Opioid free anaesthesia: myth or reality?

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Keywords: opioids; anaesthesia; pain

COI: Dominique Fletcher : consulting for Grunenthal and Biocodex

The remaining authors declare no conflict of interest.

In this issue of ACCPM, P. Forget [1] proposes a qualitative study on opioid free anaesthesia (OFA). As exposed in this review, the rationale to propose OFA is based first on the question of evidence of specific activation of pain pathways under general anaesthesia and the negative consequences related to intraoperative use of opioids

such as immune effects and opioid-induced hyperalgesia (OIH). Focusing on OIH, the International Association of the Study of Pain defines hyperalgesia as “Increased pain from a stimulus that normally provokes pain”. This postoperative hyperalgesia is the result of various mechanisms involving OIH, surgical trauma and related nociception. OIH is an important basic mechanism potentially involved in postoperative consequences of opioid use both in the acute phase with increased pain intensity, opioid tolerance, increased opioid use and related side effects but also in the long term with a potential exposure to chronic postsurgical pain (CPSP) [2]. OIH has been clearly identified in animal models, human volunteers [3] and patients [4]. Specific populations may be exposed to OIH. Genetic factors and preoperative use of opioids are potential influencing factors of OIH [5]. A clinical study including 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 [6]. In the situation of preoperative use of opioid to treat existing pain, this chronic administration of opioid can increase the risk of hyperalgesia [7]. In a study on the intraoperative use of ketamine in surgical patients treated before surgery with opioids, the benefit of ketamine in preventing OIH was sustained, with a morphine-sparing effect for 6 weeks after surgery [8]. The impact of perioperative opioid use on the development of opioid misuse is also an emerging problematic, which underlines the importance of a rational and limited use of opioid in surgical patients [9]. Concerning CPSP two studies have suggested that a higher dose of remifentanil may be predictive of a higher incidence of persistent post-surgical pain after thoracotomy or cardiac surgery [10,11].

The cumulative dose of remifentanil and the rapid withdrawal may be the predominant factors in remifentanil-induced hyperalgesia. The cumulative dose of remifentanil seems the determinant factor both in experimental and clinical research [4,12]. A quantitative review confirmed the clear association between high dose remifentanil and clinical signs of hyperalgesia [4]. However, the authors were unable to define a cut-off value responsible for this remifentanil-induced hyperalgesia. Is there other approach to prevent opioid-induced hyperalgesia in surgical patients? Beyond opioid dose reduction, different approaches have been tested including perioperative ketamine, clonidine, propofol, non-steroidal anti-inflammatory drug, propranolol or nitrous oxide [13]. However, all these approaches can be responsible for additional side effects.

OFA is emerging as a new stimulating research perspective. The aim is to avoid the negative impact of intraoperative opioid on patient's postoperative outcomes. Reducing or eliminating opioids during general anaesthesia have been proposed for many years in the literature. OFA is based on the concept of multimodal anaesthesia. One drug will not replace opioids. It is the association of drugs and /or techniques that will allow a good quality OFA. The association can combine NMDA antagonists (ketamine, lidocaine, magnesium sulfate), sodium channel blockers (local anaesthetics (LA)), anti-inflammatory drugs (NSAID, dexamethasone, LA) and alpha-2 agonists (dexmetedomidine, clonidine). Of course, all these drugs / techniques will not be administered to the same patient. Indeed, for toxicity reasons, LA can only be administered by one route at a time (either regional anaesthesia / analgesia or IV lidocaine). For haemodynamic stability, alpha-2 agonists are the drugs of choice: IV dexmetedomidine (shorter half-life) or IV clonidine. Magnesium sulfate could also help with haemodynamic stability [14]. It is however associated with a risk of

hypotension. Indeed, all these drugs administered alone have documented side effects, which have to be known and prevented by anaesthesiologists. OFA is feasible but is it associated with clinically meaningful benefits for patients? Proofs are scarce in the literature. In the past 10 years, only 10 RCTs have been published on the subject. They reported a benefit of OFA in terms of postoperative morphine sparing, pain scores reduction and PONV. However, these studies were usually small (from 20 to 124 patients) and the results need to be confirmed by large-scale studies. Anaesthesiologists around the world and P. Forget in his article are very enthusiastic about OFA. It is indeed exciting! However, we also need to be cautious, as a lot of questions are still unanswered. OFA cannot be formally recommended, as further proofs of its benefits are needed.

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