Best Practice in Anesthesia A book on "Opioid free anesthesia."

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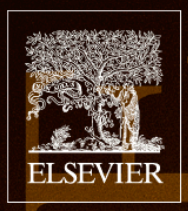

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Opioid free anaesthesia

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Preface

Opioid free general anesthesia, a new paradigm?

Before the introduction of opioids in the 1960s, hypnosis, immobility, and hemodynamic stability were achieved using high concentrations of inhalation gases or high-dose hypnotics. These agents induced strong hemodynamic suppression as a high dose was needed to suppress all noxious stimuli. Opioids were slowly added, first by Wood, who in 1853 introduced the subcutaneous administration of morphine [1]. The introduction of the balanced general anesthesia concept using different drugs for each desired effect, as first explained by Cecil Gray in 1946, was a revolution after 100 years of inhalation anesthesia [2]. Pethidine (meperidine), already synthesized in 1932, was the first synthetic opioid used to supplement a balanced general anesthesia by William Neff in 1949 [3]. It was in 1962 that Paul Janssens developed and sold fentanyl, which causes less histamine release and more hemodynamic stability, allowing an improved and balanced general anesthesia [4]. Cardiovascular diseases were difficult to diagnose and impossible to treat before 1970, while hypnotic agents induced hemodynamic instability with impaired coronary perfusion [5]. Opioids therefore were a gift to reduce the use of these hypnotics and improve anesthesia outcome at that time.

Cardiac anesthesia in 1981 moved back to mono-agent anesthesia, this time using very high doses of fentanyl and, later, sufentanyl in an effort to give perfect stress-free anesthesia without any increase in endocrine responses [6]. The introduction of shorter and stronger acting opioids such as remifentanil allowed further increases in opioid doses without prolonged sedative effects. Paul Janssens, the founder of Janssens Pharmaceuticals and inventor of most synthetic opioids, warned 20 years ago that the medical use of their formulation remifentanil could cause addiction, immune suppression, and other unknown long-term effects and stated that high-dose opioids are not needed to achieve stable anesthesia. In addition, Paul Janssens refused to bring remifentanil to the market under his company's name. Nevertheless, anesthesiologists were drawn to the use of these powerful opioids because of their seemingly short activity time. Moreover, combination with new low-dose intravenous hypnotics such as propofol, without any inhalational agent, became attractive to suppress postoperative nausea and vomiting (PONV) while retaining perfect hemodynamic stability.

Side effects of opioid anesthesia were well recognized but accepted as an essential part of a safe anesthesia. Reducing opioid use became important only recently. For enhanced recovery after surgery, it is recommended to reduce the use of postoperative opioids to a minimum or zero if possible. Sleep-disordered breathing, better known as obstructive sleep apnea syndrome, has become more prevalent than before and requires the avoidance of opioids postoperatively.

The epidemic use, abuse, and misuse of opioids in the United States today have resulted in significant morbidity and mortality. Brown addresses chronic pain physicians to solve this problem [7]. Hance Clarke in a Canadian cohort study of more than 40,000 major surgery patients measured that 50% of opioid-naïve patients leave a hospital with an opioid prescription and 3.1% continue its use after 3 months. This means that anesthesiologists and surgeons together induce addiction after major surgery and that we have to look for solutions to this problem [8]. Kumar argues that it may be difficult

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to reduce perioperative opioid use, but adjunct medications, regional anesthesia, and multimodal analgesic techniques might help [9]. The following chapters propose to combine several adjunct medications, defined as multimodal general anesthesia, to reduce intraoperative opioid use to zero. This allows further postoperative opioid reduction and almost no need to leave a hospital with an opioid prescription.

Locoregional anesthesia alone or combined with general anesthesia was introduced before synthetic opioids but is now gaining more interest as a method to reduce opioid use perioperatively.

Opioid-free intravenous general anesthesia with low-dose inhalation existed before synthetic opioids became available. In 1947, total intravenous anesthesia using 4 mg/kg procaine for 20 min was described by W Mushin [10]. SG de Clive-Lowe described in 1958 anesthesia with only intravenous lidocaine using 7 mg/kg for the first hour, followed by 3.5 mg/kg/h [11]. Alpha2 agonists as the only anesthetic were first used by veterinary anesthesiologists and verified by Vickery in 1988. The halothane concentration in dogs could be reduced to 0.1 Minimum alveolar concentration (MAC) when 10 mcg/kg of D-medetomidine (or dexmedetomidine) was used [12]. Mono-agent anesthesia is possible but requires very high doses that result in more side effects, and it induces prolonged sedation, making rapid recovery after anesthesia difficult.

In 1993, Friedberg [13] added ketamine to propofol without any opioid use for esthetic surgery. Adding intravenous lidocaine created a lot of confusion before showing effect in reducing opioid consumption and pain postoperatively [14]. M Dekock [15] showed in 1992 that intraoperatively administered alpha2 agonists reduced the opioid requirements postoperatively.

Finally, a multimodal anesthesia approach was gradually developed by combining these different non-opioid drugs at lower dose with less sedative effects but maintaining the blockade of the sympathetic system [16]. Intravenous or inhalation hypnotics further maintain hypnosis, while neuromuscular blockers maintain immobilization. This allows today an intraoperative total opioid-free anesthesia (OFA), which results in a smooth and rapid awakening with less pain. OFA avoids tolerance and hyperalgesia development and many other side effects such as nausea and vomiting that we have taken for granted after general anesthesia. Non-opioid analgesics are more effective postoperatively, while the dose of opioid analgesics as a last resort became significantly lower, frequently to zero. Major thoracic abdominal surgery can remain completely opioid free perioperatively when combined with locoregional anesthesia.

The first chapter discusses the pain perception during anesthesia and the reasons to administer drugs that suppress the pain reactions intraoperatively. Opioid side effects such as respiratory depression, tolerance and hyperalgesia, and PONV are discussed in chapters 2–4. Additives that reduce or avoid intraoperative use of opioids are discussed in chapters 5–8, ending with special emphasis on special indications for OFA.

After showing that it is possible to administer a safe and stable general anesthesia without opioids for many patients and procedures, it is time for more research on outcome differences between low and zero opioid use and on risks and situations where OFA should be avoided. The development of new opioids with fewer side effects or shorter acting sympathetic blocking drugs or antidotes for the existing additives would improve general anesthesia further. The combination of OFA with locoregional anesthesia is also an area for further development.

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1

Do we feel pain during anesthesia? A critical review on surgery-evoked circulatory changes and pain perception

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presympathetic neurons
somato-sympathetic reflex

The difficulty of defining the three so-called components of « anesthesia » is emphasized: hypnosis, absence of movement, and adequacy of anti-nociception (intraoperative « analgesia »). Data obtained from anesthetized animals or humans delineate the activation of cardiac and vasomotor sympathetic reflex (somato-sympathetic reflex) and the cardiac parasympathetic deactivation observed following somatic stimuli. Sympathetic activation and parasympathetic deactivation are used as monitors to address the adequacy of intraoperative anti-nociception. Finally, intraoperative nociception through the administration of nonopioid analgesics vs. opioid analgesics is considered to achieve minimal postoperative side effects.

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cardiac baroreflex
vasomotor baroreflex
SPI
SSI
ANI
CARDEAN
analgesics
opioid
nonopioid analgesics
hyperalgesia
alpha-2 agonist
respiratory genesis
ventilatory depression
opioid-free anesthesia
OFA

Abbreviations and glossary

A1/C1: noradrenergic/adrenergic neurons located in the vasomotor center (rostral ventrolateral medulla)
AMPT: alpha-methyl-para-tyrosine, tyrosine hydroxylase inhibitor to deplete peripheral and central noradrenergic neurons
ANI: autonomic nervous index, analgesia/nociception index (Metrodoloris)
AUC: area under the curve
BIS: bispectral index, computerized electro-encephalogram (Aspect-Covidien)
BP: blood pressure
5HT: serotonin
CARDEAN: *Car*diovascular *de*pth of *an*algesia (Alpha-2)
CHF: cardiac heart failure
CVM: cardiac vagal motoneurons located in the nucleus ambiguus projecting to the sinus node to evoke vagal bradycardia
DSP4: N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine HCl; destroys catecholaminergic neurons
EEG: Electroencephalogram
GA: general anesthesia
GABA: γ-aminobutyric acid
HF: high frequency
HR: heart rate
HRV: heart rate variability
LC: locus coeruleus, pontine noradrenergic nucleus located in the upper brain stem
MAC: minimum alveolar concentration
NA: noradrenaline
NMDA: *N*-méthyl-D-aspartate, agonist for a class of glutamate receptors
NoL: nociceptive level, index of nociception
OFA: opioid-free anesthesia
OR: operating room
PAG: periaqueductal gray matter
PD: pupillary dilation
Postsynaptic receptors, hetero-receptors: alpha-2 adrenergic receptors located on non-catecholaminergic cell bodies/terminals
Presynaptic receptors, auto-receptors: alpha-2 adrenergic receptors located on adrenergic/noradrenergic cell bodies/terminals

RR:	respiratory rate
RVLM:	rostral ventrolateral medulla, vasomotor center
SDNN:	standard deviation of normal-to-normal intervals, index of cardiac parasympathetic activity
SPI:	Surgical Plet Index (GE-Datex)
Vt:	tidal volume

Introduction

This chapter addresses the uneasy question "*Do we feel pain during anesthesia?*" and thus overviews [1] the pain pathways [2], the definitions of pain within the context of anesthesia [3], the autonomic changes associated with nociception [4], the *operational* assessment of anti-nociception (intraoperative « analgesia ») in the setting of surgical anesthesia (Fig. 1), i.e., through the monitoring of the sympathetic and parasympathetic systems, and [5] some of the drugs involved, or not, in "opioid-free anesthesia" (OFA).

