HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

REFINING PHARMACOTHERAPY FOR INFERIOR ALVEOLAR NERVE INJURIES IN MANDIBULAR FRACTURES: A PATHOPHYSIOLOGICAL AND EVIDENCE-BASED APPROACH

Akhmedov Sirojbek Quvondiq ugli
Master's Degree student, Urgench
RANCH University of Technology

Abstract: Inferior alveolar nerve (IAN) injury is a frequent and debilitating complication of mandibular fractures, leading to significant neurosensory dysfunction and a marked decline in patient quality of life. While surgical decompression and microsurgical repair form the cornerstone of management, the role of pharmacotherapy remains fragmented, largely empirical, and inconsistently applied. This article provides a comprehensive analysis of the pathophysiological cascades following IAN trauma, critically evaluates the current pharmacological armamentarium from corticosteroids and NSAIDs to neurotrophic agents and antioxidants and proposes a refined, mechanism-based, phased pharmacotherapeutic protocol. By aligning drug interventions with the temporal biology of nerve injury (acute inflammation, Wallerian degeneration, and regeneration), this review synthesizes evidence from preclinical models of peripheral nerve repair and clinical neurosensory studies to advocate for a standardized, multimodal approach. The goal is to create a neuroprotective and pro-regenerative microenvironment that complements surgical repair, minimizes persistent neuropathy, and accelerates functional sensory recovery.

Keywords: Inferior Alveolar Nerve, Mandibular Fracture, Neurosensory Disturbance, Pharmacotherapy, Nerve Regeneration, Neurotrophins, Corticosteroids

INTRODUCTION

Mandibular fractures constitute a substantial proportion of maxillofacial trauma, with epidemiological studies citing the mandible as the most frequently fractured facial bone in adults, predominantly due to interpersonal violence, motor vehicle accidents, and falls [1]. The unique anatomical course of the inferior alveolar nerve (IAN) within the bony mandibular canal renders it exceptionally vulnerable to injury during such fractures. The reported incidence of post-traumatic IAN neurosensory disturbance (NSD) varies widely from 10% to 81%, heavily influenced by fracture location, displacement, and diagnostic methodology [2, 3]. The IAN, a sensory branch of the mandibular division of the trigeminal nerve, provides general sensation to the ipsilateral lower lip, chin, buccal gingiva of the anterior teeth, and the mandibular dentition. Damage to this nerve manifests as paresthesia, dysesthesia, hypoesthesia, or, in severe cases, complete anesthesia and the development of debilitating neuropathic pain syndromes.

The clinical management of IAN injuries is a dual-pronged challenge: restoration of bony continuity and preservation/restoration of neural function. While open reduction and internal fixation (ORIF) addresses the mechanical component and may decompress the nerve, neurological recovery is often incomplete and unpredictable. The biological response to nerve trauma involves a complex interplay of acute inflammation, edema, ionic dysregulation, oxidative stress, and disrupted axoplasmic flow. Without intervention, these cascades culminate in Wallerian degeneration distal to the injury site and can lead to central sensitization and permanent functional loss [4].

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

Historically, pharmacotherapy for IAN injuries has been characterized by therapeutic nihilism or a fragmented, single-agent approach, typically relying on short-term corticosteroids for edema reduction or empirical vitamin B complex supplementation. This approach lacks a cohesive framework that matches specific pharmacological agents to the precise spatiotemporal evolution of nerve injury pathology. The critical gap in current practice is the absence of a standardized, evidence-based pharmacotherapeutic protocol designed not merely to palliate symptoms but to actively modulate the injury microenvironment and promote axonal regeneration.

Objective: This article aims to critically review the pathophysiological basis of traumatic IAN injury and systematically evaluate pharmacological agents with potential neuroprotective and neuroregenerative properties. The ultimate goal is to propose a refined, phased multimodal pharmacotherapy protocol that can be integrated into the surgical management of mandibular fractures to optimize neurosensory recovery.

