistically significant differences were identified for all three pairwise comparisons between the overall groups: Sham vs. Sect, Sham vs. Raph, and Sect vs. Raph [49] ***(Table 1, Fig. 1)***.

In the specific subgroups analyzed in this study, the SFI values were –7.9±6.7 points in the Sham subgroup, –80.6±7.5 points in the Sect subgroup, and –52.1±13.7 points in the Raph subgroup ***(see Table 1, Fig. 1)***. The SFI values for each subgroup did not differ significantly from their corresponding overall experimental groups. As in the case of the overall groups, SFI values in the examined subgroups showed significant differences in all pairwise comparisons ***(see Table 1)***. These findings confirm the representativeness of the analyzed subgroups, at least in terms of the functional-anatomical parameter SFI.

Amplitude and latency of the M-Response

In the Sham subgroup, the mean amplitude of the M-response was 9.5 (8.2; 9.5) mV, while the mean latency was 0.9 ± 0.1 ms ***(Table 2, Fig. 3)***. In the Sect subgroup, these values were 0.3 (0.3; 0.4) mV and 3.9 ± 3.1 ms, respectively. In the Raph subgroup, the amplitude was 4.4 (3.7; 4.9) mV, with a latency of 3.3 ± 1.7 ms. Statistically significant differences in M-response amplitude were

Table 1. Mean SFI values in the overall experimental groups [49] and the analyzed subgroups (M ± SD)

Animal population	Experimental animal populations		
	Sham	Sect	Raph
Analyzed subgroups	n=6; –7,9 ± 6,7 $^{*\,o}$	n=7; –80,6 ± 7,5 $^{*\,1}$	n=6; –52,1 ± 13,7 $^{*\,2}$
Overall groups [49]	n=13; –7,6 ± 6,3 $^{\dagger\,o}$	n=15; –78,5 ± 8,6 $^{\dagger\,1}$	n=14; –60,4 ± 13,0 $^{\dagger\,2}$

Notes:

* The difference in SFI values is statistically significant ($p < 0.001$, ANOVA test and Tukey's post-hoc comparisons);

† The difference in SFI values is statistically significant ($p < 0.001$, Kruskal–Wallis test and Steel–Dwass post-hoc comparisons);

$^{o,\,1,\,2}$ Differences in SFI values are statistically non-significant ($p > 0.05$, Student's t-test for independent samples).

Table 2. Mean values of M-response amplitude (mV) and latency (ms) in experimental subgroups

Experimental subgroups					
Sham (n=6)		Sect (n=7)		Raph (n=6)	
M-response amplitude, Me (Q_I-Q_{III})	M-response latency, M±SD	M-response amplitude, Me (Q_I-Q_{III})	M-response latency, M±SD	M-response amplitude, Me (Q_I-Q_{III})	M-response latency, M±SD
9,5 (8,2; 9,5) $^{*\,\dagger}$	0,9±0,1 $^{X,\,Y}$	0,3 (0,3; 0,4) $^{*\,o}$	3,9±3,1 ^{X}	4,4 (3,7; 4,9) $^{\dagger\,o}$	3,3±1,7 ^{Y}

Notes:

* *The difference in M-response amplitude between the Sham and Sect subgroups is statistically significant ($p < 0.01$, Steel–Dwass post-hoc test);*

† *The difference in M-response amplitude between the Sham and Raph subgroups is statistically significant ($p < 0.05$, Steel–Dwass post-hoc test);*

^{o} *The difference in M-response amplitude between the Sect and Raph subgroups is statistically significant ($p < 0.01$, Steel–Dwass post-hoc test);*

^{X} *The difference in M-response latency between the Sham and Sect subgroups is statistically significant ($p < 0.01$, Steel–Dwass post-hoc test);*

^{Y} *The difference in M-response latency between the Sham and Raph subgroups is statistically significant ($p < 0.05$, Steel–Dwass post-hoc test).*