I. Pain pathways

Pain pathways have been delineated previously [1]. Nociception encompasses surgical stimuli arising from the skin and from the viscerae (Fig. 2). Visceral nociception is poorly localized, evoking diffuse discomfort [2] (Fig. 3 right). Ascending nociceptive stimuli travel [3,4] (Fig. 2 and legend) through:

(a) thinly myelinated Aδ fibers through the neospinothalamic tract (fast sharp pain that can elicit fight-or-flight behavior).
(b) unmyelinated C fibers through the paleospinothalamic pathway to laminae I–VI and the ventral horn of the spinal cord ["protopathic" sensation: Rivers and Head, 1908; Ranson, 1915, quoted from [2]; slow burning pain that can engage in long-term response, sickness behavior, and immune function [4]]. Both pathways head to the thalamus and cortex: lamina I projects to multiple structures from the brain stem to the cortex (Fig. 2) through collaterals.

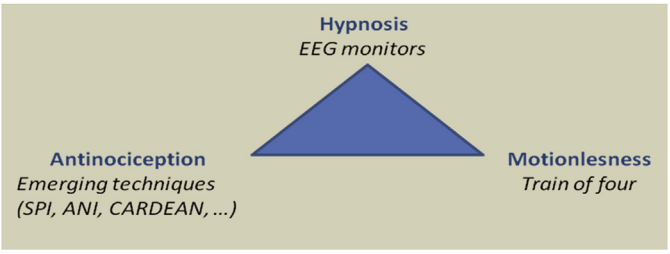
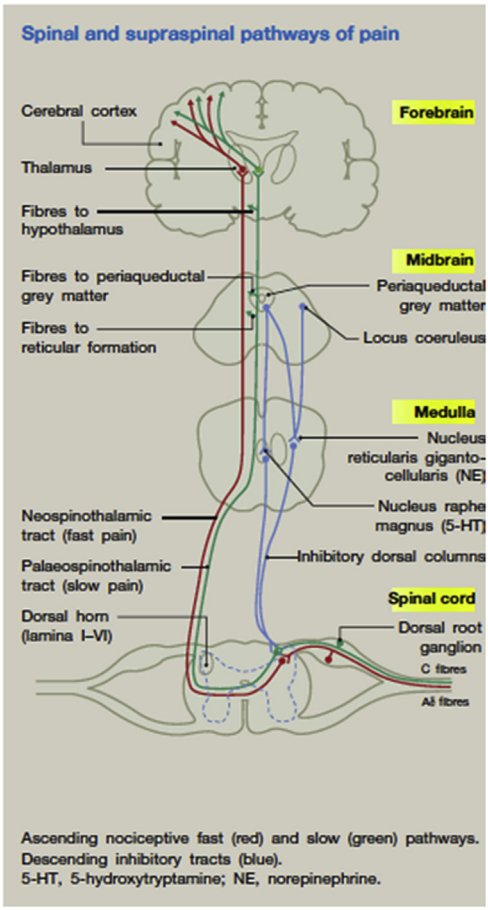


Fig. 1. Components of general anesthesia: **hypnosis, motionlessness, and anti-nociception**. These three components are relatively independent. Under a nociceptive stimulus and inadequate anti-nociception, a patient with an adequate hypnosis (electroencephalographic index: Bispectral index: BIS: 40 < BIS < 60) will present a withdrawal movement in the absence of paralysis or tachycardia + hypertension under paralysis. Care is to be exercised with regard to movement: strictly speaking, there is no monitor to detect movement. From an operational point of view, monitoring paralysis with a strain gauge ("Train-Of-Four" technique) facilitates the prevention of movement. This schema may be misleading: (a) high doses of propofol or halogenated agents block some of the tachycardia or hypertension observed following surgical stimuli. For simplicity, this will not be considered: under state-of-the-art anesthesia, hypnosis is monitored as adequately as possible (i.e., "clamped" to 40 < BIS < 60). (b) there is no interaction between adequacy of hypnosis (40 < BIS < 60) and adequacy of anti-nociception. This last view may be partially wrong (Cividjian, unpublished data): (i) a change in the delivery (i.e., speed of administration) of the opioid analgesics may evoke a change in BIS. (ii) a change in the delivery of propofol does not lead to any change in the anti-nociception index (e.g., SPI, CARDEAN), unless a large bolus of propofol is administered, e.g., in the setting of unexpected movement or of emergence of anesthesia, toward the end of surgery. (c) earlier authors [23] included circulatory and ventilatory stability as a component of anesthesia, i.e., a normalized sympathetic activity [sympathetic deactivation, "*protection neurovegetative*" [24]]. Later, sympathetic deactivation was deleted. Anesthesia was reduced to hypnosis, anti-nociception and paralysis [25].



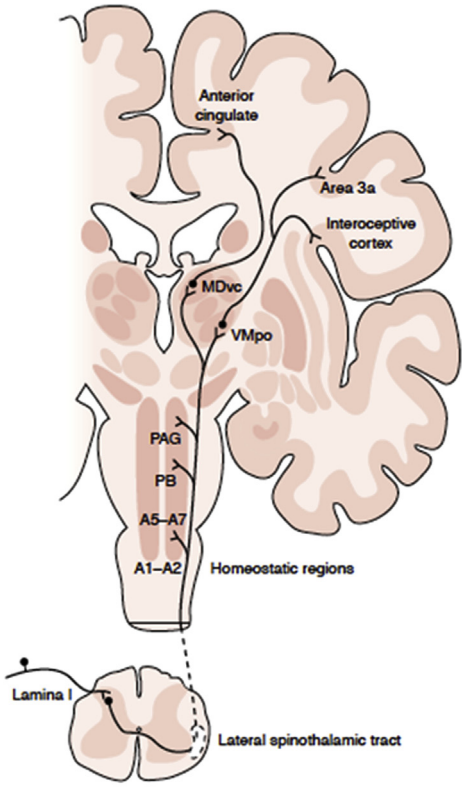


Fig. 2. Pain pathways: relationship to core autonomic circuitry. Left: **Slow vs. fast pain pathways**. Modified from Hudspith, Anesthesia & Intensive Care Medicine, 2016, [3]. Right: **Projections of lamina I** in primates send collaterals to noradrenergic groups (A1/C1 groups in the vasomotor center, pontine A5-A7), PAG, thalamus, and cortex. The afferent limb (incoming, afferent, information: green, red) is shown in Fig. 2 right. The efferent limb (blue) comprises descending projections to (i) the dorsal horn (blue: inhibitory and excitatory supra-spinal control on pain transmission) and (ii) the intermediolateral cell column (Figs. 3 and 4: pre-sympathetic neurons on sympathetic preganglionic neurons). Several neurotransmitters are involved in the afferent limb, the core autonomic circuitry (GABA-ergic vs. glutamatergic, etc.), and efferent limb (adrenergic vs. glutamatergic neurons). *The clinical implication is that one class of drug (opioid analgesics) cannot be the only pharmacological tool to provide adequate anti-nociception,* exposing to opioid-evoked hyperalgesia. Modified from Craig, Trends Neurosci, 2003, 26: 303-7 [4]. Abbreviations: PB: parabrachialis; PAG: periaqueductal gray matter; VMpo: ventromedial nucleus posterior part; MDvc: medial dorsal nucleus ventral caudal part.

A. Pain-sympathetic connections

Below the bulbar-pontine junction, projections of lamina I, through a collateral branch of the lateral spinothalamic tract, synapse *directly* [5] onto adrenergic/noradrenergic neurons located in the vasomotor center (C1 neurons located in the rostral ventrolateral medulla, RVLM) [4]; this synapse from lamina I to C1 adrenergic neurons provides a *direct* nociceptive input onto pre-sympathetic neurons and a neuroanatomical basis for the increase in blood pressure (BP) and heart rate (HR) observed upon nociceptive stimulus [“afferent limb of the autonomic nervous system” [4], “non-cardiovascular” afferences [6] on the cardiac and vasomotor baroreflex; Fig. 1 in [4] and Fig. 2 right in this chapter].

