Editorial

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The antinociceptive effect of esmolol

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Esmolol is the first intravenous, short-acting, titratable β-blocker available for use in critical care and surgical settings [1]. Esmolol is thought to be a "jack of all trades" among drugs used in anesthesia because it prevents and treats cardiovascular responses due to perioperative stimuli.

In addition to its effect on the sympathetic nervous system, esmolol influences core components of an anesthetic regimen, such as analgesia, hypnosis, and memory function [2-5].

In this edition of the Korean Journal of Anesthesiology, Lee and Lee [6] studied 60 patients who underwent a laparoscopic appendectomy under total intravenous anesthesia using propofol and remifentanil and compared a control group with another group that received continuously injected esmolol during anesthesia. Postoperative 30 minute visual analog scale (VAS) scores and diclofenac sodium use for postoperative pain control during the first 24 hours decreased significantly in the esmolol group. Also, Lee and Lee [6] adjusted the infusion rate of remifentanil to target the bispectral index (BIS) to 40−60, compared to the control group, and the total amount of remifentanil administered during approximately 57 minutes of anesthesia was significantly lower in the esmolol group. The authors attributed the decrease in postoperative pain with esmolol to its intrinsic analgesic effect, a decrease in hepatic metabolism of opioids by β-blockers to extend the analgesic effect, and a reduction in opioid tolerance.

However, there are several points that Lee and Lee [6] must consider. First, β-blockers, which decrease hepatic opioid metabolism and lengthen the analgesic effect, are limited only to those metabolized by the liver. For example, propranolol decreases its own metabolism and that of certain other drugs by eliciting a reduction in hepatic blood flow [7]. This could affect the metabolism of drugs with a large hepatic extraction ratio, such as fentanyl, and it would seem likely that propranolol use would result in prolonging the analgesic effect of fentanyl and also elicit a reduction in postoperative opioid consumption [2].

However, although the effect of esmolol on drug metabolism has not yet been thoroughly investigated, unlike most β-blockers, which are metabolized by the liver, esmolol is metabolized by esterases located in the cytosol of red blood cells [8]. Thus, it seems unlikely that esmolol infusion would alter opioid pharmacokinetics.

Furthermore, although remifentanil is a 4-anillidopiperidinemethyl μ-opioid like fentanyl, alfentanil, and sufentanil, it is not metabolized in the liver but completely metabolized by nonspecific esterases [9]. Therefore, one cannot expect alterations in remifentanil metabolism due to esmolol in the study in which Lee and Lee [6] continuously infused remifentanil.

Secondly, the drug used for postoperative pain control in the study of Lee and Lee [6] was not an opioid but diclofenac sodium, so what should be discussed is opioid induced hyperalgesia not opioid tolerance.

Opioids provide an initial analgesic effect but then reduce the pain threshold to less than baseline (opioid-induced hyperalgesia, OIH) and increase the amount of opioid required to achieve the same analgesia (opioid tolerance) [10,11]. That is, the use of opioids may be a double-edged sword. OIH is characterized by different clinical features than tolerance. OIH represents increased sensitivity to pain, whereas tolerance may reflect decreased sensitivity to opioids. Both acute opioid tolerance and OIH seem to share some similar molecular mechanism, which involves the activation of excitatory glutamate receptors of the N-methyl-D aspartate

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(NMDA) system in the central nervous system [12]. However, many other mechanisms and systems are probably involved in the development of opioid tolerance [13]. Several recent studies have reviewed and highlighted important aspects of OIH [10,11]. Even brief exposure to μ-receptor agonists can induce long-lasting hyperalgesic effect for days, which is clinically significant, because large doses of intraoperative μ-receptor agonists increase postoperative pain and opioid consumption [2,10]. Although some clinical studies have failed to demonstrate an increase in pain scores after remifentanil infusion, remifentanil has been shown to increase pain and induce mechanical hyperalgesia after a 30 min infusion at a dose 0.05−0.1 μg/kg/min in volunteers [14,15]. OIH worsens when higher doses of opioids are infused [16], so in the study of Lee and Lee [6], the effects of reducing remifentanil-induced hyperalgesia with esmolol were observed.