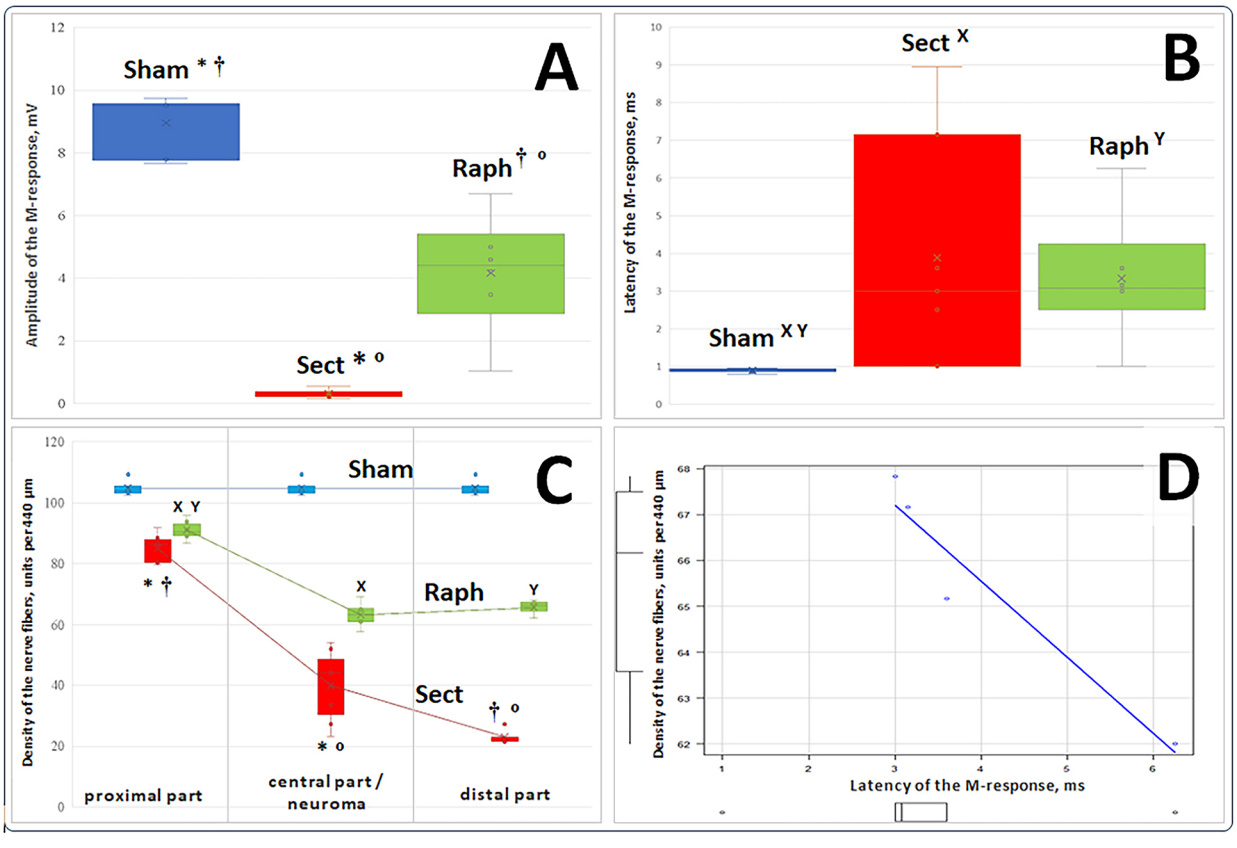

Fig. 3. Actual values (points) of M-response amplitude (mV, A), latent period (ms, B), nerve fiber density (units/440 µm, C), their medians (horizontal lines within vertical rectangles), interquartile range boundaries (lower and upper parts of the rectangles corresponding to the first and third quartiles at each time point, respectively), mean values (x), standard deviations (distance between the mean value mark and the lower or upper edge of each rectangle), and dispersion (variance) beyond the upper and lower quartiles (horizontal bars of the vertical whiskers) for three sample groups. D represents a significant strong negative correlation between individual values of the M-response latent period and nerve fiber density in the distal portion of the resected sciatic nerve trunk in the Raph sample (r = −0.96, 95% confidence interval –1.00…–0.01, p < 0.05).

Notes:
Regarding block A (M-response amplitude):

* The difference in values between the Sham and Sect groups is statistically significant (p < 0.01, Steel-Dwass test for post hoc comparisons).

† The difference in values between the Sham and Raph groups is statistically significant (p<0.05, Steel-Dwass test for post hoc comparisons).

° The difference in values between the Sect and Raph groups is statistically significant (p < 0.01, Steel-Dwass test for post hoc comparisons).

Regarding Block B (M-response latent period):

X The difference in values between the Sham and Sect groups is statistically significant (p < 0.01, Steel-Dwass test for post hoc comparisons).

Y The difference in values between the Sham and Raph groups is statistically significant (p < 0.05, Steel-Dwass test for post hoc comparisons).

Regarding Block C (nerve fiber density; results for three parts of the nerve in each group are connected by a conditional line; in the Sham group, for obvious reasons, the same nerve segment was used for all three measurements):

* The difference between the nerve fiber density values in the proximal and central parts of the nerve in the Sect group is statistically significant (p < 0.01, Steel-Dwass test for post hoc comparisons).

† The difference between the nerve fiber density values in the proximal and distal parts of the nerve in the Sect group is statistically significant (p < 0.05, Steel-Dwass test for post hoc comparisons).

° The difference between the nerve fiber density values in the central and distal parts of the nerve in the Sect group is statistically significant (p < 0.05, Steel-Dwass test for post hoc comparisons).

X The difference between the nerve fiber density values in the proximal part of the nerve and the neuroma in the Raph group is statistically significant (p < 0.001, Tukey's test for post hoc comparisons).

Y The difference between the nerve fiber density values in the proximal and distal parts of the nerve in the Raph group is statistically significant (p < 0.001, Tukey's test for post hoc comparisons).

observed across all pairwise subgroup comparisons (Sham vs. Sect, Sham vs. Raph, and Sect vs. Raph). The latency of the M-response differed significantly only in comparisons between the Sham and Sect subgroups and between the Sham and Raph subgroups.

The nerve fiber density

A macroscopic histological examination revealed qualitative visual differences in the spatial density, course, and mutual arrangement of myelinated nerve fibers in the studied segments of the sciatic nerve among animals from different experimental groups ***(Fig. 4)***.

The SFI values of the Sham sample (n = 4), used for determining nerve fiber density, exhibited sciatic function index (SFI) values that did not significantly differ from those of the overall Sham group (n = 13) [49] (p = 0.56, Student's t-test for independent samples) ***(Fig. 1D)***, with a mean–9.8 ± 6.9 points. The nerve fiber density in this sample was 104.9 ± 3.1 units/440 μm ***(Table 3)***.

In the Sect group (n = 7), the nerve fiber density in the proximal part of the nerve (n = 7) was 86.5 80.4; 87.9 units/440 μm, in the central part (n = 7) – 44.2 (30.4; 48.7) units/440 μm, and in the distal part (n = 4) – 21.6 (21.5; 23.1) units/440 μm. These values differed significantly ***(Table 3)***.

In the Raph group (n = 6), the mean nerve fiber density in the proximal part of the nerve (n = 6) was 91.1 ± 3.3 units/440 μm, in the neuroma region (n = 6) – 63.2 ± 4.1 units/440 μm, and in the distal part of the nerve (n = 4) – 65.5 ± 2.6 units/440 μm. Statistically significant differences within this group were observed only when comparing the proximal part with the neuroma and the proximal with the distal part ($p < 0.001$, Tukey's test for post hoc comparisons; ***Table 3***).

When comparing the values of the nerve fiber density between different groups, statistically significant differences were observed for all nerve segments ***(Table 4)***. Due to the limited sample size for each sample (n = 4), a statistically significant difference in the distal nerve segment was only detected when using the Wilcoxon-Mann-Whitney test ***(Table 4)***.

Correlation between the values of investigated parameters

Within each of the three experimental groups, no statistically significant correlation was found between individual values of the M-response amplitude and the M-response latency, the Sciatic Functional Index (SFI) and both electrophysiological parameters, the SFI and the density of nerve fibers (in all three examined nerve segments), or the density of nerve fibers in the three examined nerve segments and the M-response latency or amplitude. The only exception was a strong negative correlation identified between the individual values of nerve fiber density in the distal part of the nerve and the M-response latency in the Raph group ***(Fig. 3D)***.