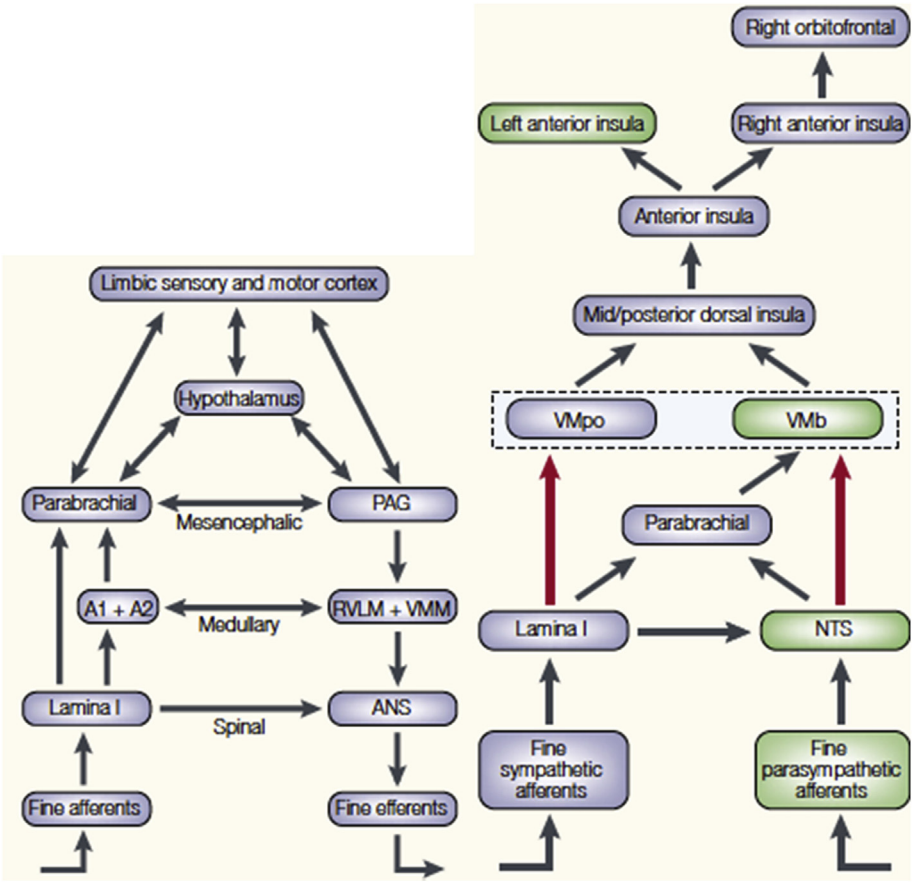


Fig. 3. Left: **Hierarchical organization of neural homeostasis involving the sympathetic nervous system**. Small diameter afferents fibers that report the physiological condition of all tissues of the body terminate in lamina I of the spinal and trigeminal dorsal horns. The ascending projections of lamina I neurons provide the basis for somato-autonomic reflexes at the spinal, medullary, and mesencephalic levels. At the spinal level, lamina I projects strongly to the sympathetic regions in the intermediolateral cell column of the thoracolumbar cord, where the sympathetic preganglionic neurons originate. In the medulla, lamina I neurons project to A1/A2 neurons catecholaminergic groups and to the rostral ventrolateral medulla, Thus, lamina I neurons are connected with the presympathetic neurons projecting to the intermediolateral cell column. The A2 group (i.e., the nucleus tractus solitarius, NTS) receives direct parasympathetic (vagal and glossopharyngeal) afferent input. In the pons and mesencephalon, lamina I neurons project to the parabrachial nucleus (major brain stem homeostatic integration site) and the periaqueductal gray (major homeostatic brain stem motor site). VMM: ventromedial medulla. Right: **Organizational chart for interoception:** Small diameter afferent fibers that innervate tissues in parallel with sympathetic efferents ("sympathetic afferents") provide input to lamina I. Small-diameter afferents that innervate tissues in parallel with parasympathetic efferents ("parasympathetic afferents") provide input to the nucleus tractus solitarius (NTS). In mammals, such activity is integrated in the parabrachial nucleus which projects to the ventromedial thalamic nucleus then the insular cortex. In primates, a direct projection from lamina I to the ventromedial nucleus and a direct projection from the nucleus tractus solitarius to the ventromedial thalamic nucleus provides a rostrocaudal contiguous column that represents all contralateral homeostatic inputs and projects topographically to the dorsal insula. In humans, this cortical image is re-represented in the anterior insula on the same side of the brain. The parasympathetic activity is then re-represented in the left dominant hemisphere. The sympathetic activity is re-represented in the right non-dominant hemisphere. These re-representations provide the basis for a subjective evaluation of interoceptive state, then forwarded to the orbitofrontal cortex, where hedonic valence is represented in mammals. Modified from Craig AD, Nature Rev Neurosci 2002, 3, 655-66 [1].

B. Pain-parasympathetic connections

To our knowledge, there is no identified direct input from lamina I to cardiac vagal motoneurons (CVMs), which project from the nucleus ambiguus to the sinus node (pre-parasympathetic neurons)

[7]; therefore, this requires study. This may represent a gap in the current knowledge rather than true absence of projection from lamina I to CVMs. However, there is (a) a monosynaptic projection from the "cardiovascular" portion of the nucleus tractus solitarius (dorsomedial medulla) to CVMs (ventrolateral medulla) [8–10] and (b) a direct projection from the vasomotor center (presympathetic neurons) to the cardiac vagal neurons [11]. The fast kinetics of response of CVMs to evoke cardiac vagal withdrawal and tachycardia favors such a direct, mono- or pauci-synaptic, anatomically unproven, afferent projection from nociceptors to efferent autonomic pathways.

Descending projections provide a complex feedback loop [5] modifying the reactivity of the laminae I–VI in the spinal cord, perhaps turning off a pain permission ascending system [12] (former "gate control" theory). Noradrenergic, serotoninergic, and dopaminergic descending pathways interact to produce optimum analgesia (A1 group in the rostral ventrolateral medulla to the dorsal horn; pontine locus coeruleus [LC] to the ventral and dorsal horn; raphe magnus to the dorsal horn; and thalamus to the dorsal horn, respectively) [12]. Projections from the rostral ventromedial medulla and the ventrolateral quadrant of the caudal medulla interact with the dorsal horn nociceptive processing through excitatory and inhibitory projections [13]. Other projections come from the periaqueductal gray matter (PAG) (Fig. 4):

(a) dorsolateral PAG, to suppress pain during fight-or-flight reaction and to address emergencies and survival.
(b) ventrolateral PAG, to engage the whole organism into restorative activities (freezing/playing dead behavior: sympathetic deactivation, immobility, etc.) [14].

C. Core autonomic circuitry

Within the brain stem, the core autonomic circuitry, which regulates HR and BP, encompasses (a) adrenergic and glutamatergic presympathetic neurons in the RVLM, projecting on sympathetic preganglionic neurons located in the intermediolateral cell column (IML) [15,16] and (b) cholinergic CVMs projecting from the nucleus ambiguus ventrolateral (ventrolateral medulla) to the sinus node [7]. The functional relationship between the pain pathways and the core autonomic central circuitry is complex:

(a) a toxin, saporin, destroys noradrenergic pathways and enhances morphine analgesia [17].
(b) hypertensive patients present hypoalgesia: sensory and pain thresholds are higher in hypertensive than in normotensive patients [18]. Accordingly, hypertensive patients present hypoalgesia during cold pressor test. There is a negative correlation between systolic BP and pain rating [19]. However, "*lowering BP does not necessarily result in changes in pain perception … hypoalgesia is not simply related to elevated BP … in human hypertension*" [20].
(c) under supine resting conditions, an overall negative relationship is present between cardiac baroreflex sensitivity and 24 h systolic BP, on the one hand, and pain threshold, on the other hand; the lower the baroreflex sensitivity, the higher is the pain threshold [21]. The data are not compelling: minimal difference in baroreflex sensitivity between normotensive and hypertensive patients (the mean slope of the cardiac baroreflex, the relationship between changes in RR interval to changes in BP: 8.76 ms/mmHg vs. 8.47, respectively) and wide scatter of the negative relationship are observed. Nevertheless, the data cannot be disregarded. However, these data were collected in conscious humans or animals; therefore, their application to a brain made dysfunctional by anesthesia is unknown.

Finally, the relation between pain pathways and core autonomic circuitry may be observed in reverse from baroreceptor afferences to pain pathways [20]: "*arousing emotional and pain stimuli elevate BP, resulting in baroreceptor stimulation that in turn induces anti-nociception. Thus arterial BP may be an important internal signal … to adjust somatosensory inflow. This mechanism may serve as a response, in addition to bradycardia and vasodilation, to prevent excessive BP elevation … CNS dampening may augment vagal and sympathetic negative feed-back mechanisms to … restore safer BP …*" [20].

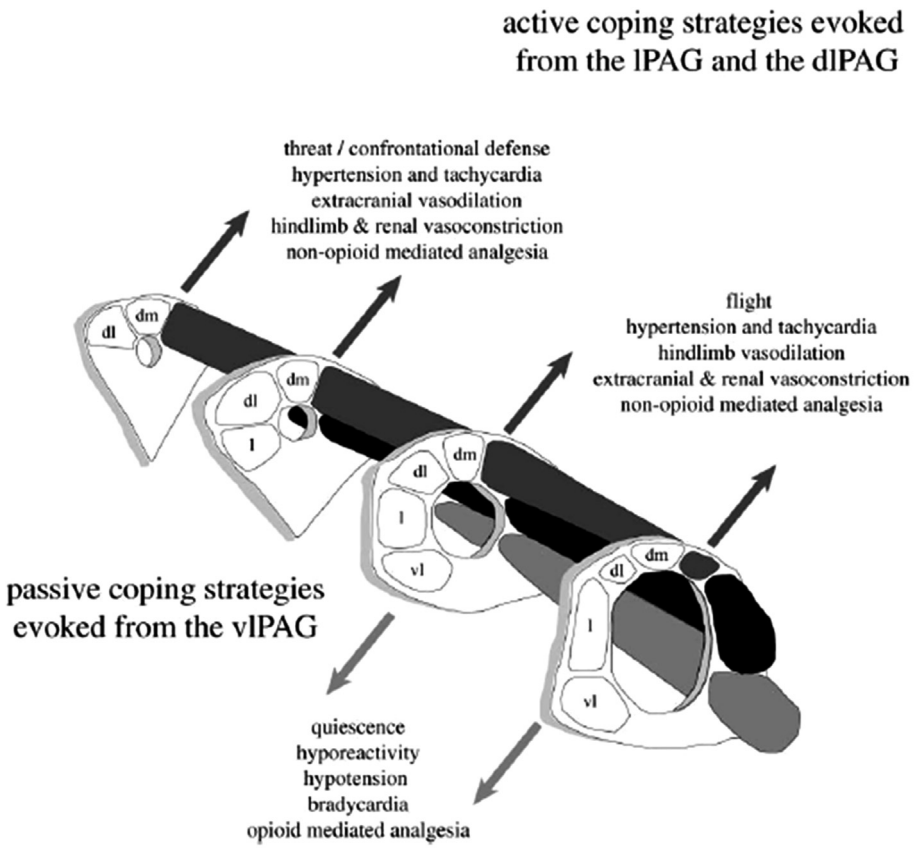


Fig. 4. Physiological responses evoked by periaqueductal gray matter (PAG). Excitatory amino acid (glutamate, etc.) injections within the dorsolateral PAG (dark shadings) vs. ventrolateral PAG (light shading) columns evoke *opposite* active vs. passive strategies. Excitatory amino acid injections in the rostral dorsolateral PAG evoke a confrontational defensive reaction (tachycardia, hypertension, decreased blood flow to limbs and viscera, and increased blood flow to extracranial vascular beds). Excitatory amino acid injections within the caudal dorsolateral PAG evoke escape or flight, tachycardia, hypertension, decreased blood flow to visceral and extracranial beds, and *increased limb blood flow* ("*defense reaction*"). A nonopioid-mediated short-term analgesia is evoked from the dorsolateral PAG, presumably to inhibit reflexive responses, which might compete with the ongoing defensive behavior. Excitatory amino acid injections in the ventrolateral PAG evoke quiescence, hyporeactivity, hypotension, and bradycardia ("*freezing"/"playing dead reaction*"). An opioid-mediated, with a long-time course, analgesia is evoked from the ventrolateral PAG, presumably favoring recovery and healing. Modified from Bandler et al., Neurosci and Biobehavioral Rev, 2001, 25, 669-78 [45] and Brain Res Bull, 2000, 53, 95–104.

