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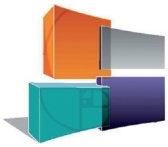

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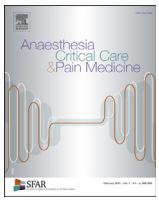

Review article

Opioid-free anaesthesia. Why and how? A contextual analysis

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ABSTRACT

If the use of natural opiates, such as opium, is more than millennial, the history of synthetic opioids begins after 1950, with the development of the so-called 'modern' anaesthetic techniques. In 1962, in Belgium, the use of fentanyl, the first synthetic opioid for use in anaesthesia, is described. Subsequently, the use of opioids at high doses during surgery became common. However, over the last twenty years, many studies have questioned this practice, highlighting the many unknowns as the side effects of these molecules. The so-called opioid-free anaesthesia (OFA) techniques were developed in parallel with a better understanding of perioperative pain. In this work, the following questions are addressed: Why is the human body producing endogenous opioids? Is the concept of pain valid during general anaesthesia? What are the effects of intraoperative opioids on postoperative pain? Is anaesthesia without opioids actually possible? With these questions, the reader can question the use of intraoperative opioids within an historical and evolutionary perspective. In the same time, if OFA is feasible, the research agenda still includes a formal testing of its added value over classical opioid-sparing techniques.

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1. Introduction

The routine use of intravenous synthetic opioids tends not to be questioned. Nevertheless, any intervention that is performed in a systematic way, without evidence that its use is associated with a more favourable evolution of the patient, should be questioned. The practice of science, as medicine, imposes a systematic questioning of practices. Thus, it is interesting to question the potential risks of intraoperative opioids and their alternatives, specifically the opioid-free anaesthetic (OFA) techniques.

2. Historical context

Natural opiates, such as opium, have been used for thousands of years. The history of synthetic opioids begins after the Second World War. At this time, no synthetic opioids were available to induce anaesthesia, rendering challenging the induction of anaesthesia in haemodynamically unstable patients. Indeed, surgeons reported that many American soldiers, during the attack on Pearl Harbor in 1941, did not survive after the induction of general anaesthesia [1]. Assigning these deaths to anaesthesia is probably exaggerated. Nevertheless, it is clear that the imperfect knowledge of physiology

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rendered difficult the control of the haemodynamic during haemorrhagic shock. In 1962, after its synthesis by Paul Janssen (in 1960), the use of fentanyl in anaesthesia is described for the first time [2]. An actual revolution is then initiated, allowing a modification of the Liverpool anaesthesia protocol by the addition of fentanyl [3]. The possibility of administering very high doses of opioids, the important acute tolerance and the remarkable haemodynamic stability associated with their use during surgery, quickly led to a trivialisation, even a generalisation, of this type of technique, called balanced anaesthesia.

However, since the sixties, anaesthesia has changed from inhalation to multimodal anaesthesia with lower doses of hypnotics. Some medications, such as ether, chlorophorm, and more recently, halothane, disappeared from the armantarium of the anaesthetist working in high incomes countries. Other techniques appeared, including associations of a hypnotic, a muscle relaxant, ketamine, with or without loco regional analgesia, permitting to provided good operating conditions, a rapid recovery with satisfactory emergence, cardiovascular stability, including in difficult settings. Now, improvement of knowledge, teaching, monitoring, and surgical techniques, permit to achieved objectives for hypnosis, haemodynamic stability, immobility and anticipation of postoperative analgesia in many cases [4].

These techniques permitted to decrease the use of opioids, to avoid their well described side effect, such as postoperative ileus, urinary retention, nausea and vomiting, shivering, respiratory depression, sleep-disordered breathing [5–7].

Since twenty years, besides the well-known side effects of opioids, many studies have questioned the use of high doses of opioids, highlighting the immune effects of these molecules, the lack of evidence of specific activation of pain pathways under general anaesthesia, the risk of opioid-induced hyperalgesia [7].