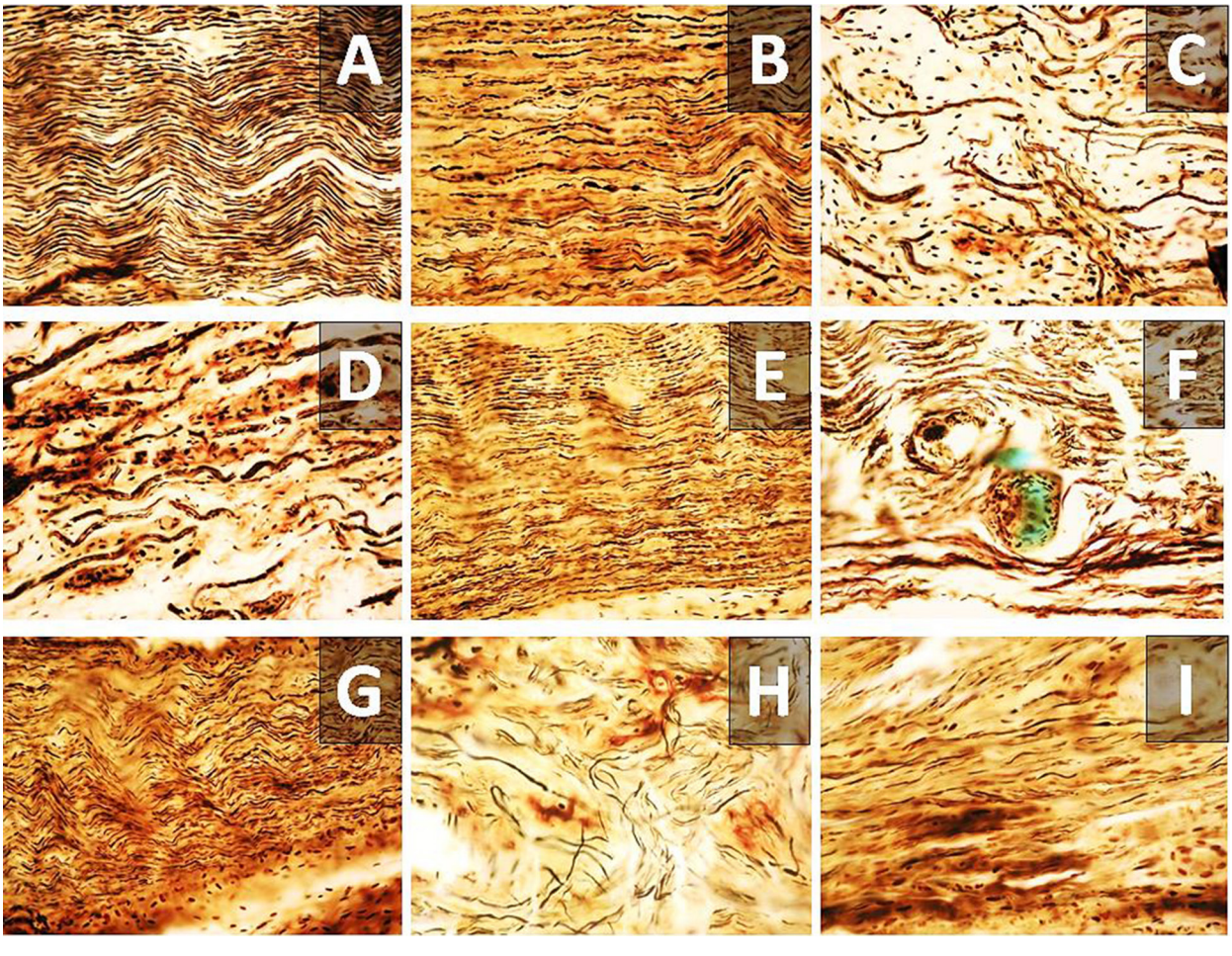

Fig. 4. Tissue structure of the examined region of the sciatic nerve in the Sham (A), Sect (B – proximal part; C, H – central part; D – distal part), and Raph (E – proximal part; F, I – neuroma; G – distal part) groups. A–G – ×200; H, I – ×400.

Table 3. The nerve fiber density (units/440 μm) in the proximal, central, and distal parts of the nerve

Experimental sample	Examined nerve fragment		
	Proximal part	**Central part/ neuroma**	**Distal part**
Sham	Mean±SD, n=4		
	104,9±3,1		
Sect	Me (Q_I-Q_{III}), n=7	Me (Q_I-Q_{III}), n=7	Me (Q_I-Q_{III}), n=4
	86,5 (80,4; 87,9) * †	44,2 (30,4; 48,7) * °	21,6 (21,5; 23,1) † °
Raph	Mean±SD, n=6	Mean±SD, n=6	Mean±SD, n=4
	91,1±3,3 X, Y	63,2±4,1 X	65,5±2,6 Y

Notes:

* Statistically significant difference in the nerve fiber density values between the proximal and central part of the nerve in the Sect sample ($p < 0.01$, Steel-Dwass test for post hoc comparisons).

† Statistically significant difference in the nerve fiber density values between the proximal and distal part of the nerve in the Sect sample ($p < 0.05$, Steel-Dwass test for post hoc comparisons).

° Statistically significant difference in the nerve fiber density values between the central and distal part of the nerve in the Sect sample ($p < 0.05$, Steel-Dwass test for post hoc comparisons).

X Statistically significant difference in the nerve fiber density values between the proximal part of the nerve and neuroma in the Raph sample ($p < 0.001$, Tukey's test for post hoc comparisons).

Y Statistically significant difference in the nerve fiber density values between the proximal and distal part of the nerve in the Raph sample ($p < 0.001$, Tukey's test for post hoc comparisons).

Table 4. Intergroup differences in the density of nerve fibers (units/440 μm) in the examined nerve fragments

Experimental sample	Examined nerve fragment		
	Proximal part, Mean±SD	**Central part/ neuroma, Me (Q_I-Q_{III})**	**Distal part, Me (Q_I-Q_{III})**
Sham	n=4		
	103,8 (103,1; 105,6) X, Y, 1, 2 АБО 104,9±3,1 * †		
Sect	n=7	n=7	n=4
	84,9±4,7 * °	44,2 (30,4; 48,7) X, Z	21,6 (21,5; 23,1) 1, 3
Raph	n=6	n=6	n=4
	91,1±3,3 † °	63,1 (60,9; 65,2) Y, Z	66,2 (64,4; 67,3) 2, 3

Notes.