MATERIALS AND METHODS

This study is structured as a narrative review and critical synthesis of literature. A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar databases for articles published between 1990 and 2025. The search strategy employed combinations of Medical Subject Headings (MeSH) and free-text terms, including "inferior alveolar nerve," "mandibular fracture," "neurosensory disturbance," "pharmacotherapy," "nerve regeneration," "neurotrophic factors," "corticosteroids," "NSAIDs," "antioxidants," "Vitamin B complex," and "NGF." Inclusion criteria encompassed original clinical research, randomized controlled trials, prospective and retrospective cohort studies, case series, and high-quality reviews. Preclinical animal studies specifically modeling peripheral trigeminal nerve or sciatic nerve crush/transection injuries were included to elucidate drug mechanisms where human data were scarce. Articles were critically analyzed for methodological rigor, relevance of outcome measures (e.g., standardized neurosensory testing light touch, two-point discrimination, pain perception), and biological plausibility. The synthesis focused on bridging the molecular biology of nerve injury with clinical pharmacodynamics to construct a rational therapeutic timeline.

3. Pathophysiology of IAN Injury: A Spatiotemporal Disease Model

Rational pharmacotherapy depends on understanding the evolving biology of nerve injury, which can be divided into three overlapping temporal phases.

Phase 1: Acute Inflammatory and Excitotoxic Phase (0–72 hours post-injury)

The initial mechanical insult be it compression, stretch (neuropraxia), crush (axonotmesis), or transection (neurotmesis) immediately disrupts the neuronal cytoskeleton and axolemma, causing an uncontrolled influx of calcium ions (Ca^{2+}). This Ca^{2+} overload activates proteases like calpains and caspases, initiating axonal degradation and triggering mitochondrial permeability transition, leading to an energy crisis and reactive oxygen species (ROS) production [5]. Concurrently, tissue disruption initiates a robust inflammatory response. Mast cells, macrophages, and neutrophils infiltrate the injury zone, releasing pro-inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and matrix metalloproteinases (MMPs). While some inflammation is necessary for clearing debris, excessive and prolonged neuroinflammation perpetuates nerve damage and hyperalgesia. Intraneural edema within the rigid mandibular canal creates a "mini-compartment syndrome," further compromising microvascular perfusion and causing ischemic neuropathy. This acute phase is the primary window for neuroprotective intervention.

Phase 2: Wallerian Degeneration and Clearance Phase (3 days – 3 weeks)

Distal to the injury, axons undergo Wallerian degeneration, a programmed clearance process. Schwann cells de-differentiate into a repair phenotype, breaking down myelin debris and secreting

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

chemokines to recruit hematogenous macrophages [6]. This creates a permissive environment for regeneration but also leaves distal end-organs temporarily denervated. Without timely reinnervation, Schwann cell tubes atrophy and fibrotic scarring occurs, permanently blocking axonal advancement. This phase represents a critical window for accelerating debris clearance and enhancing the intrinsic regenerative capacity of neurons.

Phase 3: Regeneration and Remyelination Phase (3 weeks – 12+ months)

A regenerative sprout emerges from the proximal axonal stump, guided by the bands of Büngner (aligned repair Schwann cells). Axons regenerate at an approximate rate of 1 mm/day. For an injury near the mandibular foramen, the distance to the mental nerve end-organs can exceed 100 mm, requiring months for functional recovery. This chronic phase requires sustained trophic support to prevent neuronal atrophy, promote axonal elongation, and ensure proper end-organ reinnervation and cortical remapping.

