

## Intraoperative opioids: Reduce but not refuse!

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### Abbreviations:

<b>ERAS:</b>	<b>Enhanced recovery after surgery</b>
<b>NSAIDs:</b>	<b>Non-steroidal anti-inflammatory drugs</b>
<b>OFA:</b>	<b>Opioid-free anesthesia</b>
<b>PONV:</b>	<b>Post-operative nausea and vomiting</b>
<b>PROSPECT:</b>	<b>PROcedure-SPE-cific Postoperative Pain Management</b>

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Traditionally, opioids have been extensively used in anesthesia to ensure adequate pain management intra- and post-operatively. The liberal and inappropriate use of opioids in the perioperative period can be associated with a variety of well-known adverse effects and has even been suggested to have contributed to the opioid crisis in North America. Driven by presumably good intentions, but based upon virtually absent evidence, a new phenomenon has emerged in anesthesia: opioid-free anesthesia (OFA), referring to a strategy in which no opioids are used during anesthesia in an attempt to avoid short- and long-term adverse effects of opioids<sup>1</sup>. Although the efficacy and safety of OFA has not been thoroughly documented yet, OFA has gained considerable attention, not only in response to the opioid-crisis, but also in an attempt to address several challenges frequently encountered in perioperative medicine. The concept of OFA is largely based on a variety of assumptions that are worthwhile to be critically discussed.

### Opioid crisis: USA vs. Europe

In the past 20 years, the US has been hit by a devastating national opioid epidemic. From 1999–2020, more than 564,000 people died in the US from an overdose involving any opioid, i.e., illicit and prescription opioids. Unfortunately, the number of drug-induced deaths continues to rise from year

to year, with a 38%-increase in the opioid-involved death rate from 2019-2020<sup>2</sup>. The opioid crisis has been attributed to a variety of factors including (but not limited to) the misjudgment that opioids are safe for long-term use, aggressive marketing techniques of pharmaceutical companies, and the presence of ‘pill mills’ (pharmacies or clinics inappropriately providing patients with narcotics), all of them leading to an increase in opioid prescription and abuse<sup>3,4</sup>. In 2021, more than 106 000 persons died in the U.S. from drug-involved overdose, resulting in a drug-induced mortality of 32 per 100 000 inhabitants<sup>5</sup>. In contrast, the opioid-crisis has long been virtually absent in Europe. In Belgium, only 0.82 inhabitants per 100 000 Belgians deceased because of an opioid-overdose in 2014<sup>6</sup>. Similar findings were observed in other European countries, apart from the United Kingdom (especially Scotland), where, despite the lack of an increase in opioid prescriptions<sup>7</sup>, the incidence of opioid users and opioid-related deaths increased<sup>8</sup>. Most fatalities were caused by methadone and heroine<sup>8</sup>.

Concerningly, more recent data suggest that in Belgium, the incidence of opioid dependency (in particular the use of illicit fentanyl) is also significantly rising<sup>9</sup>. In response to this, the federal government has recently set up a working group to avoid a Belgian opioid crisis.

While these developments are alarming, to date, no association or causal relationship could be found

between the intra-operative use of opioids and the development of opioid dependence. Moreover, there is no evidence that reduction of opioid use in the intra- and immediately postoperative period will resolve opioid abuse in the long-term<sup>10</sup>.

### Risk factors for opioid-dependence after surgery

Lawal and colleagues have shown that women and non-Caucasian patients have an increased risk to develop long-term opioid use post-operatively<sup>11</sup>. Preoperative medication (antidepressants, benzodiazepines and opioids) and pre-operative alcohol and tobacco abuse were also associated with persistent postoperative opioid use. Likewise, substance abuse, specific health conditions (anxiety, depression and mood disorders, diabetes, liver disease, obesity, pulmonary disease) and chronic pain (arthritis, back pain, chronic pain, fibromyalgia and migraine) are important risk factors for development of opioid-dependence. Pre-operative opioid use appears to be the most important risk factor. In one study, approximately 1% of all opioid-naïve patients undergoing non-cardiac surgery had persistent postoperative opioid use, in contrast to 20% of the patients who had already been exposed to opioid therapy preoperatively (defined as having had at least 1 opioid prescription 1 year prior to surgery)<sup>11</sup>.