For the proximal part of the nerve:

* A statistically significant difference in nerve fiber density values between the Sham and Sect samples ($p<0.001$, Tukey's post-hoc test);

† A statistically significant difference in nerve fiber density values between the Sham and Raph samples ($p<0.001$, Tukey's post-hoc test);

° A statistically significant difference in nerve fiber density values between the Sect and Raph samples ($p<0.05$, Tukey's post-hoc test).

For the central part of the nerve:

X A statistically significant difference in nerve fiber density values between the Sham and Sect samples ($p<0.05$, Steel-Dwass post-hoc test);

Y A statistically significant difference in nerve fiber density values between the Sham and Raph samples ($p<0.05$, Steel-Dwass post-hoc test);

Z A statistically significant difference in nerve fiber density values between the Sect and Raph samples ($p<0.01$, Steel-Dwass post-hoc test).

For the distal part of the nerve:

1 A statistically significant difference in nerve fiber density values between the Sham and Sect samples ($p<0.05$, Wilcoxon-Mann-Whitney test);

2 A statistically significant difference in nerve fiber density values between the Sham and Raph samples ($p<0.05$, Wilcoxon-Mann-Whitney test);

3 A statistically significant difference in nerve fiber density values between the Sect and Raph samples ($p<0.05$, Wilcoxon-Mann-Whitney test).

When the results of all three groups were pooled into a single cohort, statistically significant correlations were observed ***(Fig. 5)***. These included correlations between the individual values of the M-response amplitude and latency, the SFI and the M-response amplitude, the SFI and the M-response latency, as well as between the SFI and the density of nerve fibers in the proximal, central (or neuroma), and distal parts of the nerve. Additionally, significant correlations were found between the M-response amplitude and the nerve fiber density in the proximal, central (or neuroma), and distal parts of the nerve, as well as between the M-response latency and the nerve fiber density in the central part of the nerve (or neuroma).

