

Should the clinical study on opioid-induced cough continue?

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Since Böhrer et al. [1] reported in 1990 that administering fentanyl through a central venous catheter induces the cough reflex, it has become well-known that remifentanyl and fentanyl used for inducing general anesthesia cause a cough in various types of clinical situations. This has led to many clinical studies [2-4] thus far, and the research paper of Yoo et al. [5] is also included in this group.

The proposed mechanisms through which opioids induce a cough are as follows: (1) pulmonary chemoreflex resulting from stimulation of C-fiber receptors (J receptors) [1], (2) stimulation of irritant receptors (rapidly adapting receptors) from deformation of the tracheobronchial wall by tracheal smooth muscle constriction [6], (3) the release of histamine from lung mast cells [7], and (4) the sudden adduction of the vocal cords or supraglottic obstruction by soft tissue caused by opioid-induced muscle rigidity [8]. Based on these mechanisms, many efforts have been made to reduce the cough reflex induced by opioid agents, and it has been reported that terbutaline (a selective beta-2 agonist) [9], salbutamol [7], lidocaine [10], ephedrine [11], clonidine [12], ketamine [13], and dexamethasone [5] are effective in reducing fentanyl-induced cough (FIC) or remifentanyl induced cough (RIC).

However, Elcock [14] referred to the paper of Hung et al. [2] that was included in the 2010 volume of *Anesthesia* and raised the question whether fentanyl really induces a cough with such a high frequency (18–65%) in clinical settings. Also, he stated that his experience of using fentanyl clinically (administering 30 mg of propofol when administering 100 µg of fentanyl before inducing anesthesia) did not induce a cough, and that he was perplexed that research on fentanyl-induced cough continues, and that in actuality, it is not problematic except for

pediatric patients. As a result, he asserted that it is meaningless to conduct studies on this phenomenon because, at least for adults, the commonly used dosage of fentanyl does not pose any actual problem.

There are also recent reports that recommend not administering the medicine because FIC and RIC are temporary and the pre-treatment itself can cause problems [15]. Moreover, there are studies showing good results from adjusting the administration method of fentanyl and remifentanyl so that their blood concentration levels increase gradually, because it is the sudden rise of their blood concentration levels that trigger the cough inducing mechanisms. There are also reports of reducing coughs by administering fentanyl slowly [16] or by administering a small amount in advance, so that there is not a sudden increase in concentration [2]. Also, there are studies that coughs are reduced by administering remifentanyl in separate doses [17] and by limiting the peak plasma concentration when infusing remifentanyl by TCI [18]. The paper of Ambesh et al. [3] that was published in the *British Journal of Anesthesia* in 2010 also reported significantly reduced cough (32% to 4%) induced by 2.5 µg/kg of fentanyl if a huffing maneuver was done before inducing anesthesia.

Thus, fentanyl and remifentanyl induced cough can be significantly reduced even without medicinal prevention. The continuous repetition of the same form of clinical study for more than 20 years seems meaningless even though I do not totally agree with Elcock's opinion. I have also published a paper [19] in 1996 reporting that administration of fentanyl to pediatric patients leads to high-dosage dependency and frequent coughs, and administering lidocaine in advance reduces coughs. In 2010 I published a paper about the impact of

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FIC on endotracheal intubation in pediatric patients [4].

Although many studies have been carried out over decades, the mechanism of FIC or of RIC has not yet been found. Therefore, I believe it is more useful shed light on why a sudden increase in blood concentration induces a cough, instead of conducting studies about reducing its clinical frequency.

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