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Topical and peripheral ketamine as an analgesic

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Abstract

Ketamine, in subanesthetic doses, produces systemic analgesia in chronic pain settings, an action largely attributed to block of N-methyl-D-aspartate receptors in the spinal cord and inhibition of central sensitization processes. N-methyl-D-aspartate receptors also are located peripherally on sensory afferent nerve endings, and this provided the initial impetus for exploring peripheral applications of ketamine. Ketamine also produces several other pharmacological actions (block of ion channels and receptors, modulation of transporters, anti-inflammatory effects), and while these may require higher concentrations, after topical (e.g., as gels, creams) and peripheral application (e.g., localized injections), local tissue concentrations are higher than those after systemic administration and can engage lower affinity mechanisms. Peripheral administration of ketamine by localized injection produced some alterations in sensory thresholds in experimental trials in volunteers and in complex regional pain syndrome subjects in experimental settings, but many variables were unaltered. There are several case reports of analgesia after topical application of ketamine given alone in neuropathic pain, but controlled trials have not confirmed such effects. A combination of topical ketamine with several other agents produced pain relief in case, and case series, reports with response rates of 40% to 75% in retrospective analyses. In controlled trials of neuropathic pain with topical ketamine combinations, there were improvements in some outcomes, but optimal dosing and drug combinations were not clear. Given orally (as a gargle, throat swab, localized peritonsillar injections), ketamine produced significant oral/throat analgesia in controlled trials in postoperative settings. Topical analgesics are likely more effective in particular conditions (patient factors, disease factors), and future trials of topical ketamine should include a consideration of factors that could predispose to favorable outcomes.