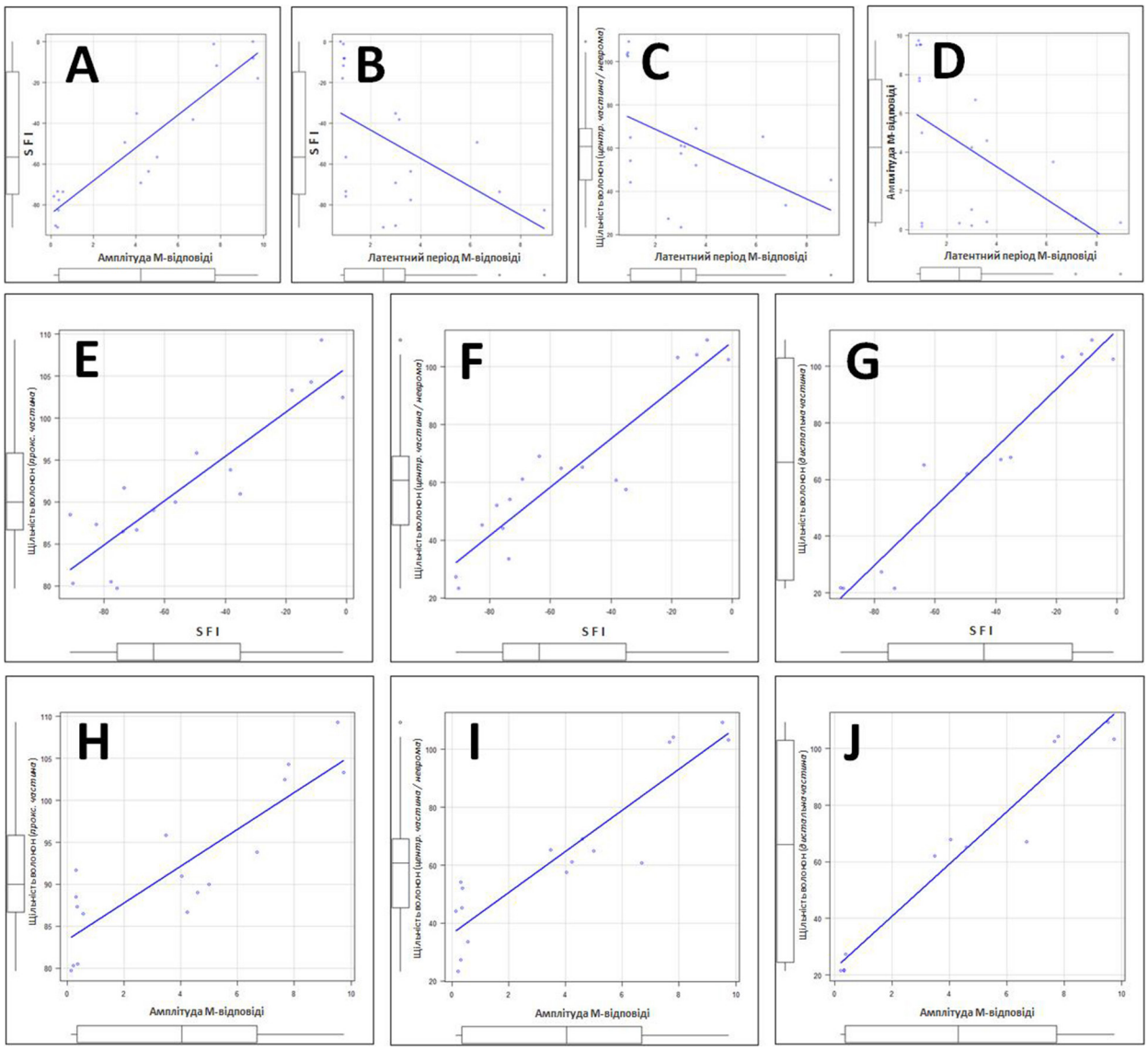

Fig. 5. Examples of statistically significant correlations between individual values of the analyzed parameters (presented in the units used in this article) within the cohort formed from animals of all experimental groups:
A – correlation between individual values of M-response amplitude and SFI (r_s = +0.88, $p < 0.001$);
B – correlation between individual values of M-response latency and SFI (r_s = –0.66, $p < 0.01$);
C – correlation between individual values of M-response latency and the density of nerve fibers in the central part of the nerve or neuroma (r_s = –0.50, $p < 0.05$);
D – correlation between individual values of M-response latency and amplitude (r_s = –0.57, $p < 0.05$);
E, F and G – correlations between individual values of SFI and the density of nerve fibers in the proximal part (E, r = 0.90, 95% CI: 0.73–0.96, $p < 0.001$), central part or neuroma (F, r = 0.92, 95% CI: 0.80–0.97, $p < 0.001$), and distal part of the nerve (G, r = 0.97, 95% CI: 0.88–0.99, $p < 0.001$);
H, I and J – correlations between individual values of M-response amplitude and the density of nerve fibers in the proximal part (H, r = 0.87, 95% CI: 0.67–0.95, $p < 0.001$), central part or neuroma (I, r = 0.92, 95% CI: 0.78–0.97, $p < 0.001$), and distal part of the nerve (J, r = 0.97, 95% CI: 0.90–0.99, $p < 0.001$)

Discussion

Peripheral nerve injury (PNI) is a common type of trauma in wartime settings [10, 11], characterized by a complex set of motor dysfunctions, sensory impairments, and chronic pain [1–5]. The effectiveness of PNI treatment remains limited [4, 31]. Promising approaches for its improvement include the development of multi-component bioengineered connectors for the ends of the injured nerve [26, 28, 52–54] and strategies to enhance neuronal network plasticity in the brain [36, 37], particularly through the use of stem cells [26, 55, 56]. The search for and validation of novel PNI treatment methods are typically conducted in experimental settings. One of the widely accepted, albeit imperfect, models of PNI is the transection of the rat sciatic nerve [42, 57], followed by a 9–12-week observation period [42] and assessment of the recovery process through functional-anatomical (SFI evaluation) [43], electrophysiological, and histological analyses [42, 58].

The relationship between three key classes of sciatic nerve status indicators — functional (SFI, locomotor activity, and exteroception), electrophysiological, and morphometric — remains unresolved. Some studies have found no correlation between SFI values and morphometric or electrophysiological parameters in certain nerve injury models ([44], see also [45, 59]), while others suggest a potential correlation for some of these three indicator classes [46, 47, 60] or for specific variables at particular time points during the recovery process [48, 61]. Additionally, several studies using similar sciatic nerve injury models (and various experimental animals) did not specifically investigate the presence of statistically significant correlations between electrophysiological, functional-anatomical, or morphometric parameters (see, for example, [62]). For example, F. Kanaya et al. (1996) [61], using a rat model of sciatic nerve transection or excision and immediate autografting or neurorrhaphy, found after 12 weeks of observation that, when comparing individual values of 14 indicators from three classes (functional-anatomical, electroneuromyographic, and histomorphometric), statistically significant correlations were only found between the SFI, calculated using the primary formula of L. de Medinaceli et al. (1982) [63], and the ratio of fiber and axon diameters, as well as between this form of SFI and the ratio of the thickness of the myelin sheath to the axon diameter. Conversely, C.A. Munro et al. (1998) [44], after analyzing a large sample of animals and finding no correlation between functional-anatomical, electrophysiological, and morphometric parameters at different time points following a 2 cm tibial nerve resection with immediate allografting [64], concluded that the hypothesis of such a mathematical relationship should be rejected.

In the present study, we examined SFI values, M-response latency and amplitude, as well as the density of nerve fibers 12 weeks after PNI modeling. This set of sciatic nerve status indicators and the assessment timeframe are consistent with other studies on experimental PNI [65–67]. The primary finding of our study is the identification of correlations between these parameters in conditions where a wide range of values is present within a single cohort. Such variability could also be obtained within a single experimental group if individual animal data were analyzed at different time points during the recovery process — an approach we plan to implement in future research.

Technical limitations of the study

In addition to the limitations of the SFI-based method for assessing paretic limb function, previously described in our earlier work [49], there are also drawbacks associated with the electroneuromyographic method. First, identifying the optimal recording site for the M-response (the motor point) within the small triceps surae muscle of the rat, especially in the presence of paretic atrophy, is unfeasible. Second, in experiments on small mammals, interindividual variations in M-response latency may be influenced not only by differences in the fiber composition of the injured nerve but also by variations in the trajectory length of the electrically evoked response between the stimulation and recording electrodes. These variations arise from both differences in animal size and discrepancies in the placement of the recording electrode insertion point. Moreover, accurately determining the trajectory length is impossible due to its complex geometry. Under such conditions, even an unlikely measurement error of 5 mm in determining the impulse propagation trajectory — at the highest conduction velocity of ~110 m/s (see [68])— would result in a latency difference of approximately 0.05 ms, while at a conduction velocity of ~50 m/s, the difference would be 0.1 ms. This is comparable to the standard deviation (SD) in the Sham group (~0.1 ms) and significantly smaller than the SD in the Sect and Raph groups (~3.1 and ~1.7 ms, respectively) ***(Table 2)***. Given these uncertainties, the interpretation of M-response latency values should be approached with caution, and measuring conduction velocity of the evoked electrical excitation under such experimental conditions should be considered impractical. In this context, it is interesting to note that T.I. Petriv et al. (2023) [69] attributed the unreliability of conduction velocity measurements in small experimental animals to the short distance between the stimulation and recording electrodes. These authors, presumably to reduce interindividual variability, analyzed not the absolute values of M-response amplitude and latency in the paretic limb but their normalized counterparts relative to the contralateral limb [69]. Nonetheless, some studies have attempted to calculate sciatic nerve conduction velocity using average trajectory length values [48, 70].

Thus, it is evident that the future of experimental electrophysiology lies in real-time monitoring techniques — including spontaneous electrical activity recording of paretic muscles [71–73] and stimulated neuromyography [72–74]. However, the development of these approaches remains challenging due to a wide range of technical obstacles [75].

Conclusions

By the 12th week of observation, the SFI values in all studied groups differed significantly. The highest values were observed in the sham-operated group, the lowest in the group where a sciatic nerve transection was modeled, and intermediate values were recorded in the group where immediate suture connection was performed following nerve transection.

