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Hakim Harkouk, Dominique Fletcher, H el ene Beloeil

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**Opioid free anaesthesia: myth or reality?**H. HARKOUK<sup>1 2</sup>, D. FLETCHER<sup>1 2</sup>, and H. BELOEIL<sup>3 4</sup>

<sup>1</sup>Service d'Anesthésie-Réanimation, CHU Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France

<sup>2</sup>Unité INSERM 987, Université de Versailles Saint-Quentin en Yvelines, 55 Avenue de Paris, 78000 Versailles France

<sup>3</sup>Service d'Anesthésie-Réanimation, CHU de Rennes, 2 Rue Henri le Guilloux, 35033 Rennes cedex 9 France

<sup>4</sup>Unité INSERM CIC 1414, NuMeCan, Université de Rennes, 2 rue du Thabor - CS 46510 35042 Rennes CEDEX France

Corresponding author: hakim.harkouk@aphp.fr

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

16 such as immune effects and opioid-induced hyperalgesia (OIH). Focusing on OIH,  
17 the International Association of the Study of Pain defines hyperalgesia as “Increased  
18 pain from a stimulus that normally provokes pain”. This postoperative hyperalgesia is  
19 the result of various mechanisms involving OIH, surgical trauma and related  
20 nociception. OIH is an important basic mechanism potentially involved in  
21 postoperative consequences of opioid use both in the acute phase with increased  
22 pain intensity, opioid tolerance, increased opioid use and related side effects but also  
23 in the long term with a potential exposure to chronic postsurgical pain (CPSP) [2].  
24 OIH has been clearly identified in animal models, human volunteers [3] and patients  
25 [4]. Specific populations may be exposed to OIH. Genetic factors and preoperative  
26 use of opioids are potential influencing factors of OIH [5]. A clinical study including 43  
27 healthy volunteers using a painful thermal stimulus found that individuals  
28 homozygous for the met (158) polymorphism of the catechol O-methyl transferase  
29 gene had greater hyperalgesia after remifentanyl [6]. In the situation of preoperative  
30 use of opioid to treat existing pain, this chronic administration of opioid can increase  
31 the risk of hyperalgesia [7]. In a study on the intraoperative use of ketamine in  
32 surgical patients treated before surgery with opioids, the benefit of ketamine in  
33 preventing OIH was sustained, with a morphine-sparing effect for 6 weeks after  
34 surgery [8]. The impact of perioperative opioid use on the development of opioid  
35 misuse is also an emerging problematic, which underlines the importance of a  
36 rational and limited use of opioid in surgical patients [9]. Concerning CPSP two  
37 studies have suggested that a higher dose of remifentanyl may be predictive of a  
38 higher incidence of persistent post-surgical pain after thoracotomy or cardiac surgery  
39 [10,11].

40 The cumulative dose of remifentanil and the rapid withdrawal may be the  
41 predominant factors in remifentanil-induced hyperalgesia. The cumulative dose of  
42 remifentanil seems the determinant factor both in experimental and clinical research  
43 [4,12]. A quantitative review confirmed the clear association between high dose  
44 remifentanil and clinical signs of hyperalgesia [4]. However, the authors were unable  
45 to define a cut-off value responsible for this remifentanil-induced hyperalgesia. Is  
46 there other approach to prevent opioid-induced hyperalgesia in surgical patients?  
47 Beyond opioid dose reduction, different approaches have been tested including  
48 perioperative ketamine, clonidine, propofol, non-steroidal anti-inflammatory drug,  
49 propranolol or nitrous oxide [13]. However, all these approaches can be responsible  
50 for additional side effects.

51 OFA is emerging as a new stimulating research perspective. The aim is to avoid the  
52 negative impact of intraoperative opioid on patient's postoperative outcomes.  
53 Reducing or eliminating opioids during general anaesthesia have been proposed for  
54 many years in the literature. OFA is based on the concept of multimodal anaesthesia.  
55 One drug will not replace opioids. It is the association of drugs and /or techniques  
56 that will allow a good quality OFA. The association can combine NMDA antagonists  
57 (ketamine, lidocaine, magnesium sulfate), sodium channel blockers (local  
58 anaesthetics (LA)), anti-inflammatory drugs (NSAID, dexamethasone, LA) and alpha-  
59 2 agonists (dexmedetomidine, clonidine). Of course, all these drugs / techniques will  
60 not be administered to the same patient. Indeed, for toxicity reasons, LA can only be  
61 administered by one route at a time (either regional anaesthesia / analgesia or IV  
62 lidocaine). For haemodynamic stability, alpha-2 agonists are the drugs of choice: IV  
63 dexmedetomidine (shorter half-life) or IV clonidine. Magnesium sulfate could also  
64 help with haemodynamic stability [14]. It is however associated with a risk of

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

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