



Do we really need opioids in anesthesia?

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ABSTRACT

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Since the 1990s, high-income countries have seen an exponential increase in opioid use, misuse, and overdose. This “opioid crisis”, or “opioid epidemic”, began in the USA, spread to Europe, and is now extending to Asia. Today, opioids are still rarely available in many low and middle-income countries. In Pakistan, for instance, the only available opioids are morphine, fentanyl, nalbuphine, and tramadol, and these too are available only in tertiary hospitals. Is there a relationship between opioid exposure during anesthesia and opioid-induced hyperalgesia, hospital readmission, opioid addiction, cancer recurrence, immune system impairment, higher risk of postoperative delirium, and cognitive dysfunction? Signs in the recent literature confirm some of these hypotheses, and reducing opioid use in anesthesia is becoming a necessity. The concept of “opioid-free anesthesia” has emerged over the years in the literature. Is opioid-free anesthesia the solution? Is it a real paradigm shift? Nevertheless, it is important to keep in mind that stress-induced postoperative pain negatively influences outcome. The use of opioids in the postoperative phase could be necessary, but they have to be titrated and reduced to the minimum needed. Opioid-free postoperative analgesia is a new debate in the literature.

Key words: Opioid-free anesthesia; Opioid-sparing anesthesia; Opioid epidemic; Multimodal approach; Opioid, history; Nociception; Hyperalgesia, opioid induced.

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HISTORY OF OPIOID USE

For more than two decades, we have witnessed an opioid crisis that began in the USA, extended to Europe, and is now threatening Asia. Death rates due to opioid overdose have exploded. At the same time, in countries where opioids are legal and unrestricted, their administration during general anesthesia (GA) has become almost systematic, with increasing doses over the years and a loss of the multimodal approach to anesthesia concepts that were already developed.^{1,2}

A wide body of literature exists on the history of opioids.^{3,4,5} Opium (or poppy) has been known since ancient times, and opium seeds and capsules were found in a Swiss Neolithic village (12,000 years ago). The oldest evidence of poppy cultures dates back to Sumerians in 3,400 BC. The name was “hall gil”, the joy plant. In

Egypt in 1552 BC, the Ebers Papyrus described a mixture of substances, including opium, that was effectively used to sedate children. Opium was also well-known in Ancient Greece (7th century BC), possibly for its hypnotic properties. Opium was certainly employed as a euphoriant, orally or inhaled, in religious rituals by priests. Hippocrates, who is considered the father of medicine, prescribed poppy juice (meconium) for its laxative, narcotic properties and to heal leukorrhea. The analgesic properties of opium were then unknown. In ancient Rome (2nd century AD), the physician Galen realized the risks of excessive opium use. His patient was Emperor Marcus Aurelius, who was officially documented as the first opium addict.

After the fall of Rome in the 5th century AD, intellectual stagnation occurred in Western Europe under the pressure of the Catholic church, which prohibited and heavily punished

all scientific progress, which lasted at least until the 15th century. This was the period when the Arabic world built solid foundations of modern science, helped by the Persians, Hindus, and even the Chinese. Opium, called “al-yun” by the Arabs, was described as the most powerful of all analgesics. In the 9th century, inhalation anesthesia with spongia somnifera, a mixture of opium, mandragora, cicuta, and hyoscine, was used by physicians for surgical procedures. During this period, the Arabs introduced opium in India, and then in China, where it was called “o-fu-yung”.

In Europe at the beginning of the Renaissance, Paracelsus, a Swiss physician who lived between 1493 and 1541, reintroduced opium for medical use in Western Europe: "Of the drugs offered by the Almighty God to relieve human suffering, none is so universal and effective as opium." A tincture of opium called “laudanum” was used until the beginning of the 20th century.

From the 17th century, to finance their ever-increasing desire for Chinese tea, silk, and porcelain, Britain began smuggling Indian opium to China. Subsequent Chinese immigration to work on the railways and the gold rush brought opium smoke to America. This resulted in addiction among the Chinese and led to the Opium Wars of the mid-19th century. In 1858, the Tianjin Convention led to the legalization of the opium trade.⁶

The 19th century was marked by the discovery and first use of morphine. In 1805, Friedrich Sertürner, a German pharmacist's assistant, worked to isolate active opium components: the "principium somniferum", or morphium. In 1816, Gay Lussac proposed changing the name of morphium to morphine, which became the permanent name. On June 3, 1845, Irish physician Francis Rynd became the first to administer subcutaneous liquid morphine. The first morphine addictions then began to appear. During the American Civil War (1861 to 1865), massive use of morphine among wounded soldiers caused the first substantial cases of morphine addiction and social problems in the USA. British soldiers during the Crimean War

and Prussian soldiers during the war between France and Germany in 1870 also used morphine injections, with the same addictive consequences.