Esmolol exerts antinociceptive and anesthetic sparing effects in animal and human subjects [17,18]. Previous studies have shown that a continuous esmolol infusion decreases the plasma propofol minimal alveolar anesthetic concentration during propofol/nitrous oxide/morphine anesthesia and reduces inhalation anesthetic minimum alveolar concentration (MAC) [17,19]. In 2001, Coloma et al. [20] suggested that perioperative esmolol is an alternative to remifentanil for maintaining stable intraoperative hemodynamics. Although intravenously administered esmolol has peripheral analgesic and cardiovascular properties, it is also thought to be involved in pain modulation [18]. Because esmolol does not cross the blood-brain barrier, it may prevent the increase in the BIS index and decrease inhalation anesthetic MAC by blocking β-adrenoceptors within the brainstem and decrease neuronal inflow traffic into the central nervous system rather than acting within the brain directly [21].

Furthermore, ONO 1101, a specific β-blocker, injected intrathecally elicits a decrease in the nociceptive behavior following formalin injection [22]. Thus, additional studies are required to better define the role of centrally administered esmolol in pain modulation. Administration of a sufficient dose of a short-acting β-blocker by a neuraxial route, for example, may be a potentially new treatment strategy for perioperative pain.

Davidson et al. [18] reported that esmolol shows direct analgesic properties in formalin-injected rats, and Hagelüken et al. [23] demonstrated G protein activation in isolated cell membranes with the use of a β-blocker. Inhibitory G protein-coupled receptor agonists act on post-synaptic inhibition via G protein-coupled potassium channels or via the pre-synaptic inhibition of neurotransmitter release through the regulation of voltage-gated Ca^{2+} channels; such a pathway underlies the antinociceptive effect of clonidine [24].

Although more reasonable discussions are needed on the study of Lee and Lee [6] due to the decrease in postoperative VAS and usage of diclofenac sodium, this may be an interesting study for one who is interested in remifentanil-based anesthesia and the resulting OIH. This study also suggests that esmolol may become a friendlier drug to anesthesiologists.

References

1. Blanski L, Lutz J, Laddu A. Esmolol, the first ultra-short-acting intravenous beta blocker for use in critically ill patients. Heart Lung 1988; 17: 80-9.
2. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. Br J Anaesth 2004; 93: 799-805.
3. Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. Br J Anaesth 2002; 89: 857-62.
4. Zaugg M, Schaub MC, Pasch T, Spahn DR. Modulation of beta-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action. Br J Anaesth 2002; 88: 101-23.
5. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003; 97: 1633-8.
6. Lee SJ, Lee JN. The effect of perioperative esmolol infusion on the postoperative nausea, vomiting and pain after laparoscopic appendectomy. Korean J Anesthesiol 2010; 59: 179-84.
7. Wood AJ, Feely J. Pharmacokinetic drug interactions with propranolol. Clin Pharmacokinet 1983; 8: 253-62.
8. Wiest D. Esmolol. A review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharmacokinet 1995; 28: 190-202.
9. Wilhelm W, Kreuer S. The place for short-acting opioids: special emphasis on remifentanil. Crit Care 2008; 12: S5.
10. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570-87.
11. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. Best Pract Res Clin Anaesthesiol 2007; 21: 65-83.
12. Warncke T, Stubhaug A, Jorum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. Pain 1997; 72: 99-106.
13. Kissin I, Bright C, Bradley L. Acute tolerance to continuously infused alfentanil: the role of cholecystokinin and N-methyl-D-aspartate-nitric oxide systems. Anesth Analg 2000; 91: 110-6.
14. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106: 49-57.
15. Singler B, Tröster A, Manering N, Schüttler J, Koppert W. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. Anesth Analg 2007; 104: 1397-403.
16. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. Pain 2002; 100: 213-7.
17. Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol

potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. Anesth Analg 1998; 87: 671-6.
18. Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. Can J Anaesth 2001; 48: 59-64.
19. Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. Anesthesiology 1997; 86: 364-71.
20. Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. Anesth Analg 2001; 92: 352-7.
21. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai CM. Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. Clin Pharmacol Ther 1983; 34: 427-34.
22. Taira Y, Kakinohana M, Kakinohana O, Okuda Y. ONO 1101, a novel ultra-short acting β_1 blocker, can reduce pain behaviour in the rat formalin test. Anesthesiology 1998; 89: A1128.
23. Hagelüken A, Grünbaum L, Nürnberg B, Harhammer R, Schunack W, Seifert R. Lipophilic beta-adrenoceptor antagonists and local anesthetics are effective direct activators of G-proteins. Biochem Pharmacol 1994; 47: 1789-95.
24. Mitrovic I, Margeta-Mitrovic M, Bader S, Stoffel M, Jan LY, Basbaum AI. Contribution of GIRK2-mediated postsynaptic signaling to opiate and alpha 2-adrenergic analgesia and analgesic sex differences. Proc Natl Acad Sci U S A 2003; 100: 271-6.