RESULTS

Corticosteroids, primarily dexamethasone and methylprednisolone, are among the most commonly used agents in the acute setting. Their primary mechanisms involve potent inhibition of phospholipase A2 (reducing prostaglandin and leukotriene synthesis) and suppression of NF-κB-mediated transcription of pro-inflammatory cytokines (TNF-α, IL-1β) [7]. In the context of IAN injury, their most critical immediate action is the reduction of intraneural edema, effectively decompressing the nerve within the bony canal. Animal models of peripheral nerve crush injury demonstrate that a short, high-dose course of corticosteroids shortly after injury reduces endoneurial edema, preserves more myelinated axons, and accelerates functional recovery [8]. Clinical evidence in maxillofacial surgery, though largely from third molar-related IAN injuries, supports a short perioperative course (e.g., intravenous dexamethasone 8–12 mg preoperatively, tapered over 3–5 days postoperatively) to lower the severity and incidence of paresthesia [9]. However, prolonged use is detrimental, inhibiting the macrophage invasion necessary for Wallerian degeneration and subsequent repair.

NSAIDs like ibuprofen and ketorolac provide analgesia and reduce inflammation via cyclooxygenase (COX) inhibition. Their role in nerve recovery is controversial. While reducing prostaglandin E2 (PGE2) can dampen pain sensitization, PGE2 also exhibits neuroprotective properties and promotes axonal outgrowth [10]. Emerging evidence suggests a superior role for selective COX-2 inhibitors, as COX-2 is highly upregulated in injured nerves and dorsal root ganglia, contributing to central sensitization and neuropathic pain. The nuanced application might involve avoiding non-selective NSAIDs in the very acute phase to permit the initial, beneficial inflammatory signaling, while using COX-2 inhibitors in the subacute phase to manage inflammatory pain without entirely blunting the reparative process.

This class represents the most direct pharmacotherapeutic approach to enhancing nerve regeneration. Nerve Growth Factor (NGF) is the prototypical target-derived neurotrophin for sensory and sympathetic neurons. It promotes neuronal survival, neurite outgrowth, and axonal guidance via the TrkA receptor. Preclinical studies of sciatic nerve transection show that local or systemic NGF administration reduces neuronal apoptosis in dorsal root ganglia and enhances nerve fiber density [11]. However, clinical application is hampered by hyperalgesia from mast cell degranulation and poor CNS penetration. A modified, non-algesic NGF mimetic or localized delivery system (e.g., within a nerve conduit or biodegradable hydrogel placed during ORIF) could circumvent this, providing a potent pro-regenerative signal directly to the injury site in the regenerative phase.

The neurotropic B vitamins (thiamine B1, pyridoxine B6, and cobalamin B12) are frequently used empirically. Preclinical data reveal mechanistic underpinnings: they promote axonal transport, support Schwann cell metabolism, and reduce oxidative stress. High-dose methylcobalamin, in

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

particular, has been shown to upregulate protein synthesis in neurons and enhance axonal regeneration in rat models of sciatic nerve crush [12]. A randomized clinical trial in patients with peripheral neuropathies demonstrated that a combination of B vitamins (particularly benfotiamine, a fat-soluble B1 analog, and methylcobalamin) significantly improved nerve conduction velocity and sensory symptoms compared to placebo [13]. For IAN injuries, a prolonged course of high-dose, bioavailable B-vitamins during the regeneration phase provides safe, sustained metabolic support for the protein-synthesis-intensive process of axonal elongation.

Oxidative stress is a central pathway in secondary neuronal damage. Alpha-lipoic acid (ALA) is a potent, amphipathic antioxidant that regenerates other antioxidants (Vitamins C, E, glutathione), chelates transition metals, and improves endoneurial blood flow. In streptozotocin-induced diabetic neuropathy models and crush injury models, ALA reduced lipid peroxidation, restored glutathione levels, and accelerated nerve conduction velocity recovery [14].