The beginning of the 20th century was marked by prohibition. Opium smoking was prohibited in the USA in 1909. In 1913, the production of diamorphine, or heroin, which was invented in 1898 and commercialized by Bayer, was stopped, as the addictive potential of diamorphine was admitted by scientific societies. The Anti-Heroin Act of 1924, a federal law of the United States, prohibited the import and possession of opium for the chemical synthesis of heroin. At that time, the concepts of tolerance and psychological and physical dependence on opioids began to be widely discussed.

MORPHINE DERIVATIVES

During the 20th century, the following morphine derivatives were developed:

- 1916: Oxycodone (Germany)
- 1924: Hydromorphone (Germany)
- 1932: Pethidine (1st synthetic – Germany)
- 1937: Methadone (Germany)
- 1960: Piritramide (Janssen - Belgium)
- 1963: Tramadol (Germany)
- 1965: Buprenorphine (USA)

The invention and development of synthetic opioids for anesthesia use was due to Dr. Baron Paul Adriaan Johannes Janssen (12 September 1926 – 11 November 2003), a Belgian physician, pharmacologist, and founder of Janssen Pharmaceutica. His well-known synthetic opioids were invented between 1956 and 1996. First, in 1956, was dextromoramide (Palfium), which was removed from the market in 2015. In 1957 was phenoperidine, known in France as R1406, which was in use until the late 1980s. Studies on new phenylpiperidine products led to fentanyl in 1960, as well as piritramide, which is still largely used in Austria, Belgium, Czech Republic, Germany, and the Netherlands. New fentanyl analogs were developed between 1974 and 1976. In 1974,

sufentanil followed by carfentanil (which is only suitable for very large animals, e.g., elephants, hippos, lions) were developed, and in 1976 alfentanil. The last fentanyl derivative created was remifentanil in 1996, a very short-acting opioid with highly interesting properties in anesthesiology.^{7,8,9}

NOCICEPTION, PAIN, AND OPIOID USE IN ANESTHESIA

There is obvious confusion in differentiating between nociception and pain.

What is nociception?

“An observable activity in the nervous system in response to an adequate stimulus (third-person perspective)”.¹⁰ Nociception is a function of a specific sensory system that acts as a warning system with an adequate stimulus, the noxious stimulus. The noxious stimulus can be seen as a stimulus that is damaging or threatening damage to normal tissues.

What is pain?

IASP has defined pain as, “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Pain is the result of network activity in the brain, an interpretation of a noxious stimulus that can only be interpreted as pain at a certain level of consciousness.

Do we feel pain during anesthesia?

To attempt to answer these difficult questions, we have to go back to the Greek definitions of analgesia (“*αναλγησία*”) and anesthesia (“*αναισθησι*”). Analgesia means loss of pain, and anesthesia means loss of sensations. If the patient is deeply asleep, do we need opioid analgesia?¹¹

The new method for measuring pain during surgery is the Nociception Level (NOL®) index. The NOL® index may reliably discriminate noxious and non-noxious stimuli. The index seems to be superior to any single index and to accurately characterize nociception during GA on an observational basis. We need to wait for the results of ongoing studies to

determine if differences exist between opioid-based, reduced, or free in terms of measured nociception.¹²

CONSEQUENCES OF PERIOPERATIVE OPIOID USE

Respiratory depression, postoperative nausea and vomiting (PONV), urinary retention, gastrointestinal dysfunction, and pruritus are the most well-known common side effects of opioids.¹³

In a survey of the exponential addiction to opioids and its spread in Asia, where they are increasingly available in perioperative anesthesia, it is difficult not to assume a relationship between perioperative use of opioids and the opioid epidemic.

Is there a relationship between the use or misuse of opioids, chronic pain and opioid addiction? When is enough opioids too much?^{14,15} What are the other reasons to avoid or reduce use of opioids in anesthesia?