3. What is the first role of endogenous opioids?

Opioid receptors are among the best conserved on an evolutionary plan in the animal kingdom, not only by vertebrates, but also by many invertebrates, including those with no central nervous system similar to ours, such as molluscs. This is because endogenous opioids have a fundamental role in the post-traumatic reaction, in particular the immune response secondary to tissue injury [8]. The analgesic effects of opioids (i.e. stress-induced analgesia) appeared only late in the evolution, precluding any restriction to their effects on pain. Many unknowns persist in these non-analgesic (i.e. immune) effects. The immune effects of opioids have been studied in many different models, and seem to depend on the type of model (surgical or not), on the dose, and on the type of opioid. These effects, various and sometimes opposite, seem to be in the direction of an immune depression for the high opioids doses and in the absence of pain (non-surgical models), at least in regards of the cell-mediated cytotoxicity [8]. Other effects of opioids, potentially promoting tumour growth and metastasis have been described, including also tumour cells aggressiveness and angiogenesis [9]. These observations may be of great importance if one remembers the crucial role that this type of immunity plays in the immunosurveillance and the elimination of cancer cells [8].

Meta-analyses have variably reported associations between longer recurrence-free and/or overall survival with regional analgesia compared with systemic opioids [10]. But, although there is a potential association between opioids use and cancer outcomes, most of the studies are limited by their retrospective design and/or the quality of data, precluding any conclusion regarding a causative link [11].

Nevertheless, beyond these potential effects on immunity, one could say that the role of opioids to control intraoperative pain is well demonstrated. However, this is far from clear.

4. To control pain under general anaesthesia?

In 1979, the International Association for the Study of Pain defined pain as a sensory and emotional experience associated with or described in terms of tissue injury. The term ‘experience’, and even more specifically ‘emotional’, necessarily implies a ‘cognitive integration’ in a ‘conscious’ subject.

More recently, regarding the major importance of attentional modulation of pain processes, electrophysiologists concluded that the activation of brain regions (in response to nociceptive inputs) is not sufficient to be referred to as ‘pain’ [12]. Neuroimaging studies show that brain functions involved in attentional processes and pain are largely overlapping and emerge from large-scale networks and not from specific regions [12]. Indeed, during painful stimuli, the activation of cortical and subcortical areas is not specific for pain and can be observed during other attentional modulation of the perception of auditory or visual stimuli [13]. During general anaesthesia, at least in animals, anaesthesia has a profound effect both on within- and between-networks interactions [14].

This is important for the anaesthetist, as the consequence is that pain cannot be processed in as in awake subjects, and probably not integrated, even implicitly.

Taken together, reactions to nociceptive inputs under general anaesthesia should not be referred as ‘pain’ as involving different processes, consequences and, then, management techniques.

Nociceptive activation and haemodynamic control will be discussed later.

5. Influence of intraoperative opioids on postoperative pain

If the concept of pain under general anaesthesia can be challenged, postoperative pain remains a real problem. Indeed, postoperative hyperalgesia can be the direct consequence of the surgical trauma. Central nervous system sensitisation can then be induced by the nociceptive response, via the involvement of excitatory amino acids implying the N-methyl-d-aspartate (NMDA) receptor.

One would say that pre-emptive analgesia, i.e. blocking the nociception-induced hyperalgesia with intraoperative opioids, could be a solution to prevent severe postoperative pain [15]. It seems to be rather the opposite. Indeed, all the opioids can potentially induce hyperalgesia, and this especially if the duration of action of the opioid is short. This effect is unmasked after the disappearance of the shorter analgesic effect [16]. Even low doses of remifentanil induce rapidly an activation of pain pathways in healthy volunteers [17]. In patients, the analgesics requirements in the post-anaesthesia care unit can be shortened by more than 20 minutes after administration of remifentanil [18]. A meta-analysis showed that intraoperative high doses of opioids are associated with increased postoperative pain, and increased postoperative opioids requirements [19]. The results of this analysis were mainly driven by remifentanil.