DISCUSSION

The central weakness of current practice is a non-phased, reactive approach. Synthesizing the evidence, it is clear that a single agent at a random timepoint is biologically insufficient. The future lies in a deliberate, protocol-driven multimodal strategy that mirrors the injury's chronological biology. I propose the following refined pharmacotherapeutic framework, integrated with surgical management:

Phase I: Acute Neuroprotection & Edema Control (First 72 hours – Perioperative)

· Dexamethasone: Initiate IV 8-12 mg immediately upon diagnosis or prior to surgical incision. Continue 4-6 mg IV/PO every 8-12 hours for 48 hours, then a rapid 3-day taper. This exploits the full anti-edema and membrane-stabilizing effect within the critical pre-degeneration window.

· Magnesium Sulfate: A single IV infusion (e.g., 30 mg/kg bolus followed by 10 mg/kg/hr for 24 hours) can be considered in severe crush or traction injuries to attenuate excitotoxicity.

· Analgesia: Prefer multimodal analgesia (paracetamol, short-term opioids) over high-dose NSAIDs to avoid blunting early, necessary inflammatory signaling. If inflammation control is needed beyond corticosteroids, a selective COX-2 inhibitor like celecoxib is theoretically preferred.

Phase II: Subacute Inflammatory Modulation & Debris Clearance (Week 1–4)

· Selective COX-2 Inhibitor: If inflammatory pain persists, a 1–2 week course (e.g., Celecoxib 200 mg PO BID) can manage pain while potentially sparing some pro-reparative effects of COX-1. This must be balanced with surgical healing and patient pain levels.

· Alpha-Lipoic Acid (ALA): Initiate oral ALA 600-800 mg daily in divided doses. Its antioxidant and microcirculatory effects are ideal for establishing a healing milieu free of chronic oxidative stress.

· Early Neurotrophic Initiation: Begin high-dose Methylcobalamin (1500-3000 mcg/day PO) and Benfotiamine (300-600 mg/day PO) to charge the neuronal metabolism and support early Schwann cell repair activity without the hyperalgesic risk of NGF.

Phase III: Pro-Regeneration & Remyelination (Week 4–6 months+)

· Sustained Neurotrophic Support: Continue the B-vitamin complex and ALA for a minimum of 3-6 months. This provides the metabolic ‘fuel’ for axonal transport and protein synthesis over the long distance required for IAN regeneration.

· Citicoline: Introduce Citicoline 1000-2000 mg/day PO, especially if recovery plateaus. Its role in membrane repair and acetylcholine precursor provision supports the high metabolic demand of regenerating nerve fibers and remyelination.

· Targeted Neurotrophin Therapy (Future Direction): The most significant future advancement lies in localized, sustained-release NGF or other neurotrophin mimetics. Development of biocompatible, NGF-eluting microspheres or hydrogels injected via a catheter near the mental foramen or the ORIF site could provide a high-concentration, non-systemic pro-regenerative signal precisely

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

during this phase. This pharmacotherapeutic protocol must be viewed as an adjuvant to, not a substitute for, meticulous surgery. Anatomical nerve decompression via accurate fracture reduction and rigid fixation remains the primary treatment. Pharmacotherapy cannot overcome a severed nerve that is unrepaired, nor a bony spicule continuously impinging on the nerve. Furthermore, the mental state of the patient is critical. Chronic neurosensory loss is psychologically traumatic; thus, early and transparent communication about the recovery timeline (months, not weeks) and the proactive pharmacological strategy combats helplessness and may positively modulate the central perception of sensation.

CONCLUSION

Traumatic IAN injury during mandibular fracture repair is a complex biological disease whose management demands a pharmacological sophistication mirroring its complexity. The era of a single, perioperative dose of dexamethasone or empirical B-vitamins is insufficient. A refined pharmacotherapeutic approach, grounded in the temporal pathophysiology of nerve injury acute neuroprotection, subacute inflammatory modulation, and sustained pro-regenerative metabolic support offers a rational pathway to improve patient outcomes. The multimodal protocol proposed herein, leveraging corticosteroids, targeted analgesics, potent antioxidants, and sustained neurotrophic support, represents a systematic attempt to bridge the gap between clinical neurosensory deficits and the rich potential of molecular nerve repair. The future hinges on the clinical validation of such protocols in well-designed randomized controlled trials, and the development of sophisticated drug delivery systems that can precisely target the healing nerve in its hostile post-traumatic environment. Through this evolution, the standard of care can shift from mere observation to active, evidence-based biological optimization of neural recovery.

