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Ascorbic Acid in the Chronic Constriction Injury Model: Consolidating the Antioxidant Rationale and Confronting the Translational Gap

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Dear Editor,

The chronic constriction injury (CCI) of the sciatic nerve, first described by Bennett and Xie, remains the most widely used rodent model of peripheral neuropathic pain, reproducing the mechanical allodynia, thermal hyperalgesia and spontaneous pain that characterise the human condition.[1] Over the past decade the model has become a proving ground for antioxidant therapeutics, and ascorbic acid (vitamin C) has emerged as one of the more mechanistically attractive candidates. We write to consolidate what the preclinical literature now permits us to claim about vitamin C in this model and, more importantly, to draw attention to the widening gap between an increasingly coherent laboratory rationale and an unresolved clinical evidence base.

The mechanistic case is straightforward. Reactive oxygen and nitrogen species are established contributors to the peripheral and central sensitisation that follow nerve injury.[2] Superoxide generated in excess after CCI combines with nitric oxide to form peroxynitrite, a potent mediator of neuronal oxidative damage. Ascorbate, a water-soluble chain-breaking antioxidant, scavenges superoxide directly, thereby limiting peroxynitrite formation, and additionally regenerates α-tocopherol at the lipid-membrane interface. These are not merely theoretical properties: in the CCI model, ascorbic acid modulates the nitric oxide pathway to antinociceptive effect,[3] and systemic vitamin C — alone and in combination with vitamin E — attenuates both mechanical and thermal nociception while improving the sciatic functional index.[4] Combined vitamin C and E administration increases total antioxidant capacity and lowers lipid hydroperoxides in the injured nerve, and the same combination modulates thiol content and superoxide generation in the spinal cord, situating the effect at both peripheral and central levels.[4,5]

Two features of this evidence deserve emphasis for their translational implications. First, the antinociceptive benefit is greater when vitamin C is co-administered with gabapentin than with gabapentin alone,[4] which reframes ascorbate not as a standalone analgesic but as a plausible adjuvant capable of augmenting — and potentially sparing — first-line agents. Second, the effect is dose- and route-dependent in ways the preclinical literature has not fully disentangled; the intraperitoneal doses that produce clear biochemical and behavioural signals (of the order of 30 mg/kg/day) do not translate simply to the pharmacokinetics of oral ascorbate, whose plasma concentration is tightly constrained by saturable intestinal absorption.

Against this reasonably coherent preclinical picture, the clinical evidence remains conspicuously unsettled. The most-cited human application of vitamin C in a comparable pain phenotype is the prevention of complex regional pain syndrome (CRPS) after distal radius fracture — a condition Bennett and Xie themselves invoked as the clinical correlate of CCI. Here the trial record is genuinely mixed: an early randomised study reported a marked reduction in CRPS incidence,[6] and pooled analyses have at times favoured vitamin C,[7] yet subsequent adequately blinded trials have found no benefit on range of motion, function or pain, and meta-analytic estimates carry substantial heterogeneity. The discordance is instructive. It suggests that the laboratory effect, though real, is conditional — on timing, dose, baseline oxidative status, and the specific pain phenotype under study.

If the field is to close this gap, three methodological commitments would help. Preclinical reports should (i) pair behavioural endpoints with a defined oxidative-stress and, ideally, neuroinflammatory panel in the same animals, so that a claimed antioxidant mechanism is evidenced rather than assumed; (ii) distinguish explicitly between prophylactic and therapeutic dosing, since the clinical hypothesis is almost entirely one of prevention whereas many rodent protocols treat established injury; and (iii) report dose-response and, where combinations are used, formal isobolographic analysis before any claim of synergy. Adherence to ARRIVE 2.0 reporting — randomisation, blinded assessment and a priori sample-size justification — would materially raise the quality of a literature that remains uneven on these points.

Ascorbic acid is inexpensive, well tolerated and mechanistically rational, which makes it an appealing candidate and, for the same reasons, one at risk of premature clinical enthusiasm. The CCI model has given us a credible account of how vitamin C might protect the injured nerve; the task now is to test that account with the methodological rigour required to justify — or to close — the translational step.

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Yours sincerely,

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