The M-response latency significantly differed between the sham-operated and nerve transection groups, as well as between the sham-operated and animals that underwent suture connection of the nerve stumps.

The values of the density of nerve fibers of the proximal part, central part or neuroma, and distal part of the nerve differed significantly when comparing the three samples with each other.

Within each experimental group, a strong negative correlation was identified only between M-response latency and fiber density in the distal nerve segment of animals that underwent suture connection of its stump. However, when data from all three groups were combined into a single cohort, statistically significant correlations emerged between the majority of the studied parameters at the individual level.

Thus, a statistically significant relationship exists between SFI, M-response amplitude, M-response latency, and nerve fiber density, which becomes evident when a sufficient number of observations with a wide range of individual parameter values are analyzed.

Disclosures

Conflict of Interest

The authors declare no conflicts of interest.

Ethical Standards

All procedures performed on the experimental animals complied with ethical guidelines and were approved by the ethics committee of the research institution where the study was conducted.

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Case Report

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Intermittent neurogenic claudication-induced gait disturbance treated with Ayurveda: A case report

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This case report details the Ayurvedic treatment of a 49-year-old male with gait difficulties and pain due to lumbar canal stenosis. A three-week course of Ayurvedic therapies, including massage and oral medications, resulted in significant pain reduction (low back pain VAS from 5 to 2; leg pain from 6 to 2) and improvement in the straight leg raise test (40 to 60 degrees). While some gait parameters showed minimal change (step length 0.70m to 0.69m; stride length unchanged; step time 0.48s to 0.49s; stride time unchanged), walking speed increased (1.24 m/s to 1.39 m/s) and gait asymmetry decreased (22% to 20%). While suggesting potential benefits of Ayurveda for pain management in lumbar canal stenosis, the limited impact on gait parameters underscores the need for further research, including objective gait analysis and controlled studies, to confirm efficacy.

Keywords: *sciatica; lumbar spinal stenosis; intermittent neurogenic claudication; gait disorder; case report; Ayurveda*

Introduction

Gait disorders significantly impact an individual's quality of life, affecting daily activities and increasing fall risk [1]. Intermittent Neurogenic Claudication (INC), a common symptom of Degenerative Lumbar Spinal Stenosis (DLSS), often manifests as leg pain, numbness, and lower back pain, contributing to gait disturbances [2]. While the exact pathophysiology of INC in DLSS remains unclear, it is postulated that reduced intervertebral disc nutrition plays a critical role. This impaired gait can significantly diminish an individual's mobility and overall well-being [3].

Ayurveda, the traditional Indian system of medicine, offers a holistic approach to managing such conditions by emphasizing the restoration of balance and harmony within the body [4-5]. Although, conventional treatments for DLSS and associated gait disorders exist, some individuals seek complementary or alternative therapies like Ayurveda. However, there is limited research specifically exploring the efficacy of Ayurvedic interventions for gait disorders secondary to INC. This case report presents the Ayurvedic management of a patient experiencing gait disturbance due to INC, aiming to contribute to the existing literature on this topic [6-7].

The patient, a 49-year-old male, presented with difficulty walking and an unsteady gait. Initial evaluation revealed no apparent neurological deficits; however, the patient reported imbalance and decreased confidence in ambulating. An Ayurvedic assessment identified an imbalance in the patient's *Vata* dosha, the principle governing movement and nervous system function. The treatment plan incorporated herbal remedies, lifestyle modifications, and targeted *Panchakarma* therapy. The patient's progress was closely monitored, with adjustments to the treatment plan as needed. Over time, the patient demonstrated significant improvements in gait and balance, regaining confidence in performing daily activities.

Case Presentation

A 49-year-old male presented with unsteady gait and instability following episodes of lower back pain and leg cramps. Initial neurological examination was unremarkable, however, the patient reported subjective imbalance and decreased confidence in ambulation. The patient's pain was assessed using a numerical rating scale (NRS), with reported pain intensity of 6/10 in the lower back and 5/10 in the left leg.

The patient also exhibited difficulty maintaining an erect posture while standing and walking. The pain intensified after ambulating approximately 50 meters and was relieved by assuming a seated position.

Additionally, the patient experienced paraesthesia in the left lower extremity. Symptom exacerbation was noted during the winter months. The patient's primary

concerns were the onset of leg pain after ambulating short distances and postural instability.

The patient, of low socioeconomic status, is the primary provider and sole wage earner for his family. His occupation involves driving a private passenger van between Gandhinagar and neighbouring towns, often under overcrowded conditions requiring prolonged driving in an uncomfortable posture. In addition to this occupation, he engages in various forms of manual labour in his rural community. The patient has a history of tobacco use including tobacco products for over 10 years. The patient's medical history is unremarkable for trauma, hypertension, diabetes, psychiatric illness, vascular disease, Pott's disease, or arthritis.

He initially sought treatment at a government hospital orthopaedic clinic, where he received nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy for 15 days. Four months later, upon recurrence of symptoms, spinal decompression surgery was recommended. However, due to financial constraints and inability to take leave from work for postoperative recovery, the patient opted to manage pain exacerbations with NSAIDs ***(Table 1)***.

The patient presented to our hospital accompanied by a relative and agreed to Ayurvedic treatment after being assured of affordable care. Physical examination revealed a medium-built individual (height 162.56 cm, weight 57 kg) with normal vital signs. The straight leg raise (SLR) test was positive at 45 degrees for the left leg, accompanied by hyperreflexia in the left foot. The SLR and reflexes were normal in the right leg. Dorsalis pedis and posterior tibial pulses were palpable and normal bilaterally. The patient demonstrated an abnormal gait and experienced leg cramps after ambulating for 10-15 minutes. The pain was absent during spinal flexion and while seated.

Based on accompanying medical records, the patient had been diagnosed with lumbar spinal stenosis with intermittent neurogenic claudication by an orthopedic consultant, attributed as the cause of the patient's pain and gait abnormalities. While the records indicated prior analgesic medication and a recommendation for spinal surgery, imaging studies were not available for review. The initial pain episode occurred six years prior. Subsequent gait abnormalities and progressive restriction of movement developed over the following 2-3 years, with the current condition remaining stable for the past year.