Opioids and cancer

Dozens of contradictory publications are available concerning opioid use in anesthesia, cancer growth, recurrence, and metastasis. There is no formal proof of any of the major doubts, which have all been based on retrospective analysis. Ongoing prospective studies will confirm or disprove this supposition. Do we really have to wait until these prospective studies are published to consider that opioids have a negative effect on cancer growth?^{16,17}

Immunosuppressive effects of opioids

There have been doubts since 1979 regarding the immunosuppressive effects of opioids.¹⁸ Morphine decreases natural and acquired immunity, both directly and indirectly via the activation of central receptors. Opioid-induced changes in the immune system may affect surgical outcomes, including bacterial and viral infections or cancer, and could be particularly dangerous in vulnerable populations, such as elderly or immunocompromised patients.¹⁹

Opioid-induced hyperalgesia

Patients receiving opioids at low dose become more sensitive to pain and will need higher doses of morphine postoperatively.^{20,21} Intrinsic activation of specific pro-nociceptive processes, such as opioid-induced hyperalgesia, may lead to an exaggeration of surgical injury-induced hyperalgesia, increasing postoperative pain and possibly underlying the development of persistent pain in some patients.²²

Opioids and hospital readmission after ambulatory surgery

An association exists between perioperative opioid use and 30-day readmission when the patient is discharged the same day.²³ Operations in ambulatory surgery can represent up to 80% of the surgical activity in some countries, such as the USA. GA in an ambulatory setting can illustrate the negative consequences of opioid-based anesthesia and the advantages of opioid-sparing or opioid-free anesthesia.

Opioids and postoperative delirium and cognitive dysfunction

Postoperative delirium in elderly patient is often debated, with no clear answer regarding its prevention. Opioids have to be prescribed to treat pain in the elderly, but the risk of delirium due to opioids must be considered when prescribing them, though the relationship between opioids and postoperative delirium has never been clearly established.²⁴ In addition, whether postoperative cognitive dysfunction is related to postoperative delirium is not known.²⁵

Opioids and trauma

An association certainly exists between opioid use and injury recovery. Non-union complications after trauma could be influenced by perioperative opioid use, and is also an issue in pediatric patients.^{26,27}

THE CONCEPT OF A MULTIMODAL APPROACH TO ANESTHESIA

To avoid or reduce the use of opioids perioperatively, GA will be based on a combination of hypnosis and immobilization using propofol TIVA/TCI, inhalational agents, and muscle relaxants combined with:

- Multimodal analgesics (non-opioids)
 - Paracetamol, NSAIDs
 - Dexamethasone
 - Lidocaine
 - Low dose ketamine.
 - Magnesium sulfate
- Direct sympathetic block, central – peripheral:
 - Clonidine, dexmedetomidine, beta-blockers
- Local infiltration analgesia, nerve and truncal blocks, neuraxial analgesia techniques
- Opioids used but only titrated at low dose.

Key features:

- a) Paracetamol and NSAIDs are the basic non-opioid painkillers. They are inexpensive, accessible, and have few contraindications, which nevertheless need to be respected. They need to be administered at sufficient dose to rapidly achieve an effective blood concentration at the beginning of the surgery. For example, 2 g intravenous paracetamol in adults (or 30 mg/kg) is recommended.²⁸
- b) The positive effects of dexamethasone in anesthesia have been known since 1959.²⁹

Dexamethasone reduces PONV and significantly decreases postoperative opioid use.^{30,31} The recommended dose is 0.2 mg/kg, preferentially administered at the beginning of the intervention. Neither stable diabetes nor cancer surgery are a contraindication.^{32,33}
- c) The analgesic effects of intravenous local anesthetics, such as procaine, have been known since 1943.³⁴ The anesthesia-sparing effects of intravenous lidocaine have been studied, with interesting results, since 1951.³⁵

In 1960, the first clinical evaluation was published in *Anesthesia & Analgesia*.³⁶

Lidocaine IV results in 33% reduction in opioid consumption vs. placebo when postoperative infusion was maintained for 1 hour, and up to 83% when maintained for 24 hours. An earlier return of bowel

function is generally observed, allowing a precocious rehabilitation and shorter hospital stay, which is reduced by an average 1.1 days. Intravenous lidocaine does not result in toxicity or clinically adverse events. After the cessation of infusion, the effect of lidocaine will continue up to 8.5 hours.^{37,38}

Intravenous lidocaine stimulates natural killer (NK) cell activity, resulting in less immunosuppression and a positive effect on cancer growth and metastasis.³⁹ The recommendations are a 1 to 2 mg/kg bolus (based on adjusted weight), followed by 1 to 2 mg/kg/h until discharge from the recovery room.⁴⁰ Intravenous infusion of lidocaine without continuous monitoring is not recommended.

