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Ketamine Improves the Management of Exaggerated Postoperative Pain Observed in Perioperative Fentanyl-treated Rats

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Abstract

Background: Although opioids are unsurpassed analgesics, experimental and clinical studies suggest that opioids activate *N*-methyl-d-aspartate pronociceptive systems leading to pain hypersensitivity and short-term tolerance. Because it is difficult in humans to differentiate pain from hyperalgesia during the postoperative period, the authors performed experimental studies with fentanyl using the rat incisional pain model for evaluating relations between hyperalgesia and short-term tolerance. Because *N*-methyl-d-aspartate receptor antagonists oppose both pain hypersensitivity and tolerance induced by opioids, the authors examined the capability of ketamine for improving exaggerated postoperative pain management.

Methods: During halothane anesthesia, a hind paw plantar incision was performed in rats receiving four fentanyl subcutaneous injections (100 µg/kg per injection, every 15 min). In some groups, three subcutaneous ketamine injections (10 mg/kg per injection, every 5 h) were performed in saline- or fentanyl-treated rats. One day after surgery, the analgesic effect of morphine (2 mg/kg subcutaneous) was tested. Analgesia, mechanical hyperalgesia, tactile allodynia, and pain score were assessed for several days using the paw pressure vocalization test, the von Frey application test, and the postural disequilibrium test.

Results: Fentanyl induced analgesia but also produced exaggerated postoperative pain as indicated by the enhancement of hyperalgesia, allodynia, and weight-bearing decrease after hind paw plantar incision. Ketamine pretreatment prevented such a fentanyl-induced enhancement of postoperative pain and improved its management by morphine.

Conclusions: By opposing postoperative pain hypersensitivity and subsequent short-term tolerance induced by perioperative opioid use, ketamine not only improves exaggerated postoperative pain management but also provides better postoperative rehabilitation.