REFERENCES

1. Ellis, E., 3rd, Moos, K. F., & el-Attar, A. (1985). Ten years of mandibular fractures: an analysis of 2,137 cases. Oral Surgery, Oral Medicine, Oral Pathology, 59(2), 120–129.
2. Haug, R. H., Prather, J., & Indresano, A. T. (1990). An epidemiologic survey of facial fractures and concomitant injuries. Journal of Oral and Maxillofacial Surgery, 48(9), 926–932.
3. Marchena, J. M., Padwa, B. L., & Kaban, L. B. (1998). Sensory abnormalities associated with mandibular fractures: incidence and natural history. Journal of Oral and Maxillofacial Surgery, 56(7), 822–826.
4. Scholz, J., & Woolf, C. J. (2007). The neuropathic pain triad: neurons, immune cells and glia. Nature Neuroscience, 10(11), 1361–1368.
5. Stys, P. K. (2005). General mechanisms of axonal damage and its prevention. Journal of the Neurological Sciences, 233(1-2), 3–13.
6. Chen, Z. L., Yu, W. M., & Strickland, S. (2007). Peripheral regeneration.
7. [25.06.2026 17:39] Fardu: Annual Review of Neuroscience, 30, 209–233.
8. Barnes, P. J. (1998). Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clinical Science, 94(6), 557–572.
9. Galloway, E. B., 3rd, Jensen, R. L., Dailey, A. T., Thompson, B. G., & Shelton, C. (2000). Role of topical steroids in reducing dysfunction after nerve injury. Laryngoscope, 110(11), 1907–1910.
10. Tiwana, P. S., Foy, S. P., Shugars, D. A., et al. (2005). The impact of intravenous corticosteroids on the incidence of neurosensory disturbance following third molar surgery. Journal of Oral and Maxillofacial Surgery, 63(8 Suppl 1), 9.
11. Jiang, L., & Li, Z. (2013). Differential role of prostaglandin E2 receptors in nerve regeneration and pain. Neuroscience Bulletin, 29(5), 619–627.

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

12. Rich, K. M., Luszczynski, J. R., Osborne, P. A., & Johnson, E. M., Jr. (1987). Nerve growth factor protects adult sensory neurons from cell death and atrophy caused by nerve injury. Journal of Neurocytology, 16(2), 261–268.
13. Hobbenaghi, R., Javanbakht, J., Hosseini, E., et al. (2013). Neuropathological and neuroprotective features of methylcobalamin in a model of sciatic nerve injury. Folia Neuropathologica, 51(3), 238–245.
14. Stracke, H., Lindemann, A., & Federlin, K. (1996). A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. Experimental and Clinical Endocrinology & Diabetes, 104(4), 311–316.
15. Stevens, M. J., Obrosova, I., Cao, X., Van Huysen, C., & Greene, D. A. (2000). Effects of DL-alpha-lipoic acid on peripheral nerve conduction, blood flow, energy metabolism, and oxidative stress in experimental diabetic neuropathy. Diabetes, 49(6), 1006–1015.
16. Ozay, R., Yuruker, S., Ozturk, A., et al. (2007). The effects of citicoline on peripheral nerve regeneration in a rat model. Journal of Reconstructive Microsurgery, 23(4), 211–216.
17. Fels, J. A., & Duman, R. S. (2012). Magnesium and the treatment of neuropathic pain. Neurochemical Research, 37(5), 847–858.
18. Plane, J. M., Shen, Y., Pleasure, D. E., & Deng, W. (2010). Prospects for minocycline neuroprotection. Archives of Neurology, 67(12), 1442–1448.