These risk factors have been confirmed by Liu et al. who investigated persistent opioid use after cardiac surgery<sup>12</sup>. Women, tobacco and alcohol use, congestive heart failure, diabetes, chronic lung disease, chronic kidney disease and length of hospital stay (being a surrogate for the cumulative opioid dose received during hospitalization and postoperatively) increased the risk to be opioid-dependent 3 months after surgery. Only 5% of opioid-naïve patients but 20% of patients being opioid-exposed before surgery remained chronic opioid users after cardiac surgery<sup>12</sup>.

Moreover, the problem of postoperative opioid abuse appears to be associated with opioid treatment in the postoperative period after discharge rather than with opioid administration in the perioperative period during hospital stay<sup>13,14</sup>. Prescribing opioids at surgical discharge has been identified as a major risk factor for persistent postoperative opioid use and increases the risk of adverse events without improving adequate pain control at any time point post-operatively.

In conclusion, these data suggest that postoperative opioid dependence seems to be unrelated to the intra- and immediate postoperative use of opioids.

### Multimodal analgesia and the safety of analgesic adjuncts

Multimodal analgesia strategies are currently advocated in various guidelines published by e.g. the American Society of Anesthesiologists<sup>15</sup>, PROcedure-SPE-cific Postoperative Pain Management (PROSPECT)<sup>16</sup>, and various enhanced recovery after surgery (ERAS) societies<sup>17</sup>. Multimodal analgesia allows to manage acute pain during and after surgery by combining opioids with non-opioid analgesics including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), metamizole, dexamethasone, and regional anesthesia techniques. In addition, analgesic adjuncts including alpha 2 adrenergic agonists, ketamine and gabapentinoids are increasingly used for multimodal analgesia<sup>18</sup>. The combination of opioids with non-opioid analgesics allows to reduce the dose of opioids and targets different nociceptive pathways resulting in more efficient analgesia.

However, analgesic adjuncts and non-opioid analgesics are less potent than opioids and can also have serious side-effects. Unfortunately, concerns about their safety seem to be frequently ignored or neglected. Even the short-term use of NSAIDs leads to a considerable excess mortality largely attributed to upper gastrointestinal complications<sup>19</sup>. While the exact magnitude is still an ongoing matter of debate, the use of metamizole has been linked to agranulocytosis<sup>20,21</sup>.

Recently, a French multicentre randomized controlled trial investigated the efficacy and safety of OFA by allocating patients to either standard opioid-based analgesia (remifentanyl and morphine) or OFA (dexmedetomidine)<sup>22</sup>. The study had to be prematurely stopped due to the occurrence of severe bradycardia with subsequent asystole in the dexmedetomidine group. Moreover, the OFA-group had an increased incidence of hypoxemia and bradycardia, experienced a longer stay on the post-anesthesia care unit and suffered from delayed extubation<sup>22</sup>. Cumulative 48h morphine consumption was statistically significantly reduced by 5mg in the OFA-group, a reduction of probably questionable clinical relevance. This study clearly refuted the hypothesis that OFA would lead to a reduction of opioid-related adverse events and demonstrated that OFA is not without serious risks.

Other protocols of OFA often include gabapentin as alternative to opioids (next to ketamine, lidocaine and alpha-2-agonists including dexmedetomidine and clonidine)<sup>1</sup>. Historically, gabapentin has been prescribed (with opioids) to treat neuropathic pain. However, concomitant opioid use increases the risk

for developing respiratory depression. Recently, the US Center for Disease Control and Prevention reported that gabapentin involvement in opioid-induced death has even increased over the last years<sup>23</sup>. Besides respiratory depression, gabapentin is associated with the development of vertigo and visual symptoms. In addition, older patients are prone to develop delirium, pneumonia and are more likely to be prescribed anti-psychotic drugs when gabapentin is included in their peri-operative medication scheme. These effects are more pronounced in patients with more comorbidities and presence of chronic kidney disease. Moreover, high-quality evidence for reducing peri-operative pain by gabapentin is lacking<sup>24</sup>.

