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EDITORIAL

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## Can estazolam plus remimazolam as an anxiolytic reduce remifentanil-induced postoperative hyperalgesia?

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Over the last few decades, scientific research on the mechanism, prevention and/or reduction of remifentanil-induced hyperalgesia (RIH) has been increasing. Opioid-induced hyperalgesia, especially remifentanil-induced postoperative hyperalgesia, is described as a paradoxically increased response to noxious stimuli, possibly as a result of nociceptive sensitization, after remifentanil infusion. Hyperalgesia is generally expressed as either a decrease in pain threshold or a decrease in pain tolerance after opioid exposure.<sup>1-3</sup> According to the results of a meta-analysis of nine randomized controlled trials in healthy volunteers, remifentanil withdrawal was reported to induce a mild degree of hyperalgesia, which was largely associated with a decreased pain threshold.<sup>4</sup> Hyperalgesia may lead to greater opioid consumption and increased pain sensitivity in the postoperative period, as well as impaired patient comfort and longer hospital stays than expected. Although the mechanism of remifentanil-induced hyperalgesia (RIH) has not been fully revealed, many experimental and clinical study results have been published on this topic. Some studies reported that remifentanil-induced postoperative hyperalgesia is thought to be highly related to the abrupt discontinuation of higher and longer doses of remifentanil.<sup>5, 6</sup> It has been reported that the development of central sensitization due to the role of glutamate,

which acts through the activation of N-methyl-d-aspartate (NMDA) receptors, as a result of the injection of opioids, including remifentanil, may lead to hyperalgesia.<sup>7</sup> In addition, Wang *et al.*<sup>8</sup> reported in an experimental animal study that the NMDA receptor-Ca MKII pathway plays an important role in the development of RIH and that the NMDA receptor antagonist esketamine may be a new therapeutic option in the prevention and treatment of RIH. On the other hand, inhibiting the GABAergic system plays an important role in the development mechanism of remifentanil-induced hyperalgesia. Gao *et al.*<sup>9</sup> reported that remifentanil-induced hyperalgesia started to decrease in GABA release and that downregulation of GABAAR and KCC2 receptors contributed to the spinal modulation of hyperalgesia. Apart from all this, it has been shown in an animal model study that PAK4 activation in the spinal cord modulates microglial activation via the NF- $\kappa$ B/NLRP3 pathway, thereby leading to the inflammatory response that plays a role in the development of RIH.<sup>10</sup> Many studies have been published on preventing or treating remifentanil-induced hyperalgesia. It has been shown in laparoscopic hysterectomy patients that gradual withdrawal and postoperative infusion of remifentanil can prevent hyperalgesia.<sup>11</sup> In a randomized, placebo-controlled, double-blind study, gradual reduction of remifentanil

infusion rates compared to abrupt stopping was reported to prevent remifentanyl-induced hyperalgesia. Even at remifentanyl infusion doses as high as  $4.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , the addition of propofol infusion to remifentanyl may reduce or prevent the occurrence of remifentanyl-induced hyperalgesia. The possible mechanism for this may be related to propofol's inhibition of NMDA and supraspinal GABA receptors.<sup>12</sup> The combination of remimazolam, a new benzodiazepine that acts on the GABA-A receptor, and estazolam, a sedative that provides long-term effects in perioperative use, relieves patient anxiety and provides stable hemodynamics. In addition, Sun *et al.*<sup>13</sup> reported that the combination of remimazolam and estazolam can provide positive results such as effective hemodynamic stabilization, low anxiety level and relieved pain after laparoscopic gastrointestinal surgery. In a very recently published study in *Minerva Anesthesiologica*, Huang *et al.*,<sup>14</sup> reported that the combination of estazolam, an anxiolytic and hypnotic agent, and remimazolam, an ultra-short-acting benzodiazepine, prevented remifentanyl-induced postoperative hyperalgesia in elective gynecological laparoscopic surgery. In this study, the anesthesia duration lasted approximately 123 minutes and maintenance of anesthesia was achieved with  $4\text{-}6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  propofol and  $0.2\text{-}0.3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{minute}^{-1}$  remifentanyl infusions. They claimed that in this study they chose two GABA receptor agonist anxiolytic drugs, estazolam and remimazolam, and that these medications relieved preoperative anxiety and thus reduced postoperative remifentanyl-induced hyperalgesia. Some previous clinical studies have reported that preoperative anxiety can weaken the GABAergic system, leading to hyperalgesia, and that anxiolytic drugs can overcome preoperative anxiety and thus relieve postoperative pain.<sup>15, 16</sup> In addition, Huang *et al.*,<sup>14</sup> stated that anxiolytic drugs can relieve postoperative pain through GABA receptor action and that anxiolytic medication can relieve postoperative pain by relieving anxiety. In conclusion, more animal and clinical studies will continue to be conducted on the mechanism, prevention and treatment of remifentanyl-induced postoperative hyperalgesia. However, it should also be taken into consideration that anxiolytic

medications such as remimazolam and estazolam administered preoperatively can overcome perioperative anxiety and thus prevent postoperative hyperalgesia by acting on GABAergic receptors.

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*Conflicts of interest*

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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