To sum up, in a teleological manner, pain pathways and core autonomic circuitry may be schematically viewed as feedback loops of ascending alerting information and descending suppressing control to elicit fight-or-flight or freezing behavior: an interplay exists between the circuitry involved in pain processing and in circulatory adaptation within an evolving environment. The whole organism generates a coordinated response to pain or stressful events, e.g., in the setting of fight-or-flight and freezing/playing dead behavior (Fig. 4). Further studies should understand these relationships to manipulate them in the clinical setting.

II. Pain during anesthesia?

Balanced anesthesia combines drugs to minimize the side effects of anesthesia (Fig. 1): operationally, (a) hypnosis is evoked by hypnotics/general anesthetics (pentobarbital, propofol, halogenated agents, etc.); (b) anti-nociception is evoked by analgesics, most often by opioid analgesics; and (c)

immobility is evoked by neuromuscular blockers. Historically, “anesthesia” was modified to “balanced anesthesia”: a single drug (ether alone, pentobarbital alone, etc.) was replaced by three different classes of drugs. Each class was to evoke one component of anesthesia. The use of three different classes of drugs with three different sites of action was expected to generate anesthesia with minimal side effects (hypnotics vs. opioid analgesics vs. neuromuscular blocker). When evoking general anesthesia (GA), this combines intravenous hypnotics (e.g., pentobarbital, propofol, etc. for induction) with halogenated volatile agents for maintenance. Therefore, no rationale exists for using *only one* class of drug (i.e., opioid analgesics) to achieve intraoperative anti-nociception and minimal postoperative hyperalgesia, rather than combining several analgesics, for example opioid analgesics and non-opioid analgesics, or several non-opioid analgesics, from the induction of anesthesia onward. This is the basis of balanced or multimodal analgesia [22].

A. Conventional views

Addressing the question that opens this chapter is uneasy; there is no accepted definition of « anesthesia, » a concatenation generated during the 19th century to describe a state of insensitivity to surgery. Schematically, (a) the patient wants neither recall nor any unpleasant feeling; (b) the surgeon considers immobility as the gold standard of anesthesia; and (c) the anesthesiologist is looking for ventilatory and circulatory stability. Therefore, the least common denominator is no recall, immobility, and cardio-ventilatory stability (Fig. 1).

An early attempt [23] to disentangle anesthesia included blockade of sensory (analgesia, anesthesia) vs. motor (relaxation to paralysis) vs. reflex (sympathetic deactivation: « *protection neuro-végétative* » [24]) vs. mental (ataraxia to deep sleep: hypnosis) outputs [23]. Later, sympathetic deactivation was forgotten to reduce anesthesia to hypnosis, analgesia, and paralysis [25] (Fig. 1). Unfortunately, the story is not that simple:

(a) muscle relaxation is *not* a component of anesthesia: high end-tidal volatile anesthetics evoke adequate muscle relaxation to access the abdominal cavity. In contrast, muscle relaxation is not an alternative to adequate anesthesia, as intraoperative awareness shows [26].
(b) analgesia is *not* a component of anesthesia: « *a soldier in the battle may experience severe injury and nociception without experiencing pain* » [27]: approximately 32% of wounded soldiers experienced no pain in a field hospital [28]. Furthermore, *nociception, strictly speaking, is stimulation of nociceptive receptors* (Fig. 2). Thus, anti-nociception relates only to the suppression of the consequences of stimulation of skin nociceptors. Nevertheless, operationally, the common practice is to equate (i) nociception with increased BP and HR and (ii) adequate anti-nociception with stable circulatory parameters. Therefore, we are following this use of nociception and anti-nociception throughout this chapter.
(c) unconsciousness is not well-defined and includes amnesia and hypnosis [27].

Furthermore, an operational definition of anesthesia generated from, or focusing on, the effects of drugs yields to inconsistencies: (a) morphine and halothane summate to provide absence of withdrawal (paralysis) to nociceptive input. In contrast, morphine and halothane antagonize themselves when attenuation of HR response to the same nociceptive stimulus is considered [25]. (b) fentanyl and thiopentone summate with respect to unconsciousness and antagonize with respect to withdrawal movement to nociceptive stimulus [25].

Therefore, the only definition of pain on which one may agree is a *conscious*, unpleasant perception of a noxious stimulus [26]: logically, analgesia is abolished perception of pain in a *conscious* patient. In addition to severe discomfort in the conscious patient, nociceptive stimuli evoke behavioral (withdrawal movement), autonomic (increased BP and HR), and ventilatory (hyperpnea, tachypnea) changes. In the anesthetized patient, only nociception may be observed, or more accurately measured by increased HR and BP.

Operationally, increased HR and BP are often the only considered variables in the operating room (OR) to indicate inadequate anti-nociception in the anesthetized paralyzed patient. In the

postanesthesia care and critical care unit, the patient is (often) conscious and able to document his own pain verbally or quantify it using a visual analogic score. As baseline HR and BP are measured in the awake, conscious patient during the preoperative visit or immediately prior to induction, baseline circulatory variables may be increased because of anxiety ["de novo" hypertension [29]]. Therefore, some take into account the HR and BP observed immediately after the induction of GA and prior to tracheal intubation or to skin incision, away from administration of vasoactive drugs, to eliminate the sympathetically evoked increased pressure (Cividjian, personal communication).

Finally, ventilation is to be observed closely in the spontaneously breathing anesthetized patient to address the adequacy of anti-nociception through changes in Vt and respiratory rate (RR). Indeed, away from the anesthesia setting, during transition from wake to sleep, changes in ventilation patterns occur earlier than electro-encephalographic (EEG) changes [30].

B. Unconventional views

A caveat is needed here: operationally, anti-nociception is defined only as the dose of analgesics to be administered to achieve stable HR and BP intraoperatively or postoperatively, as compared to baseline (awake, conscious patient). In an even more restrictive point of view, anti-nociception is usually defined as the dose of *opioid* analgesics necessary to achieve stable intraoperative HR and BP. This view is suboptimal.

First, administration of opioid analgesics to suppress increased HR and BP following surgical stimulation (considered by conventional definition as anti-nociception) does not necessarily mean that nociception is addressed by opioid analgesics in a pharmacologically specific manner. The conventional reasoning is that opioid analgesics control increased HR and BP; thus, anti-nociception is the place for opioid analgesics alone. Then adequacy of anti-nociception is assessed from the dose of opioid analgesics necessary to evoke stable HR and BP under surgical stimuli. This is a *circular* reasoning. There are many transmitters in the pain pathways (enkephalins, noradrenaline, serotonin, etc.). Thus, administration of opioid analgesics may equally be viewed as handling increased HR and BP by blocking only one transmitter within the pain pathways (enkephalins): opioid analgesics cannot be viewed as specifically handling pain transmission but are only a pharmacological tool to achieve pain blockade. Furthermore, several transmitters are involved in BP and HR regulation (adrenaline, glutamate, GABA, acetylcholine, etc.): does it make sense to skip the possibility to act on any of these transmitters? In fact, the only goal is to achieve stability of BP and HR through central or peripheral manipulation of BP and HR, using various pharmacological tools acting on the ascending pain pathways or on the descending autonomic pathways.

Second, relying on opioid analgesics only to suppress changes in HR and BP under surgical stimuli may lead to opioid-related postoperative hyperalgesia, occurring in addition to traumatic/surgery-related hyperalgesia. Moreover, the use of intraoperative opioid analgesics may lead to hyperalgesia [31–33] quoted from [34]. A meta-analysis [35] shows that (a) high intraoperative dose of remifentanil is associated with higher early postoperative pain and postoperative morphine requirements; (b) higher morphine requirements were observed in patients who received relatively high-dose opioid analgesics; (c) lower pain thresholds were observed in the relatively high-dose opioid group; (d) remifentanil was associated with higher pain scores and morphine requirements than other opioids; (e) intraoperative inhalation agents were associated with higher postoperative morphine consumption. This was not observed with propofol: "*remifentanil may be administered … at the lowest possible dose and associated with propofol …*" [35]. In this regard, (a) high-dose intraoperative systemic remifentanil is associated with postoperative hyperalgesia and prevented by intraoperative ketamine [36] (b) intraoperative epidural anesthesia (bupivacaine–sufentanil–clonidine) combined with ketamine evokes better postoperative antihyperalgesia than other regimens (intravenous intraoperative, intravenous postoperative, and postoperative epidural) [37]. Thus, opioid analgesics could be viewed as necessary but not sufficient to handle anti-nociception. Intraoperative administration of nonopioid drugs (ketamine [36], alpha-2 agonist [38–40], beta-blocker [41,42], lidocaine, regional anesthesia, acetaminophen/paracetamol, and non-steroidal anti-inflammatory agents including COX-2 inhibitors) to suppress increased HR and BP is followed by reduced postoperative administration of opioid analgesics.

To sum up, under anesthesia, the evaluation of pain can rest only on changes in circulatory variables (nociception in a restrictive meaning: increased HR and BP). A problem arises with the

baseline values considered appropriate for HR and BP (anesthesia consultation? data obtained prior to induction? data obtained preincision without the support of any cardio-active drug?). Adequacy of anti-nociception is quantified through the dose of opioid analgesics administered to suppress increases in HR and BP. This accepted practice is a circular reasoning: (a) postoperative hyperalgesia (i.e., beyond the injured/traumatized site) is associated with the use of opioid analgesics and (b) pain pathways involve many transmitters, which may rationally contribute to stable intraoperative HR and BP.