Likewise, also other analgesic adjuncts can have detrimental adverse effects including hallucinations and nightmares caused by ketamine<sup>25</sup>, an increased risk of hypotension and stroke associated with  $\beta$ -blockers<sup>26,27</sup>, and arrhythmias, potentiation of neuromuscular blockade and an increased risk of residual paralysis caused by magnesium<sup>28</sup>.

### Chronic pain and opioid-induced hyperalgesia

Another claim to avoid the intraoperative use of opioids is the hypothetical prevention of developing chronic postoperative pain, in part being attributed to the hyperalgesic effects of opioids. However, there is neither convincing evidence that transition from acute to chronic postoperative pain can be prevented by analgesic adjuncts (gabapentinoids, ketamine, NSAIDs) nor that it is triggered by the intraoperative use of opioids<sup>13</sup>.

Opioid-induced hyperalgesia can develop in patients with a dysfunctional endogenous opioid system, especially when high doses of short-acting opioids are administered. However, limiting the dose rate of remifentanyl to less than 0.2  $\mu$ g/kg/min decreases the risk for developing hyperalgesia postoperatively<sup>29</sup>.

### ERAS protocols

Opioid-related adverse events such as postoperative nausea and vomiting, respiratory depression, ileus and somnolence interfere with the goals of ERAS concepts. However, while ERAS guidelines clearly advise to reduce opioids during anesthesia, not a single guideline advocates to avoid opioids<sup>30</sup>. The PROSPECT collaboration even considers the use of OFA questionable due to the lack of documented improvements in post-operative outcome after OFA<sup>30</sup>. Not a single ERAS guideline recommends opioid eradication. In addition, opioid avoidance is not feasible in every type of surgery<sup>10</sup>.

### Opioid stewardship

Patient education on post-operative pain management, limiting the post-operative use of opioids and employing multimodal analgesia strategies can help to reduce the risk of opioid dependence after surgery. In the UK, it even has been advised that health care takers should discuss the risks of tolerance and opioid dependence with their patients prior to surgery<sup>31</sup>.

Pre-operative screening and identification of patients at risk for development of opioid misuse is important. Moreover, modifiable risk factors (pre-operative medication, tobacco and alcohol abuse) should be addressed before perioperative opioid exposure. Close post-operative monitoring of patients at risk, adequate dosing and very limited duration of opioid prescription (only after major surgery) might help to decrease the risk of chronic opioid-dependence<sup>11,12,32</sup>.

### Conclusion

Opioids remain the mainstay of modern balanced anesthesia. It has to be acknowledged though that past concepts relying on high-dose or even mono-opioid anesthesia are associated with major untoward effects and should be abandoned. For the benefits of enhanced recovery of our ever-aging patient population, it is clearly indicated to reduce intra- and postoperative opioid use (a concept commonly referred to as “opioid-sparing anesthesia”). In our opinion, opioid eradication is not the solution. The positive effects of OFA seem to be largely limited to a reduction in PONV, an effect that can also easily be achieved by employing appropriate PONV prophylaxis. While OFA has been linked to an increase in adverse events, effects on persistent postoperative opioid use and abuse have not been documented yet. Therefore, opioids remain important analgesics in the peri-operative period. Opioids should be carefully titrated intra- and postoperatively and embedded in multi-modal analgesia concepts. Opioid-free analgesia after discharge is crucial in reducing the risk for opioid dependence. Identification of patients at risk and monitoring of these patients post-operatively might be crucial to decrease the incidence of opioid dependence after surgery.

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