Opioid Free Anesthesia (OFA), a paradigm shift?

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Before the introduction of opioids in the 1960s, hypnosis, immobility, and hemodynamic stability were achieved using deep inhalational or high-dose hypnotics such as pentothal. These agents also induced strong hemodynamic suppression, however. Therefore, the introduction of balanced anesthesia was a gift. Opioids support hemodynamic stability by suppressing the sympathetic system. In addition, opioids are the strongest analgesics, and analgesia then came to be an essential part of balanced anesthesia, together with hypnosis and immobility.

Is it time today to enhance this vision? Paul Janssens, the founder of Janssens Pharmaceuticals and inventor of the synthetic opioids, warned 20 years ago that medical use of their formulation Remifentanyl could cause addiction, immunosuppression, and other unknown long-term effects, and he stated that high-dose opioids are not needed to achieve anesthesia. Further, Janssens refused to bring Remifentanyl to the market under his company's name. [1] Nevertheless, anesthesiologists were drawn to the use of these powerful opioids due to their seemingly rapid activity. Moreover, the combination of opioids and new low-dose intravenous hypnotics such as propofol, without inhalational agents, became attractive to suppress postoperative nausea and vomiting (PONV) and retain hemodynamic stability. Side effects of the inhalational agents were avoided, but are the side effects of opioids not more dramatic and prolonged?

Do we need to avoid perioperative opioids? Why?

Most common side effects of opioids are well known: respiratory depression, pruritus, nausea and vomiting, ileus, constipation, urinary retention, tolerance by desensitization, immediate hyperalgesia that may evolve into chronic pain syndrome, reduced cardiac output, dizziness, somnolence, and short-duration central muscle stiffness. [2] Opioid-induced ventilatory impairment is well known by anesthesiologists and easily treated in the post-anesthesia care unit, but this complication is still problematic postoperatively on the ward. [3] A lesser known side effect is pharyngeal muscle weakness, contributing to obstructive breathing patterns in every patient. This side effect should certainly be avoided in obese patients [4] [5] [6] and patients with obstructive sleep apnea (OSA), given the potential for aggravation and further breathing obstruction. Accordingly, recommendations for anesthesiologists are to avoid or minimize the perioperative use of opioids in these patients. [7]

Each year several reasons are added for reducing or avoiding the use of synthetic opioids. Enhanced postoperative recovery may be achieved by reducing opioid use to improve healing and to avoid immune system suppression. If no opioids are used during surgery, fewer opioids are needed to achieve a pain-free recovery, as addiction has not yet destroyed the mu receptor system. Oncology patients may have better survival outcomes when no opioids are used during surgery, but further studies are needed to confirm this effect.[8] Brain dysfunction is certainly less in neonates when opiates are

avoided. [5] Sleep disturbance is more frequent in patients taking opioids. [9] Postoperative urinary retention (POUR), a frequent complication after general anesthesia, seems to occur less frequently after opioid free anesthesia (OFA). Shivering and feeling cold when waking up are also less common after OFA[10], but these differences could be attributed to the alternative drugs used. Opioid-induced hyperalgesia and chronic pain syndromes are more frequent when high-dose opioids are used perioperatively. [11] [12]

Postoperative needs are different from perioperative needs.

Analgesia, or being pain-free, is only important postoperatively when patients are awake. Perioperatively, we need a stress-free anesthesia, or a para- and orthosympathetic block to achieve hemodynamic and general physiological stability. Immobility might be required, but this could also be achieved by other measures. What actually counts is supporting the function of all organs by guaranteeing sufficient tissue perfusion to provide nutrients and oxygen and to remove carbon dioxide and waste. Cortisol levels can also become elevated following organ stress as a result of sympathetic stimulation. Opioids were the ideal agents to address these needs in the past, but today it is possible to block sympathetic reactions and achieve hemodynamic stability without cortisol reactions. But are patient outcomes also better without opioids? A retrospective matched cohort study found that adverse events occurred more frequently in patients receiving higher doses of opioids following surgery. The higher doses of opioids following surgery were associated with an increased length of stay (LOS). [13]

Hypnosis-only anesthesia is not enough; what patients are most afraid of is awareness. Therefore, sufficient hypnosis with amnesia is what should be achieved. Immobilization is what is needed most frequently. Many procedures, such as intubation and laparoscopy, require deep muscle relaxation. Deep hypnosis or high-dose opioids can improve immobilization and block respiration, but these will never produce the same degree of muscle relaxation as can be achieved using neuromuscular blocking agents.

A new approach?

The new approach in anesthesia should provide hypnosis with amnesia and muscle relaxation at the moment the anesthesiologist or surgeon requires it, while also maintaining sufficient tissue perfusion and sympathetic stability to protect organs. Avoiding opioids during anesthesia is possible without hemodynamic instability. We need to stabilize the sympathetic system and avoid cardiovascular instability. In the past, high-dose opioids were the ideal agents to achieve this stability.

The introduction of opioids was important because hypnotics at that time were strong cardiovascular depressants, and in that period, many patients had undiagnosed and untreated cardiovascular coronary diseases. Giving high doses of opioids allowed the reduction of hypnotics and muscle relaxants. Today, we have safer hypnotics and neuromuscular blocking agents that can be used to achieve a sufficient depth of hypnosis and muscle relaxation. And most patients are treated for their cardiovascular problems.