III. Sympathetic and parasympathetic responses to nociception

A difference exists between the somato-sympathetic reflex (vasoconstriction), the defense reaction (limb vasodilation), and the playing dead reaction. Evoked by somatic stimuli, the somato-sympathetic reflex engages sympathetic preganglionic neurons located in the RVLM [43,44] (Fig. 5) and generates hypertension + tachycardia and likely generalized *vasoconstriction* following nociceptive stimulus under anesthesia. Presumably, the somato-sympathetic reflex mimics the pattern observed in the anesthetized human under surgical stimuli.

In contrast, (a) the defense reaction (« visceral alerting reaction », "rage" behavior) observed in the anesthetized animal (hypertension, tachycardia, vasoconstriction in the skin and intestine, pupil dilatation, pilo-erection, etc.) is generated through the dorso-lateral PAG and associated with hind limb *muscular vasodilation* [45]. In the conscious animal, this behavior is termed flight-or-attack or fight-or-flight behavior [45]. (b) the freezing/playing dead reaction is generated by the ventrolateral PAG [details in Fig. 5 and [46]].

A. Somato-sympathetic reflex

The somato-sympathetic reflex is the increase in HR and BP secondary to somatic stimuli. Somato-sympathetic reflex has been delineated from an electrophysiological point of view in anesthetized animals [44,47] (Fig. 5). The sympathetic cardiac and vasomotor baroreflex is the change in sympathetic cardiac and vasomotor activity evoked by increased or decreased BP: an increase in BP leads to decreased sympathetic activity on the heart (bradycardia) and on the vasculature (vasodilation). Following changes in the environment (e.g., rest to somatic stimulus or vice versa), the somato-sympathetic reflex switches, back and forth, with the sympathetic vasomotor baroreflex: when BP increases, the somato-sympathetic reflex is over-ridden by the cardiac and vasomotor sympathetic baroreflex [48]. Conversely, somatic stimulation suppresses the cardiac and vasomotor sympathetic baroreflex [49] ("occlusion" of the baroreflex).

The cardiac parasympathetic baroreflex (cardiac vagal baroreflex) interacts. Presumably, the cardiac parasympathetic reflex and the somato-sympathetic vascular reflex are switching, back and forth, according to the changing environment within which the whole organism interacts. This neuronal plasticity allows the behaving conscious animal to adapt immediately to changing conditions (rest vs. emergency) and, in the OR under anesthesia, allows monitoring the adequacy of anti-nociception (see below). Schematically, (a) during natural sleep, away from anesthesia, cardiac parasympathetic dominance exists: increased BP leads to bradycardia. This is not true during some phases of rapid-eye-movement sleep under sympathetic dominance; (b) under anesthesia with inadequate anti-nociception, during nociceptive stimulus, sympathetic vascular and cardiac dominance exists: surgical stimulus leads to increased BP and HR (somato-sympathetic reflex). Thus, the cardiac baroreflex is over-ridden by the somato-sympathetic reflex: hypertension + bradycardia (« cardiac vagal and sympathetic baroreflex ») observed under adequate anesthesia is converted to hypertension + tachycardia ("somato-sympathetic vasomotor and cardiac reflex") under inadequate anesthesia and immediately before movement (Fig. 4) [50].

B. Cardiac parasympathetic response

In anesthetized animals, stimulation of the PAG evokes « defense reaction » (Fig. 5). When increased BP is evoked (stimulation of the PAG; microinjection of an excitatory amino acid, glutamate, in the

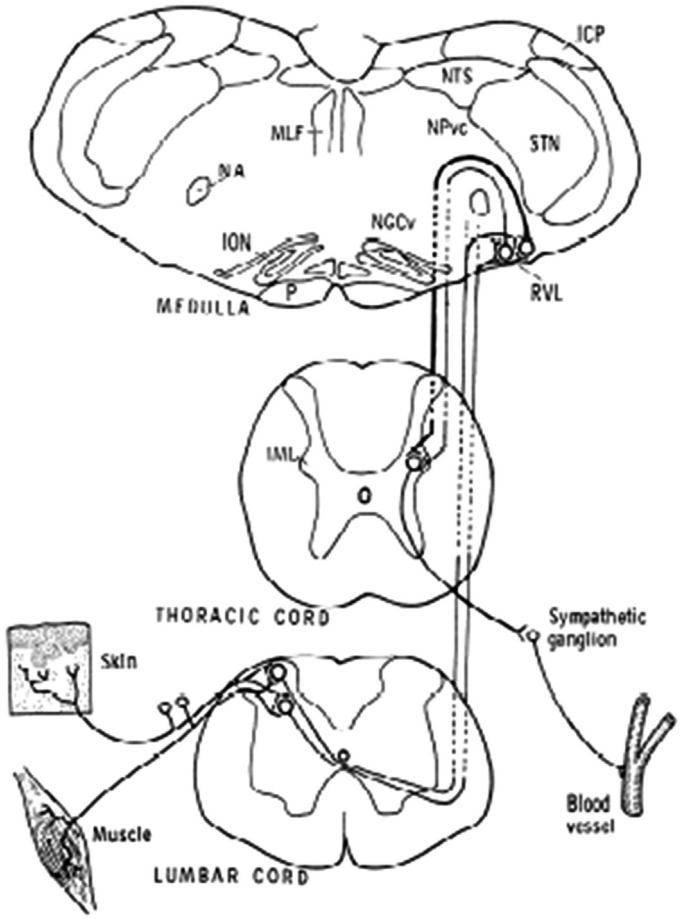


Fig. 5. Somatosympathetic reflex pathway in rat. Somatic afferents from skin and muscle activate spino-bulbar pathways that course in contralateral spinal cord through axons of two different conduction velocities. These ascending afferents excite slow- and fast-conducting descending bulbo-spinal sympatho-excitatory neurons located in the rostral ventrolateral medulla (RVLM [vaso-motor center]: the presympathetic neurons project directly from lower brain stem to tractus intermediolateralis [IML] of the spinal cord). This excitation results in a biphasic increase in pre- and postganglionic sympathetic nerve activity: increased heart rate and blood pressure. Modified from Morrison, Am J Physiol, 1989, 256: R1084-97 [43]. Abbreviations: ICP: inferior cerebellar peduncle; ION: inferior olivary nucleus; MLF: medial longitudinal fasciculus; NA: nucleus ambiguous; NGCv: nucleus reticularis gigan-tocellularis pars ventralis; NPvc: nucleus reticularis parvocellularis; NTS: nucleus of the tractus solitarius; P: corticospinal tract; STN: spinal trigeminal nucleus.

nucleus ambiguus), the activity of presumed CVMs (located in the nucleus ambiguus and projecting to the sinus node) is suppressed, as is the cardiac vagal bradycardia evoked by aortic depressor nerve stimulation [51]. As CVMs are preganglionic parasympathetic neurons, the bradycardia observed during hypertension (cardiac vagal baroreflex) is suppressed [51]: no acetylcholine release occurs anymore through the postganglionic neurons on the sinus node. Furthermore, a direct inhibition is present from the vasomotor center (RVLM) to the CVMs [11]. Therefore, there are at least two pathways involved in blocking the cardiac vagal baroreflex.

In humans, when anesthetized state is compared to the conscious state, the amplitude of the changes in RR interval [« sinus arrhythmia, » « heart rate variability » (HRV), an index of cardiac parasympathetic activity: « modulation of vagal tone » [52]] evoked by CVMs is reduced. Under anesthesia, surgical stimulation reduces HRV [53–55], especially when anti-nociception is inadequate

[56]. Therefore, under anesthesia and surgical stimulation, changes in RR interval assess the adequacy of anti-nociception (see below).

C. Monitoring the adequacy of anti-nociception

This overview is biased as all the prospective studies guiding the intraoperative administration of anti-nociceptive drugs were conducted only with opioid analgesics. To our knowledge, no study was conducted using OFA.

1. Untested hypotheses

There are several untested hypotheses bordering to dogma:

(a) "there is a coordinated response to nociceptive stimuli":
In the anesthetized, unparalyzed patient, withdrawal movement occurs as increased HR and BP and as EEG changes are observed. Postulating a coordinated and simultaneous spinal, brain stem, and cortical responses re-acting in concert to surgical stimuli is probably wrong (Fig. 6 upper panel): a spinal response (withdrawal movement) may occur at some point of the anesthetic without circulatory changes, followed by a brain stem (circulatory) response occurring at a later interval during the same surgical procedure without cortical changes and lastly by a cortical response later during the same surgical procedure without circulatory changes; processing of nociception is not as simple as traced out from the anatomy of pain pathways. Could this plasticity fit with the multiple projections from lamina I to the various levels of the neuraxis (spinal vs. brain stem vs. cortex: Fig. 2)? Nevertheless, the implications are (a) spinal, brain stem, and cortical responses under surgical stimuli should be recorded to generate a database and evaluate the responses occurring at the various levels of the neuraxis throughout the surgical procedure and (b) any monitoring of adequacy of anti-nociception under anesthesia cannot rest on any single line of monitoring, i.e., movement only vs. cortex only vs. brain stem only. A combination of indices is necessary.

(b) "there is no interaction between adequacy of hypnosis ($40 < BIS < 60$) and adequacy of anti-nociception" (Fig. 1). This may be partially wrong (Cividjian, unpublished data):
i) a change in the delivery (i.e., speed of administration) of the opioid analgesics may evoke a change in the electroencephalographic index (Bispectral index: BIS).
ii) a change in the delivery of propofol does not change the anti-nociception index CARDEAN. However, a large bolus of propofol leads to change in the CARDEAN index (e.g., in the setting of unexpected movement or emergence of anesthesia toward the end of surgery).