When combining continuous intravenous lidocaine with local infiltration or locoregional anesthesia (e.g., interfascial blocks), a toxic dose may be reached. The safety margin is certainly higher than what we previously thought, but the acceptable maximum dose still needs to be evaluated based on expected postoperative pain, patient weight, age and history.

Ketamine was widely used before the explosion in opioid use. It is still the most widely administered anesthetic drug in developing countries. The interest in low dose ketamine for postoperative pain began as early as 1975.⁴¹

The mechanism of action is the blockade of N-methyl-D-aspartate (NMDA) and Hyperpolarization-Activated Cyclic Nucleotide Channel-1 (HCN1) receptors. Cholinergic, aminergic, and opioid systems appear to play both a positive and negative modulatory role in both sedation and analgesia.⁴²

Low dose ketamine lowers opioid use by 40% without any major complications when given up to 48 hours postoperatively. It reduces the time to first analgesic request, opioid-induced hyperalgesia, PONV, and

the incidence of chronic postsurgical pain.^{43,44}

Ketamine possibly has positive, and surely no negative, effects on postoperative delirium and postoperative cognitive dysfunction.⁴⁵

The ideal dose is still not known, and more studies are needed. The recommendations are a 0.2 – 0.4 mg/kg loading dose, followed eventually by a continuous infusion of 0.2 mg/kg/h until the end of surgery. In very painful surgery, ketamine infusion may be maintained up to 48 hours.

- d) The first publications about the interesting effects of magnesium in anesthesia were in 1996. Magnesium sulfate is a very interesting adjuvant to GA.⁴⁶ The mechanism of the analgesic effect of magnesium is not clear, but interference with calcium channels and NMDA receptor seems to play an important role. Magnesium sulfate considerably reduces perioperative and postoperative opioid use.^{47,48}

Administration of magnesium sulfate will result in a lower bispectral index, which has to be considered as a consequence of magnesium on anesthesia depth.⁴⁹

The recommended loading dose is less than 40 mg/kg, eventually followed by 10 mg/kg/h.⁵⁰

- e) The alpha-2 adrenergic agonists⁵¹ used in anesthesiology are clonidine and dexmedetomidine.⁵² Clonidine was patented in 1961, and its medical use began in 1966. The opioid-sparing effect of clonidine was first published in 1987.

Clonidine gained in popularity in GA, neuro-axial and peripheral blockade, from the 1990s. During GA, it lowers the anesthetic requirement, and it has a perioperative and postoperative opioid-sparing effect. Hypotension and drowsiness are the major side effects limiting its use.⁵³

The recommended intravenous dose has not been precisely established; a 1 to 4 mcg/kg loading dose in 30-60 minutes is advised.

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist. The first publication describing the inhalational anesthetic sparing effect appeared in 1988.⁵⁴ It was approved in 1999 by the US Food and Drug Administration (FDA) as a short-term sedative and analgesic (< 24 hours) for critically ill or injured people on mechanical ventilation in the intensive care unit. In 2008, the FDA expanded its indication to include non-intubated people requiring sedation for surgical or non-surgical procedures.⁵⁵

Dexmedetomidine is now widely used in GA, with several publications on its use in epidural, spinal, and peripheral blocks (off label). Its major side effects are bradycardia and drowsiness. No prolongation of recovery has been stated.⁵⁶

- f) Esmolol is a short-acting intravenous beta-blocker. Its place in anesthesia can be seen as incongruous. Reducing the stress response, esmolol is very useful in, for example, laparoscopic surgery and tonsillectomy. Esmolol contributes to a significant decrease in postoperative pain up to 3 days, decreased PONV, and facilitates earlier discharge.^{57,58,59}
- g) Local infiltration analgesia, wound infiltration, interfascial plain block, and neuraxial analgesia are different techniques that alone are not sufficient to allow surgical procedures, but will result in sufficient pain relief to avoid or limit the use of opioids. The use of long-acting local anesthetics combined with adjuvants has to be considered to offer the longest postoperative pain relief possible.^{60,61} Local infiltration analgesia and wound infiltration need to be performed systematically, infiltrating the most important layers. When using a high volume of local anesthetics, the use of epinephrine is highly recommended, also with ropivacaine to avoid systemic toxicity.

