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-anillidopiperidine methyl 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...
(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 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**


10. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570-87.


17. Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol

18. 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 Ca²⁺ channels; such a pathway underlies the antinociceptive effect of clonidine [24].