EEG-derived indices (BIS "clamped" to $40 < BIS < 60$ intraoperatively, etc.) reduce awareness and avoid deep sedation but poorly predict adequate intraoperative nociception. Thus, this paragraph focuses on autonomic-derived indices to address anti-nociception. Given the data summarized above, three lines of research address intraoperative anti-nociception: (a) changes in vasomotor and cardiac sympathetic activity; (b) changes in cardiac parasympathetic activity; and (c) a combination of thereof.

2. Vascular and cardiac sympathetic monitoring

(a) Surgical pleth index (SPI, formerly surgical stress index; Datex-General Electric, Helsinki, Finland) generated by changes in the amplitude of the photoplethysmographic signal (peripheral O_2 saturation: SpO_2 signal) and the changes in the RR interval: $SPI = 100\text{-}(0.33 \times RR\ interval + 0.67 \times photoplethysmogram\ amplitude$; 100: minimal anti-nociception; 0: excellent anti-nociception) in patients with normal sinus rhythm [57]. In the setting of ear–nose–throat surgery (American Society of Anesthesiologists, ASA I-II patients), SPI allows one reducing the dose to reduce the dose of opioid analgesics and the incidence of untoward events (hypertension, hypotension, tachycardia, and movement) [58]. In the setting of outpatient anesthesia (ASA

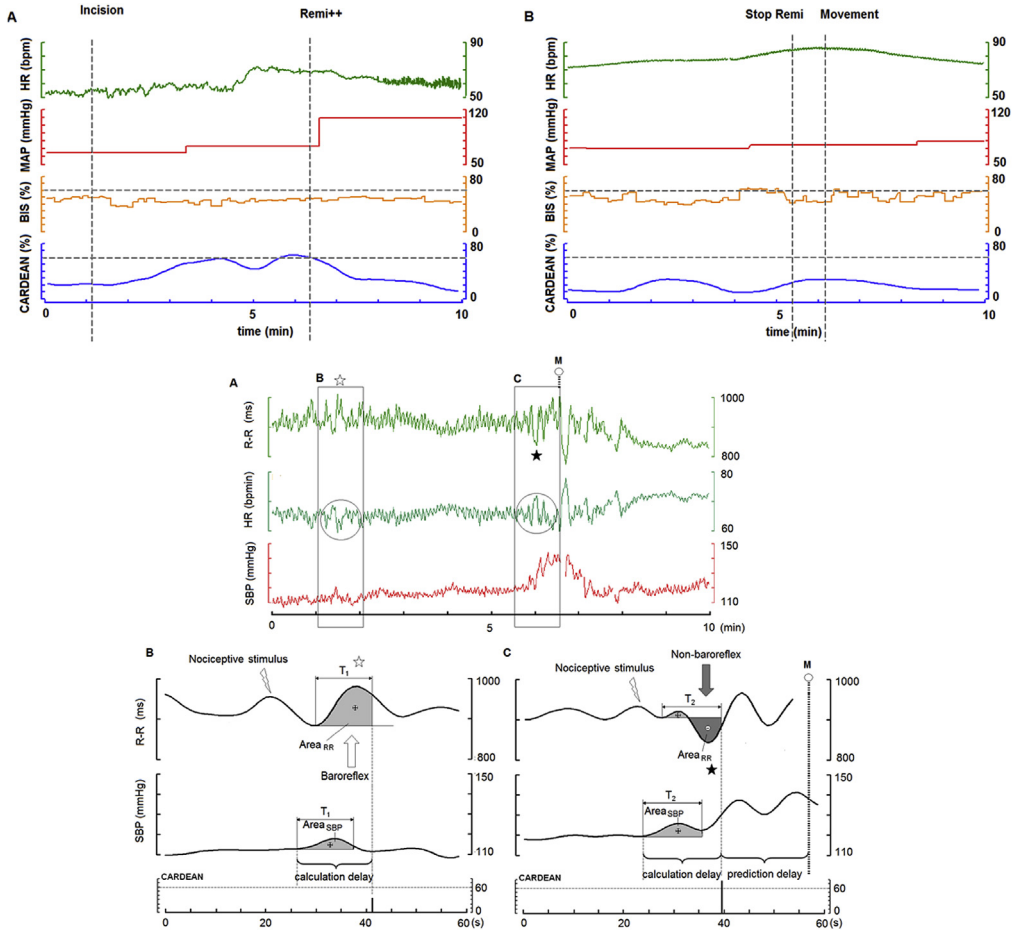


Fig. 6. Upper panel: **Dissociations between spinal, bulbar sympathetic, and cortical indices of anesthesia**: A: Beat-by-beat HR, brachial noninvasive MAP, BIS, and CARDEAN indices after incision in an 81-year-old patient undergoing abdominal surgery. Remifentanil effect site concentration was increased at t = 6.3 min following increased HR. The CARDEAN index increased approximately 1 min before increased HR, while BIS was stable under 60. Thus CARDEAN may predict sympathetic micro-"arousal" without cortical involvement. B: Emergence of anesthesia upon skin closure in a beta-blocked 64-year-old patient undergoing abdominal surgery. The patient moved the hand approximately 1 min following cessation of remifentanil infusion. BIS increased above 60 before the movement, showing a cortical arousal before spinal withdrawal movement. Simultaneously, CARDEAN shows no sympathetic microarousal. The spinal, bulbar, and cortical mechanisms involved within nociception are partially independent. Lower panel: **Hypertension + bradycardia (cardiac vagal baroreflex) switches to hypertension + tachycardia (somato-sympathetic reflex) before movement under inadequate anti-nociception in an anesthetized human** [60]. A: raw beat-by-beat RR interval, from ECG, and SBP, from non-invasive beat-by-beat BP acquisition [63]. An unexpected movement M occurs at interval t = 6.5 min (M+dotted lines), which could not be predicted by changes in HR (circle): indeed, before/after movement, the changes in HR are too small (±5 bp min) and of identical amplitude. However, CARDEAN detects different changes within the HR and SBP signals during stable (left: inset and figure B; open star) and unstable (right: inset and fig C; black star) periods. B: Low-pass filters suppress ventilation-evoked changes in B and C. When the cardiac baroreflex is engaged, an increase in pressure evokes a bradycardia, i.e., increased in RR interval: consequently, the RR area>0 and RR area/SBP area ratio are >0, then 0 < CARDEAN < 60. C: a non-baroreflex regulation, presumably the somato-sympathetic reflex, over-rides the cardiac baroreflex. Then, increased SBP evokes a tachycardia (decrease in RR interval) with RR area and RRarea/SBP area ratio of <0: 60 < CARDEAN < 100. Here, prediction of movement occurs 17 s before movement. Data acquisition leads to a calculation delay [beginning of increase in SBP and end of estimation period on RR interval signal: 27–111 s [114]]. Prediction of movement occurs 12–389 s [61,62,114] before inadequate anti-nociception/movement.

I-III patients), SPI reduces the doses of remifentanil and propofol and shortens emergence and extubation times [59]. However SPI is affected by low intravascular volume and chronic hypertension [60].

(b) « *Car*diovascular *de*pth of *an*algesia » (CARDEAN™, Alpha-2 Ltd, Lyon, France) tracks the switch between the cardiac vagal baroreflex and the vasomotor and cardiac somato-sympathetic reflex in the setting of adequate vs. inadequate anti-nociception [61] (Fig. 6 lower panel). Given $40 < BIS < 60$, in the setting of colonoscopy, CARDEAN halves the incidence of movements [62]. Again, with $40 < BIS < 60$, in the setting of abdominal surgery under laparoscopy, CARDEAN halves the incidence of tachycardia and sufentanil requirement [63]. Similar results were observed in the setting of orthopedic surgery ($n = 76$, Cividjian et al., in preparation). The index CARDEAN is now generated from the ECG and SpO_2 signals by a software running on a PC integrated within a Philips IntelliVue® monitor. To monitor intraoperative anti-nociception, there is no need for a noninvasive beat-by-beat BP monitor [Finapres/Nexfin [64]], as opposed to conventional noninvasive automated BP cuff measurement: estimation of changes in BP from the photoplethysmographic/SpO_2 signal is appropriate. These results are to be considered in the setting of normothermia (active rewarming of the arm and hand throughout the procedure), normovolemia, and sinus rhythm in ASA I–III patients, including elderly hypertensive or cardiac heart failure patients. When compared to autonomic nervous index (ANI) (see below), CARDEAN appears superior in conscious and spontaneously breathing burned patients undergoing dressing changes [65]. Finally, CARDEAN addresses anti-nociception in the setting of patients having received intraoperative alpha-2 agonists or chronic preoperative beta-blockers (Cividjian, in preparation).

(c) Changes in skin conductance follow within 1 s the volleys of skin sympathetic nervous discharge. Theoretically, this would make skin conductance a very interesting candidate for guiding intraoperative administration of analgesics. To our knowledge, there is no such published paper.

3. *Cardiac vagal activity monitoring*

Changes in RR intervals reflect phasic vagal activity, leading to sinus arrhythmia. Simple « time-domain » parameters [e.g., standard deviation of normal-to-normal intervals (SDNN)] vs. complex « frequency-domain » parameters [area under the curve (AUC) of high-frequency (HF) power (HF: 0.15–0.4 Hz) through a fast Fourier transform] vs. sophisticated « chaos » analysis are used. As HF power is a function of cardiac vagal activity *and* ventilation, changes from spontaneous to controlled mechanical ventilation dramatically reduce HF power. HF ventilation further suppresses HF power almost entirely in sedated-paralyzed patients [66]. Therefore, constant frequency of controlled mechanical ventilation is mandatory if HF power is to be used intraoperatively to assess anti-nociception through changes in RR interval. The autonomic nervous index/analgesia-nociception index uses frequency-domain analysis to monitor cardiac parasympathetic activity from changes in RR intervals (ANI, MetroDoloris, Lille, France; ANI = 100: adequate anti-nociception; ANI = 0: inadequacy of anti-nociception = poor “analgesia”). Induction of GA increases ANI. Surgery is followed by a decrease in ANI. Completion of surgery returns ANI to 90, close to adequate anti-nociception [56]. ANI guides prospectively the administration of intraoperative analgesics in ASA I-III patients in the setting of vascular surgery [67].