An Ayurvedic assessment identified a *Vata dosha* imbalance. *Vata* is the principle governing movement and nervous system function. The patient's pain radiated from the gluteal region to the upper and lower back, knee, and sole of the left foot, consistent with the Ayurvedic diagnosis of *Ghridhrasi*. Furthermore, the patient's gait exhibited a vulture-like limp, further supporting this diagnosis with a *Vata*-dominant subtype ***(Fig. 1, Fig. 2, Fig. 3).***

Based on the Ayurvedic diagnosis, a treatment plan was implemented consisting of *Panchakarma* therapies, oral Ayurvedic medications, and dietary modifications. Informed consent was obtained prior to the initiation of *Panchakarma* procedure.

Abhyanga (oil massage) was performed to the whole body by two practitioners for 30-45 minutes using lukewarm sesame oil.

Swedana (heat therapy) was administered following massage. The patient was seated in a wooden cabinet connected to a steam generator containing vaporized Ayurvedic decoctions. This treatment was administered for 10 minutes to induce full-body sweating. Ayurvedic management involved a comprehensive assessment of the patient's prakriti (constitutional type) and *Dosha* imbalance. The treatment plan incorporated herbal remedies, lifestyle modifications, and targeted physical therapy.

Oral Ayurvedic medicines

Trayodashang Guggulu, a classical Ayurvedic polyherbal formulation officially listed in the *Ayurvedic Formulary of India* and *Ayurvedic Pharmacopoeia of India*, was prescribed. Traditionally indicated for conditions such as arthritis, lumbar-sacral and knee stiffness, sciatica, arm pain, ligament injuries, and fractures. This formulation contains 13 herbs in addition to *Guggul, Babula, Ashwagandha, Hapusa, Guduchi, Shatavari, Gokshuara, Vradadaru, Rasana, Satavha, Sati, Yavani, Sunthi,* and *Goghrat* (ghee). The patient was prescribed 250 mg three times daily with warm water before breakfast and after lunch and dinner.

Sinhanad Guggulu, containing *Trifala* (a combination of *Emblica officinalis, Terminalia chebula, and Terminalia bellirica*), *guggul, Gandhak* (sulfur), and *Erandamool*, was also prescribed for lower back pain, disability, and leg pain, following the same dosage regimen as *Trayodashang Guggulu*.

Table 1. Timeline of symptoms

Year	Symptoms
2017	The patient initially presented with lower back pain and leg pain, which responded to NSAIDs prescribed by an orthopaedic specialist.
2019	Symptom severity increased, with the patient experiencing postural instability during walking and standing. Spinal surgery was recommended but deferred due to financial constraints.
2023	The patient, referred by a relative, sought alternative treatment at our facility.

This article contains some figures that are displayed in color online but in black and white in the print edition.

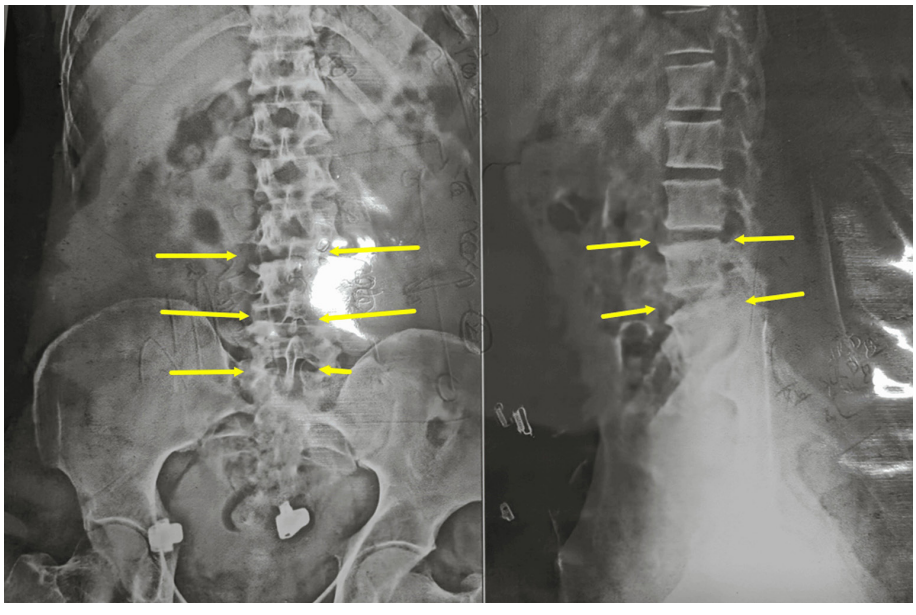

Fig. 1. X-ray of the Lumbar spine (AP view) showing degenerative changes from L3 to S1

Fig. 2. Gait view anteriorly before treatment

Fig. 3. Gait view posteriorly before treatment

Dashmool Kwatha, a decoction prepared from ten herbs, was also administered. A freshly prepared decoction was provided by the hospital pharmacy.

Duration of the treatment lasted 3 weeks.

An Ayurvedic diet was prescribed. The patient was instructed to ambulate each morning within the hospital premises under nursing staff supervision, recording the distance covered. The patient was instructed to ambulate to the limit of his comfort level.

The patient's progress was monitored closely, and adjustments were made to the treatment plan as needed. Over time, the patient's gait and balance improved significantly, and he regained his confidence in performing daily activities.

The patient was assessed according to the following parameters:

Pain intensity for both low back pain and leg pain was assessed using the Visual Analogue Scale (VAS). Patients rated their pain on a 0-10 scale (0 = no pain, 10 = worst imaginable pain). VAS scores were recorded before and after the treatment periods.

Lumbar radiculopathy was assessed using the Extended Straight Leg Raise (ESLR) Test. A positive test, indicated by radiating pain down the affected leg during passive hip flexion with knee extension (particularly at angles less than 45 degrees), suggests L5 or S1 nerve root involvement. ESLR was assessed before and after the treatment periods.

Ambulation distance, measured as a functional outcome, was assessed by instructing the patient to walk at a comfortable pace to the limit of their tolerance. Walking distance was recorded before and after the treatment periods.

