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EDITORIAL II

Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter?

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In a recent issue of the *British Journal of Anaesthesia*, Echevarría and colleagues[1] reported that nitrous oxide (N_2O) reduced postoperative opioid-induced hyperalgesia (OIH) after remifentanil–propofol anaesthesia. In their study, 50 adult ASA I–II patients undergoing elective open septorhinoplasty under general anaesthesia were assigned to receive N_2O (70%) or 100% oxygen. Mechanical pain thresholds were measured before surgery and 2 and 12–18 h after

surgery. Pain measurements were performed on the arm using hand-held von Frey filaments. Baseline pain thresholds to mechanical stimuli were similar in both groups, with the mean values of 69 [95% confidence interval (CI): 50.2, 95.1] g in the group without N_2O and 71 (95% CI: 45.7, 112.1) g in the group with N_2O. Postoperative pain scores and cumulative morphine consumption were similar between the groups. The analysis revealed a decrease in the threshold value in both groups. However, *post hoc* comparisons showed that at 12–18 h after surgery, the decrease in mechanical threshold was greater in the group without N_2O than the group with N_2O.

OIH has been clearly identified in animal models[2] and in human volunteers.[3] Opioids which are potentially responsible for OIH in these experimental conditions include remifentanil and fentanyl. The neurobiology of OIH is complex and likely to involve more than one system, with probable differences between acute and chronic settings at both pre- and post-synaptic levels, affecting *N*-methyl-D-aspartate receptor activity, G-proteins, and intracellular systems.[4] The cumulative dose of remifentanil and the rapid withdrawal may be factors in remifentanil-induced hyperalgesia.[5 6] In a model of incisional pain in mice, remifentanil induced pro-nociceptive effects, which were dose-dependent but unaltered by the duration of administration.[5] The importance of the cumulative dose of opioid appears to be confirmed by clinical studies of remifentanil-induced hyperalgesia in surgical patients. In negative studies, the cumulative dose range used was 20–30 $\mu g\ kg^{-1}$,[6–10] in contrast to a range of 80–120 $\mu g\ kg^{-1}$ used in positive studies.[11–15] An *in vitro* study showed that abrupt withdrawal of opioid agonists induced long-term potentiation at the first synapse in pain pathways.[16] This provides a previously unrecognized target for selectively combating pro-nociceptive effects of opioids without compromising opioid analgesia. The importance of tapered withdrawal to reduce the expression of remifentanil-induced hyperalgesia has not been investigated in humans.

How is OIH defined in the surgical patient? The International Association of the Study of Pain defines hyperalgesia as 'Increased pain from a stimulus that normally provokes pain'. Therefore, the increased perception of pain after opioid-based anaesthesia could be the key factor associated with OIH. In addition, tolerance with the increased use of opioid after surgery is another potential, coexisting aspect of OIH. The mechanisms of opioid tolerance were recently addressed in an editorial accompanying a study of the role of β-arrestin 2 in a rodent model of opioid tolerance.[17 18] These two phenomena may be interrelated by common neural substrates.[19] In surgical patients, OIH, tolerance, or both have been identified mainly after remifentanil-based anaesthesia.[11–15 20] However, of these studies, only two have tested pain sensitivity to clearly identify OIH.[12 20]

Although OIH is an interesting concept, does its prevention matter for surgical patients? Different methods to prevent OIH have been tested, including perioperative ketamine,[12] magnesium,[15] propofol,[14] and nitrous oxide.[1] In these clinical studies aimed at preventing OIH, the clinical benefit in the immediate postoperative period is either absent,[1] limited to a moderate opioid-sparing effect,[12 14] or a slight reduction in pain scores.[14 15] None of these studies found that the morphine-sparing effect had any impact on the opioid-related side-effects. Finally, these studies were not powered to adequately estimate the side-effects related to the prevention technique. Therefore, the clinical benefit–tolerance ratio of OIH prevention in the immediate postoperative period needs further evaluation.

In which conditions may the prevention of OIH have more clinical significance? In certain groups of patients, OIH prevention might be more beneficial. Genetic factors and preoperative use of opioids are potential influences on the benefit related to OIH prevention. A clinical study of 43 healthy volunteers using a painful thermal stimulus found that individuals homozygous for the met (158) polymorphism of the catechol *O*-methyl transferase gene had greater hyperalgesia after remifentanil.[21] Preoperative screening of genetic factors is not feasible on a daily basis but may in the future help to define a prevention strategy. In the situation of preoperative use of opioid to treat existing pain, this chronic administration of opioid can increase the risk of hyperalgesia.[22] The additional impact of preoperative opioid might increase the severity of OIH. In a study of the intraoperative use of ketamine in surgical patients treated before operation with opioids, the benefit in the prevention of OIH was sustained, with a morphine-sparing effect for 6 weeks after surgery.[23]

The immediate postoperative period may not be the optimal period to detect the benefit of OIH prevention. One study has suggested that a higher dose of remifentanil may be predictive of a higher incidence of persistent post-surgical pain after thoracotomy.[20] In this study, a high dose of remifentanil (effect-site concentration 5.6 ng ml^{-1}) was compared with a low dose of remifentanil (effect-site concentration 2 ng ml^{-1}). There was an incidence of persistent post-surgical pain of 70% in the high-dose group compared with 16.7% in the low-dose group. Although the methodology of this study had some potential bias as epidural analgesia timing was different in the two groups, the potential connection between OIH and the development of persistent post-surgical pain is interesting. The incidence of persistent post-surgical pain 6 months after surgery has been previously shown correlated to the area of peri-incisional punctuate mechanical allodynia after colorectal surgery.[24] A recent study also observed that the intraoperative use of nitrous oxide reduced the risk of persistent post-surgical pain after thoracotomy by more than half.[25] This may suggest that Echevarría and colleagues[1] did not observe the potential clinical benefit related to preoperative nitrous oxide as their study focused on the immediate postoperative period. Overall, these clinical studies suggest that in the prevention of hyperalgesia related to opioid or surgical inflammation-induced hyperalgesia, it may be of interest to limit the incidence of persistent post-surgical pain rather than to improve immediate postoperative pain control. However, this hypothesis will need additional clinical data to confirm it before it could be included in guidelines.

In conclusion, it is not clear yet whether using strategies to prevent OIH in the surgical patient is clinically worthwhile. In the immediate postoperative period, the benefit is not clinically significant. Clinical studies with prolonged follow-up of persistent post-surgical pain or OIH prevention in selected populations may help to determine the value of this prevention.

Declaration of interest

None declared.

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