4. *Pupillary dilation*

Pupillary dilation (PD) is a function of sympathetic dilation and parasympathetic constriction. PD in response to a nociceptive stimulus persists under GA. In the awake, conscious patient, PD is abolished by an alpha-1 antagonist administered through eye drops, compatible with a sympathetic involvement. Under GA, PD may be independent from the sympathetic system and somehow dependent upon the parasympathetic system [68]. Under stable anesthesia, nociception is associated with PD preceding circulatory response. Thus, PD is an excellent window on the autonomic nervous system to assess anti-nociception. The problems are (a) the difficulty to continuously assess PD throughout the procedure, given the increased risk of infection or corneal trauma associated with multiple eye openings and (b) the absence of a prospective randomized trial to guide the administration of analgesics with PD.

5. *Overview*

Therefore,

(a) a *combination* of cardiac parasympathetic deactivation (ANI) and cardiac and vasomotor activation (SPI and/or CARDEAN) may be necessary to achieve the high sensitivity *and* specificity required by the anesthesiologist if computerized assessment of anti-nociception is to be used in the OR on a daily basis. Accordingly, (i) the association of CARDEAN (AUC for pain prediction = 0.83) and ANI (AUC = 0.75) appears superior (AUC = 0.87) to any of the two indices alone to assess pain in conscious, spontaneously breathing patients on an observational basis [Fig. 3 in [65]]. (ii) An index of nociceptive level (NoL) combines HR, HRV (i.e., ANI), plethysmogram wave amplitude (i.e., SPI), and skin conductance fluctuations [69]: NoL was superior to any single index and accurately characterizes nociception during GA on an *observational* basis [70]. Any such combination of indices (BIS, NoL, SPI, CARDEAN, and ANI) will have to be implemented into robotic anesthesia [71].

(b) temperature, arrhythmiae, volemia, and respiratory frequency are to be kept constant if anti-nociception is to be addressed specifically.

(c) the interactions between hypnosis and anti-nociception (§ III C) reported above have to be implemented into robotic anesthesia.

To sum up, addressing nociception with high specificity and sensitivity is likely to rest on a *combination* of spinal, brain stem, and cortical indices. In addition, to deliver appropriately analgesics, a pain robot should also handle circulatory (e.g., hypovolemia) and ventilatory status, heading toward a near-autonomous pain/anesthesia robot, in charge of *routine* care.

IV. Blocking the sympathetic and parasympathetic reactions

A. Opioid analgesics

The "state-of-the-art" technique to block the sympathetic activation observed during surgical stimulation (increased HR and BP) is through opioid analgesics. However, even very high-dose fentanyl (100–160 $\mu g\ kg^{-1}$) does not fully suppress hypertension and tachycardia in paralyzed patients [72,73]. Therefore, a combination of opioid analgesics and circulatory drugs [e.g., betablockers [41], alpha-2 agonists [38]] was used to achieve better circulatory stability.

It is possible to selectively block excitatory nociceptive inputs afferent to the major pontine noradrenergic nucleus, the locus coeruleus, by using kappa agonists (e.g., U50488) [74]. These drugs have not yet reached clinical use, despite their anti-nociceptive and anti-inflammatory activities. In contrast, mu agonists depress the response of LC neurons to *all* physiological inputs, including nociceptive inputs [75]. The implication is that mu agonists cannot be seen as specific for pain pathways or for blocking the somato-sympathetic reflex, contrary to the current belief. This aspecificity for pain has to be considered as mu agonists present side effects such as nausea, vomiting, constipation, ileus, bladder dysfunction, pruritis, sedation, visual hallucinations, depressed respiratory genesis and ventilatory depression, long-term physical dependence, addiction liability, and hyperalgesia [76].

B. Alpha-2 agonists

This overview will not cover all the interactions between noradrenergic, serotoninergic, glutamatergic, and GABA-ergic pathways and their clinical pharmacology.

In the early 1960s, while Bohringer–Ingelheim was assessing alpha-1 agonists acting as nasal decongestants, alpha-2 agonists were discovered as a serendipity. During the late 1960s, they were marketed as centrally acting anti-hypertensive agents [77]. Indeed, these drugs act specifically on one subtype of presympathetic neurons, the adrenergic slow-conducting bulbo-spinal neurons, which project from the vasomotor center (RVLM) to the IML [78]. Later data showed that both adrenergic and

glutamatergic RVLM neurons are inhibited by clonidine [79]. Furthermore, sympatho-inhibition evoked by alpha-2 agonists cannot be ascribed to a site of action restricted to the RVLM [79].

Alpha-2 agonists present sedative and analgesic properties that bear no relationship to their circulatory effects [80]. Therefore, the decision to market alpha-2 agonists as circulatory drugs was an arbitrary decision based purely on marketing considerations: alpha-2 agonists cannot be reduced to drugs acting only on the cardiovascular system according to their early, cardiological, regulatory approval. Conversely, alpha-2 agonists cannot be viewed only as sedative drugs according to their late, critical care, regulatory approval. These sedative/analgesic properties were used in the setting of veterinary anesthesia (xylazine) for a decade before human anesthesiologists took over [38]: in the anesthesia setting, alpha-2 agonists were used as an adjunct to high-dose opioid analgesics [38,81] and then in the setting of balanced anesthesia [39,82] to improve circulatory stability. Indeed, very high-dose opioid analgesics do not evoke full circulatory stability [72,73]. The use of EEG processing (Lifescan, Neurometrics, San Diego, CA) allowed one to observe lowered opioid analgesics requirement and improved circulatory stability when alpha-2 agonists were added to high-dose opioid analgesia [38]. The idea (MG and LQ) was to replace beta-blockers [41,83] with drugs presenting with no bronchial [84] and negative inotropic side effects [85] to lower opioid requirement and achieve better circulatory stability in patients presenting with contra-indications to beta blockers. Later, the reasoning was extended (MdK) to alpha-2 agonists, alone, providing adequate intraoperative anti-nociception: there is virtually no need to add opioid analgesics during major abdominal surgery [86]. This echoed earlier findings in cats [87]. This proposition [86] generated modern OFA as opposed to high-dose opioid anesthesia and "straight" general anesthesia.

In this respect, alpha-2 agonists.

(a) reduce the pain evoked by ice-cold water (cold pressor test applied to the foot) [88] without modifying the vasoconstrictive response [89].
(b) modify the affective motivational component of experimental pain in volunteers ("unpleasantness", analgognosia) without modifying the intensity of pain itself (amplitude of the sensory discriminative component) [90].

1. Dorsal noradrenergic bundle

The mechanism through which alpha-2 agonists exert their anesthetic adjunct/sedative effects remains elusive. The problem is as follows: there are alpha-2 adrenergic receptors on (a) noradrenergic/adrenergic neurons (cell bodies or terminals): auto-receptors and presynaptic receptors and (b) *non*-noradrenergic/adrenergic neurons (e.g., glutamatergic, GABA-ergic, or acetylcholinergic neurons): hetero-receptors and "post"-synaptic receptors. Which ones are responsible for the sedative effect of alpha-2 agonists?

(a) An alpha-2 agonist, azepexole, reduces MAC up to 85% and is reversed by an alpha-2 antagonist, idazoxan [91] or yohimbine. Thus, an alpha-2 adrenergic receptor is involved somewhere in the brain, e.g., on noradrenergic or *non*-adrenergic neurons; nothing more can be inferred at this juncture. This experiment [91] does *not* allow one to conclude on central noradrenergic neurons or « *central noradrenergic transmission regulat[ing] anesthetic depth* » [92]. In fact, the term noradrenergic neurotransmission is misleading: it conflates anatomy and pharmacology, i.e., the noradrenergic systems with alpha-2 adrenergic receptors, which are neither identical nor necessarily colocated on the same neurons.
(b) destruction of the whole noradrenergic system (cell bodies, axons, and terminals) with a toxin, DSP4, or depletion of NA stores (alpha-methyl-para-tyrosine [AMPT] or reserpine or alpha-methyl-dopa, Aldomet®, a centrally acting anti-hypertensive agent) reduces the MAC of halothane by 30–50% [93,94]: central noradrenergic cell bodies or terminals are *involved* in evoking a lower concentration of halogenated agent necessary to evoke full anesthesia ("regulation of anesthetic depth" lowering MAC by −30 to −50%. The destruction (DSP4) or depletion (AMPT) of noradrenergic neurons is *not* necessary and sufficient to evoke full anesthesia. Any implication that noradrenergic systems (noradrenergic neurons themselves) may be *causal* in the genesis of anesthesia (*control and regulation of* anesthesia) generates confusion.

(c) the near-complete MAC reduction (approximately −90 to −100%) evoked by a high dose of an alpha-2 agonist, dexmedetomidine, is *identical,* whether the NA systems are intact (vehicle), destroyed (DSP4), or depleted (AMPT) [93]: the alpha-2 adrenergic receptor is somewhere involved in the presence (vehicle) or the absence (DSP4) of the central NA systems. Complete anesthesia may be evoked by the alpha-2 agonist itself even when the noradrenergic system has been destroyed, or not. Thus, central NA systems are *not* causal in the genesis of anesthesia. Contra Maze [92], « *central noradrenergic transmission [does not regulate] anesthetic depth* » but is simply involved in baseline vigilance [93,94], defined as the concentration of halogenated agent necessary to evoke absence of withdrawal movement upon nociceptive stimulus. More precisely, central noradrenergic systems modify the dose of anesthetics (MAC) necessary to evoke the absence of response to a nociceptive stimulus. Similarly, alpha-2 adrenergic receptors, which lower MAC, are not "auto"-receptors located on NA cell bodies or terminals ("pre"-synaptic receptors) but located on non-adrenergic neurons ("post"-synaptic receptors, « hetero »-receptors).