Gait examination - A stride, or gait cycle, is defined as two consecutive steps, completing a full cycle of foot movement. Each gait cycle consists of stance phase (foot in contact with the ground) and swing phase (foot off the ground, moving forward). Gait analysis can further evaluate double support time (both feet in contact with the ground) and single support time (one foot in contact with the ground). These phases can be expressed as percentages of the gait cycle and compared to normative values: stance (60%), swing (40%), and double support time (20%) [8] ***(Fig. 4, Fig. 5)***.

Spatial and temporal gait parameters were collected. [9]

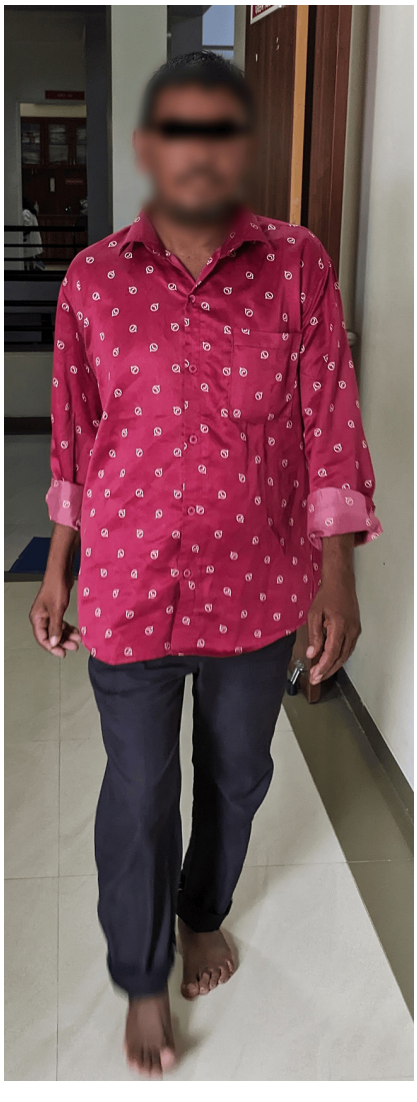

Fig. 4. Gait view anteriorly after treatment

Fig. 5. Gait view posteriorly after treatment

Spatial Parameters

Step Length: Average distance between consecutive foot contacts (meters).

Stride Length: Average distance between consecutive contacts of the same foot (meters).

Temporal Parameters

Step Time: Average time between consecutive foot contacts (seconds).

Stride Time: Average time between consecutive contacts of the same foot (seconds).

Walking Speed: Average distance traveled per second (meters/second).

Cadence: Average number of steps per minute.

Step Time Asymmetry: Average difference in step time between left and right feet (seconds) ***(Table 2)***.

No changes were made to the patient's medications or procedures due to reported tolerance and the absence of adverse drug reactions.

Discussion

This case report describes the Ayurvedic management of a 49-year-old male patient with lumbar spinal stenosis and intermittent neurogenic claudication, presenting with abnormal gait, moderate lumbar pain, leg cramps, and severely limited walking distance. The patient received Ayurvedic massage and hot fomentation with herbal decoction daily for three weeks, without the use of conventional analgesics. The treatment resulted in marked improvement in pain and lumbar disability, with slight improvement in gait abnormalities.

Significant improvements were observed in both low back pain (reduced from 5 to 2) and leg pain (reduced from 6 to 2), likely attributable to the combined effects of Ayurvedic medications and *Panchakarma* therapies. The increased range of motion in the Straight Leg Raise Test (from 40 to 60 degrees) further suggests substantial relief from pain and muscle spasm following treatment.

Minimal changes were observed in most gait parameters with pre- and post-treatment values were as follows: step length (0.70 m to 0.69 m), stride length (72 cm to 72 cm), step time (0.48 sec to 0.49 sec), stride time (0.98 sec to 0.98 sec), walking speed (1.24 m/s to 1.39 m/s), cadence (172/min to 180/min), and step time asymmetry (22% to 20%). Improvements were noted in walking speed and step time asymmetry, potentially attributable to pain and spasm reduction facilitated by the Ayurvedic treatment.

While lumbar spinal stenosis with intermittent neurogenic claudication is typically managed with conventional medical interventions, including pharmacotherapy, physical therapy, and in some cases, surgery [10], this case highlights the potential of Ayurvedic approaches. The observed improvements in pain and function suggest that Ayurvedic massage and fomentation may offer a complementary or alternative approach for managing symptoms associated with lumbar spinal stenosis. The mechanisms by which these therapies exert their effects are not fully understood but may involve improved circulation, reduced muscle tension, and modulation of inflammatory processes [10].

It is important to note the limitations of this case report, including the small sample size (n=1) and the lack of a control group. These limitations preclude definitive conclusions about the efficacy of Ayurvedic treatment for lumbar spinal stenosis. Further research, including randomized controlled trials, is needed to rigorously evaluate the effectiveness and safety of these therapies. Additionally, the specific details of the Ayurvedic interventions, including the composition of the herbal decoction, could be further elaborated in future studies.

Conclusion

This case study suggests that a three-week course of Ayurvedic treatment may reduce pain and disability associated with lumbar spinal stenosis and intermittent neurogenic claudication, while also potentially improving gait disturbances. While prior research has explored the use of Ayurveda for spinal conditions like LSS, its impact on gait abnormalities stemming from INC in LSS patients remained to be investigated. Though Ayurveda may offer benefits for pain associated with lumbar canal stenosis, its limited effect on gait necessitates further investigation with objective gait analysis and controlled trials to establish clinical efficacy.

Table 2. Observations before and after treatment

Parameter	BT	AT
Low back pain (VAS)	5	2
Leg pain (VAS)	6	2
SLR Test positive	40 degrees	60 degrees
Step length	0.70 m	0.69 m
Stride length	72 cm	72 cm
Step Time	0.48 sec	0.49 sec
Stride Time	0.98 sec	0.98 sec
Walking speed	1.24 m/s	1.39 m/s
Cadence	172/min	180/min
Step Time Asymmetry	22%	20%

Disclosures

Human subjects

Consent was obtained or waived by all participants in this study.

Conflicts of interest

In compliance with the International Committee of Medical Journal Editors uniform disclosure form, all authors declare the following:

Payment/services info

All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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