We now have drugs that can stabilize the sympathetic nervous system, including alpha 2 agonists [14] (clonidine, dexmedetomidine); locoregional anesthetics given intravenously (lidocaine, procaine) [15], magnesium [16]; and gamma-aminobutyric acid modulators (gabapentin). [17] When these are given together in a multimodal approach, you can avoid all intraoperative opioids. Most of them will reduce the intra operative opioid use when given alone in a sufficient high dose creating problems of prolonged sedation. The advantage of such an approach is that postoperative opioids given as analgesics are then also dramatically reduced. This is called the Opioid Paradox: the more opioids you give perioperatively, the more opioids you need postoperatively. Since 2011, we have frequently used OFA for bariatric procedures in Bruges. In a retrospective cohort of 5000 patients, we found a dramatic reduction in postoperative opioid use in the first 24 hours, (mean and SD of morphine equivalents 21 mg and SD 0.99 versus 6 mg and SD 0.48), with fewer complications and a shorter LOS. In this cohort, patients with OSA were not found to have more complications compared with non-OSA patients after OFA. [18]

Indications and contraindications for OFA

The best indications for OFA today are obesity, OSA, opioid addiction, and hyperalgesia or chronic pain syndromes, better known as complex regional pain syndromes and previously termed causalgia, Suddeck's atrophy, Raynaud's syndrome, or reflex sympathetic dystrophy.

Possible relative contraindications to OFA are nodal block and disorders of the autonomic system, including orthostatic hypotension, as occurs in multiple system atrophy. Patients with a known critical coronary stenosis or an acute coronary ischemia should not receive OFA for the moment. OFA should also be avoided in non-stabilized hypovolemic shock and polytrauma patients, since peripheral vasodilation can limit the perfusion of critical central organs, in contrast to opioids that induce peripheral vasoconstriction while maintaining cardiocerebral perfusion.

A practical approach for OFA

Gabapentin 150–300 mg can be given as premedication orally and continued the next day postoperatively, when the patient can again take oral medication. Dexmedetomidine loading of 0.25 μg kg^{-1} is given 15 minutes before induction. The dose is further increased to 0.5 or 1 μg kg^{-1} and continued with 0.5–1 μg kg^{-1} h^{-1} if the procedure takes longer than two hours. Rapid awakening requires the use of the lowest possible dexmedetomidine dose (<0.5 μg kg^{-1}), frequently without maintenance doses. Clonidine has a much longer half-life and is therefore less suitable for short procedures. Lidocaine 1.5 mg kg^{-1} and magnesium 40 mg kg^{-1} given at induction and by infusion (lidocaine or procaine 1–3 mg kg^{-1} h^{-1} and magnesium 5–15 mg kg^{-1} h^{-1}) further improve the multimodal approach. Ketorolac (0.5 mg kg^{-1}) or diclofenac (150 mg) and dexamethasone (10 mg) are administered before surgery to reduce inflammation. The use of propofol combined with a sympathetic block is possible but requires high propofol doses, while inhalation can be given below one minimum alveolar concentration value. Most of these doses are calculated for lean body weight or ideal body weight (IBW) + 20%, which is easier to calculate, instead of total body weight.

When opioids are avoided, the respiratory center is not depressed. Pressure support ventilation, being more natural and driven by the patient's needs, is always possible under OFA, even when high-dose muscle relaxants are given to obtain a deep neuromuscular block. Total OFA is possible using such an approach with some or all of these non-opioid medications. [19] [20] Side effects of opioids, for instance PONV, are reduced when using OFA. [21]

Postoperative analgesia after OFA

When waking the patient, give a loading dose of paracetamol and continue with paracetamol 1 g every six hours for several days, if needed. Add a non-steroidal anti-inflammatory (NSAID) drug such as diclofenac 75 mg every 12 hours for up to the first two days. Continue with oral gabapentine 150–300 mg/day when possible. Continue the sympathetic block by loading up with an extra dose of clonidine 75–150 mcg, lidocaine 1 mg kg^{-1}, and ketamine 25 mg, at the end of anesthesia if not already done. It is better to keep giving these in a continuous infusion bag or pump over the next 10–24 hours. Medication choices for infusion include clonidine 0.1 µg kg^{-1} h^{-1} or dexmedetomidine 0.1 µg kg^{-1} h^{-1}, lidocaine 1 mg kg^{-1} h^{-1} or procaine 1 mg kg^{-1} h^{-1}, ketamine 0.05 mg kg^{-1} h^{-1} and magnesium 5 mg kg^{-1} h^{-1}. Dexmedetomidine and procaine are shorter acting and therefore preferable. A continuous infusion of dexmedetomidine, magnesium, ketamine or lidocaine might require follow-up on a high dependency care unit.

Be aware that although most of these drugs are given postoperatively below sedation levels, dose reduction may be required if residual sedation persists postoperatively in older and frail patients.

Conclusion

OFA is something one has to learn. Opioids are faster than alpha 2 agonists in blocking the sympathetic system. Postoperative bradycardia and hypotension are more common after alpha 2 agonists but not problematic. [22] Giving the correct hypnotics remains important, and bispectral index can measure this. Clinical factors such as heart rate and blood pressure or more specific tools that measure para- and orthosympathetic tonus may be helpful.

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