In the longer term, it is possible that remifentanil increases the risk of chronicisation of postoperative pain [20]. Prevention of this type of phenomenon by greater opioid administration seems to be a bad answer, data suggesting a dose-dependent effect [7,21]. But is it possible to do otherwise?

6. Is anaesthesia possible without opioids?

In the 1990s, Marc De Kock and colleagues developed anti-hyperalgesic techniques to improve postoperative pain control. Later, during the 2000s, these opioid-sparing techniques challenged the added value of intraoperative opioids [22–27]. Concretely, the primary goal was not, and must not be necessarily

today the total avoidance of intraoperative opioids. But the desirable goal is rather the use of opioids-sparing strategies, which can have, as welcome consequence, the disappearance for the need for any intraoperative opioids. Consequently, OFA during general anaesthesia can be defined as the combination of various opioids-sparing techniques leading to the disappearance of the intraoperative opioids.

In the first place of these techniques, the use of alpha-2-agonists, such as clonidine, and more recently dexmedetomidine, has been proposed as component of opioid-sparing strategies, or even permitting to obtain haemodynamic stability during anaesthesia [28,29]. The unique, spinal and supraspinal mode of action of these agents makes them unique in anaesthesia. Other benefits include the sparing of other anaesthetic agents, improvement of haemodynamic stability, reduction of bleeding, prevention of shivering, without prolongation of the awakening phase [22]. The significance of the 5 percent hypotension and bradycardia found in some studies, like in the largest, the POISE-2 trial, but not in other, is still unknown [30]. So far, no data is available on the clinical consequences of intraoperative hypotension and/or bradycardia induced by alpha-2 agonists.

OFA is also ideally, but not compulsorily, performed with loco regional analgesia (i.e. peripheral nerve blocks or epidural analgesia), to improve pain management. Independently from the use of opioids, epidural analgesia has been proposed to prevent the occurrence of postoperative hyperalgesia [23]. Adjuvants to local anaesthetics may, be non-opioid, for example clonidine [22].

Ketamine also has an important place, at anti-hyperalgesic dose, either in bolus or in continuous infusion, not only to reduce the use of opioids but also to improve the intraoperative haemodynamic stability (in particular the arterial pressure). Its use improves the management of postoperative pain [23].

To improve haemodynamic stability, magnesium sulphate is associated with a reduction in heart rate variability without causing more hypotension [31].

Intravenous lidocaine is recommended in major surgery, in particular in major abdominal surgery, as well as dexamethasone [32].

7. Risk/benefit balance, added value vs. safety and research agenda

If most of these techniques are now used from decades, the literature on total avoidance of intraoperative opioids remains scarce. Nevertheless, the available evidence (i.e. a positive benefit/risk balance) is in favour of opioid-sparing strategies, at least in some situations, as recommended in national guidelines [32]. What is not clear is the added value of the total avoidance of intraoperative opioids, when opioid-sparing strategies are applied (e.g. to decrease the postoperative opioid-related adverse events). To answer to this question, the Postoperative and Opioid Free Anesthesia (POFA) randomised-controlled trial is now ongoing (NCT03316339), recruiting 400 patients in intermediate to major non-cardiac surgery. The results will permit to test the superiority of the OFA, but could also give information regarding non-inferiority and safety of OFA. This non-inferiority may pave the way to a more specific exploration of a more specific place of OFA, i.e. where opioids may represent a significant problem (regarding to the settings and/or the patients).

Indeed, even if the clinical experience is growing, the obvious feasibility of OFA is not sufficient to recommend it formally. Nevertheless, in the absence of any signal of specific adverse outcomes in the literature, and when opioids use can be already largely decreased, their added value can be questioned.

8. Conclusion

The interest of opioids during anaesthesia can be balanced within an historical and evolutionary perspective. Opioid-sparing strategies, permitting to reduce the use of intraoperative opioids, are now recommended. But, if it became obvious that OFA is possible, the research agenda still includes a formal testing of the added value of OFA over opioid-sparing techniques.

Ethics committee approval

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Author's contributions

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