Multimodal anesthesia means that all of the medications cited above have to be administered before surgical incision, which requires some

organization from the anesthesia team. Different combinations are possible depending on the surgical indication and patient condition.

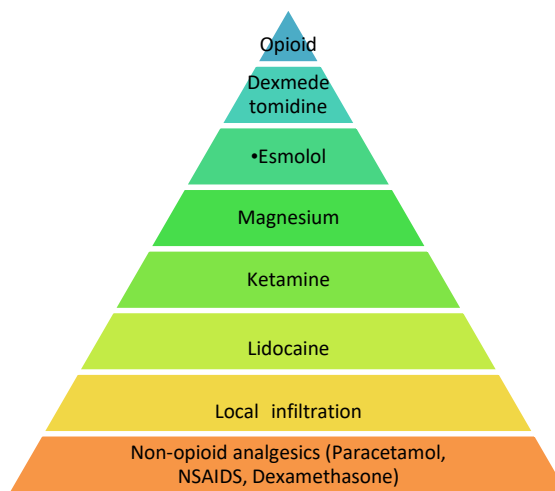


Figure 1: Multimodal anesthesia pyramid

POSTOPERATIVE PAIN RELIEF

The postoperative pain score has to be < 4 on the visual analog scale at rest, not 0 using opioids. Prescribing opioids at hospital discharge for a prolonged period is determinant of persistent postoperative opioid use. In opioid-naïve patients, it will result in a high risk of chronic opioid use one year after discharge. Explaining to the patient that experiencing some pain after surgery is normal and prescribing opioids only for as short a period as possible could avoid opioid abuse.^{62,63,64,65}

CONCLUSION

Do we really need opioids in anesthesia? Is opioid-sparing or opioid-free anesthesia the future of anesthesia?

Since the early 1990s, opioid-based anesthesia has played an increasing role in anesthesiology, becoming almost state of the art for administering GA. We forgot how did we proceed in the past, until the opioid crisis became a hard reality. The concept of opioid-reduced, eventually opioid-free, anesthesia in limited indications was denounced as nonsense;

however, it is slowly but surely being considered the best way to give GA.

Is it a paradigm shift or a step back to what the high-income countries forgot when under the influence of marketing, which led to an easy and irresponsible use of opioids in peri-operative care?

*"Successive transition from one paradigm to another via revolution is the usual developmental pattern of mature science."*⁶⁶

It is obvious that we have to limit opioid use in anesthesia. Multimodal anesthesia with reduced opioid use instead of opioid-based anesthesia with non-opioid medication as rescue should be the actual recommendation. Opioid-free anesthesia is feasible, and certainly of interest, in some indications (e.g., morbid obesity combined with obstructive sleep apnea, severe COPD, complex regional pain syndrome, documented allergic and anaphylactic reactions to opioids, opioid addiction).⁶⁷ There is actually no evidence that opioid-free anesthesia offers any real advantages outside the cited indications. More studies focused on outcome quality are needed.⁶⁸

We need to keep in mind that stress-induced postoperative pain has a negative influence on outcome; use opioids if needed but titrate them. Postoperative opioid-free analgesia is also the new debate in the literature.⁶⁹

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There are very few contraindications for opioid-free or opioid-sparing anesthesia:

- ✓ Allergy or contraindication for one of the drugs
- ✓ Bad patient condition with high-risk comorbidities, such as severe heart disease, low LVEF, acute bleeding, ASA 4.

Paracetamol, ibuprofen, ketamine, dexamethasone, and lidocaine are some of the important non-opioid drugs on the 21st WHO Model List of Essential Medicines 2019.⁷⁰ They are necessary to provide quality anesthesia worldwide, even more so in countries where opioids are not readily available. Drug shortages in low- and middle-income countries are a major problem, with disastrous consequences for the quality of care, patient safety, and outcome.^{71,72}

To answer the question of whether we really need opioids in anesthesia, yes, we definitely need opioids in anesthesia, but opioid-based anesthesia is certainly no longer an option from this time on. Opioid-free anesthesia cannot show any real superiority in daily practice.⁷³

“Well, let's begin opioid sparing!”

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