

REVIEW ARTICLE

Specific neurotoxicity of local anaesthetics revisited

An evidence-based narrative review

Pierre Goffin, Jean-Pierre Lecoq, Michele Carella, Hipolito Labandeyra, Marti Flò Csefkó and Xavier Sala-Blanch

Local anaesthetics are essential to regional anaesthesia but may exert neurotoxic effects on peripheral nerves under specific conditions. Although perioperative nerve injury is increasingly recognised, the contribution of local-anaesthetic neurotoxicity, the relative toxicity of different agents and concentrations, and the influence of patient-related risk factors remain incompletely defined. This evidence-based narrative review synthesises experimental and clinical data on peripheral nerve neurotoxicity associated with local anaesthetics and discusses implications for clinical practice and future research. A prospectively registered search was conducted across major biomedical databases for studies published between 1990 and 2024. Experimental evidence consistently demonstrates dose-dependent and time-dependent neurotoxicity for all clinically used local anaesthetics, characterised by ultrastructural damage, oxidative stress, mitochondrial dysfunction and activation of apoptotic and intracellular signalling pathways. Relative toxicity varies

between agents and concentrations, with lidocaine and bupivacaine often appearing more potent than ropivacaine or chloroprocaine in preclinical models, while findings for articaine remain heterogeneous. Diabetic and metabolically compromised nerves exhibit increased susceptibility, supporting a ‘two-hit’ model of injury. In contrast, clinical evidence directly linking specific agents, concentrations or exposure durations to permanent peripheral nerve injury is limited, and such injuries are typically multifactorial. Overall, chemical neurotoxicity should be considered one component of a broader perioperative risk profile. Risk mitigation should prioritise avoidance of intraneural injection, adherence to recommended doses and cautious use of high concentrations or prolonged exposure, particularly in vulnerable nerves. Further research should integrate mechanistic and clinical outcomes while accounting for patient-level risk factors.

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KEY POINTS

- Experimental signal: all clinically used local anaesthetics show dose- and time-dependent peripheral nerve neurotoxicity in preclinical models.
- New mechanistic cascades: are demonstrated including induced oxidative stress with mitochondrial depolarisation and calcium overload, activating p38 MAPK/JNK signalling and culminating in caspase-dependent apoptosis.
- Heterogeneous risk: relative toxicity varies by agent/concentration (often lidocaine and bupivacaine

>ropivacaine/chloroprocaine); diabetes/metabolic compromise increases susceptibility (‘two-hit’ model).

- Clinical translation remains uncertain: direct evidence linking local anaesthetics to permanent nerve injury is limited and likely multifactorial; therefore, regional anaesthesia decisions should be based on the overall perioperative risk profile.

Introduction

Peripheral nerve blocks are now a central pillar of perioperative analgesia and enhanced recovery pathways.^{1,2} Local anaesthetics (LAs) used for these techniques

From the Human Anatomy and Embryology, Facultat de Medicina, Universitat de Barcelona, Barcelona, Catalunya, Spain (PG), Department of Anaesthesia and Intensive Care Medicine, MontLegia Hospital, Groupe Sante CHC (PG), Department of Anaesthesia and Intensive Care Medicine, University Hospital of Liege, Liege, Belgium (JPL, MC), Anaesthesia, HM Delfos (HL), Centre de Recursos per l'Aprenentatge i la Investigació, Universitat de Barcelona (MFC) and Anaesthesia, Hospital Clinic de Barcelona, Barcelona, Catalunya, Spain (XS-B)

Correspondence to Dr Pierre Goffin, Hopital MontLegia, Anesthésie, Bvd Patience & Beaujonc 2, 4000 Liège, Belgium.
E-mail: pierre.goffin@chc.be

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