To solve the controversy, four groups of experiments are needed: (a) destruction of NA systems: effects on MAC reduction of alpha-2 agonists on MAC reduction in vehicle vs. DSP4-treated animals; (b) destruction of LC cell bodies: as ibotenic acid destroys the cell bodies of LC neurons, effect on MAC reduction of injection of alpha-2 agonists in the LC of rats treated with vehicle vs. ibotenic acid; and (c) destruction of NA systems and LC cell bodies: effect on MAC reduction of alpha-2 agonists injected in the LC of rats treated with vehicle vs. DSP4, after vehicle vs. ibotenic acid injection in the LC. After the destruction of central NA systems (DSP4) *and* the destruction of LC cell bodies, a definitive answer may be at hand.

Irrespective of the mechanism and its anatomical location, alpha-2 agonists are of help to reduce central NA and circulatory hyperactivity in the setting of anesthesia [38,39,81,82,95,96] and critical care [97–102]. Furthermore, high dose of alpha-2 agonists evokes near-total anesthesia in animals [93] or in the setting of total intravenous anesthesia (dexmedetomidine 5–10 μg.kg-1.h-1) *when avoidance of ventilatory depression* is required [103–106]. Again, *alpha-2 adrenergic receptors are certainly involved in the genesis or maintenance of anesthesia and therefore clinically relevant. However, central NA systems are not causal in evoking anesthesia.*

2. Ventral noradrenergic bundle

Similarly, the anti-hypertensive effects of alpha-2 agonists are not observed any longer following depletion [107] or destruction [108] of noradrenergic/adrenergic cell bodies and terminals. Thus, the anti-hypertensive effects of alpha-2 agonists are related to alpha-2 adrenergic receptors located on *non*-adrenergic cell bodies or terminals (« postsynaptic » receptors and alpha-2 hetero-receptors located on glutamatergic presympathetic neurons in the vasomotor center?). Nevertheless, alpha-2 agonists inhibit adrenergic presympathetic neurons located in the vasomotor center (slow conducting RVLM barosensitive-bulbospinal neurons) [78] and decelerate the turnover of NA in the intermediolateral cell column of the spinal cord [80]. There is no necessary link between the circulatory effects of alpha-2 agonists and the decelerated turnover of NA (e.g., sedation, analgesia). Circulation and sedation may be events occurring simultaneously but bearing no causal, or other, relationship ("unrelated" events linked to the dorsal noradrenergic bundle or the ventral noradrenergic bundle) [80].

To sum up, the accepted [92] theories regarding alpha-2 agonists acting only or primarily on alpha-2 "auto"-receptors ("presynaptic") on LC noradrenergic cell bodies are, at best, partial.

3. Spinal vs. supra spinal site of action of alpha-2 agonists

The site of action of alpha-2 agonists with regard to anti-nociception is considered through two theories as follows:

1) spinal: in spinalized cats, alpha-2 agonists present anti-nociceptive effects [109]. Furthermore, (a) spinal transection partially suppresses morphine-evoked analgesia, while it leaves clonidine-

evoked analgesia untouched [110]. (b) the anti-nociceptive effect of an alpha-2 agonist is increased following lesion of the locus coeruleus, which is compatible with the upregulation of alpha-2 "hetero"-receptors located on *non*-noradrenergic cell bodies/terminals ("post"-synaptic receptors) [111].

(2) supra-spinal: under *physiological* conditions in the behaving conscious animal exposed to salient stimuli, e.g., switch from rest to emergency, how an activation of LC neurons evokes spinal inhibition of pain processing? Under *pharmacological* conditions, i.e., systemic administration of an alpha-2 agonist in an anesthetized animal, how does supra-spinal descending inhibition of pain processing occur? The possibilities are delineated in Fig. 7 [112].

A final point is the absence, to our knowledge, of the clinical use of serotonin (5HT)-specific drugs [113] (fluoxetine, ketanserin, etc.). Could 5HT neurons heavily involved in pain pathways (Fig. 2 left) be used to evoke intraoperative anti-nociception?

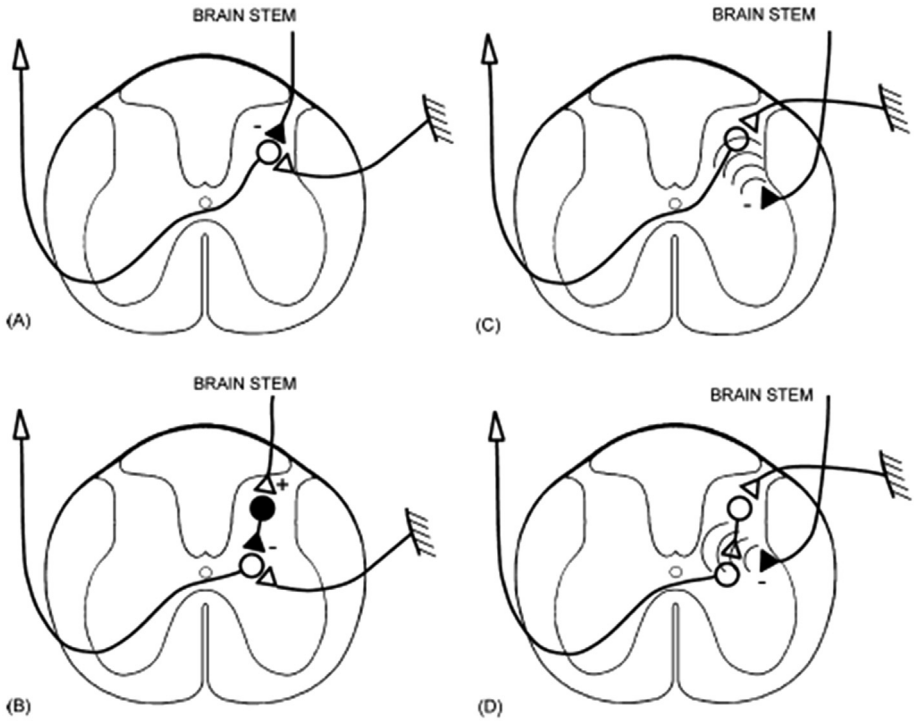


Fig. 7. Putative pain inhibitory noradrenergic circuitries in the spinal dorsal horn [modified from Pertovaara A, *Prog Neurobiol* 2006; 80:53–83 [112]]: Open symbols: excitatory synapses and neurons; Filled symbols: inhibitory actions. A. Pontospinal noradrenergic axons synapse with spinal pain relay neurons and inhibit their activity due to the action of postsynaptic alpha-2 adrenoceptors. B. Pontospinal noradrenergic axons activate alpha-1 adrenoceptors on inhibitory interneurons (GABA, glycine), leading to inhibition of pain-relay neurons in the spinal dorsal horn. C. Pontospinal noradrenergic axons release norepinephrine that inhibits nociception through alpha-2A adrenoceptors on central axonal terminals of nociceptive primary afferent nerve fibers. This presynaptic effect of noradrenaline produces anti-nociception by reducing the release of excitatory neurotransmitters from nociceptive primary afferent fibers. Because axo-axonal synapses between noradrenergic and nociceptive axons are rare in the spinal cord, noradrenaline may spread from the site of release to the central terminals of nociceptive nerve fibers through "*volume transmission*" [115]. D. Pontospinal noradrenergic axons release noradrenaline that diffuses through volume transmission on alpha-2C adrenoceptors located on axon terminals of excitatory interneurons that synapse with pain relay neurons. This circuitry needs neurophysiological documentation.

Conclusion

The use of mu agonists (opioid analgesics) as the only pharmacological tool to suppress circulatory changes observed during surgical stimuli is a widely accepted clinical practice. However, the equation of adequate intraoperative anti-nociception = opioid analgesics borders to a harmful dogma, given opioid-evoked hyperalgesia and respiratory genesis depression. A cursory look at the organization of pain pathways and central mono-aminergic systems suggests many possibilities in modifying anti-nociception beyond the use of opioid analgesics. Therefore, the rationale behind balanced anesthesia, i.e., the use of various drugs acting at various sites of action may well be extended to tear down anti-nociception evoked *only* by opioid analgesics. Other transmitters not considered here (NMDA, GABA, etc.) should be taken into account when the clinician considers reducing [38,39] or skipping [84] the use of opioid analgesics in the setting of OFA. In addition to opioid analgesics, the suppression of circulatory changes evoked by surgical stimuli may be obtained with ketamine, alpha-2 agonists, beta-blockers, systemic lidocaine, magnesium, anti-inflammatory nonsteroidal drugs, etc. Therefore, non-opioid analgesics may be used as first-line agents, with opioid analgesics as "rescue" analgesic medication [76]: the pendulum is to be switched back again!

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Conflict of interest

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Practice points

- Intraoperative anti-nociception is assessed by following changes in the heart rate and blood pressure.
- Anti-nociception is commonly achieved using opioid analgesics, with side effects such as respiratory depression, immunosuppression, and hyperalgesia.
- The ascending pain pathways and descending autonomic pathways are within a loop. This loop involves many transmitters, including serotonin, noradrenaline, enkephalins, and peptides and there is no reason to achieve anti-nociception just by interfering with the enkephalins using only opioid analgesics.

Research agenda

- Delineating the lower brain stem anatomical, neurochemical, and functional connection between ascending pain pathways and descending autonomic pathways.
- Addressing monitoring tools for anti-nociception in the setting of an opioid-free anesthesia.
- Addressing nonopioid analgesics through transmitters such as serotonin and peptides.

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Opioids, respiratory depression, and sleep-disordered breathing

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The increasing use of opioids in the perioperative period has increased opioid-associated morbidity and mortality. There is a well-established connection between opioids, sleep-disordered breathing (SDB), and respiratory depression. The treatment of postoperative pain with opioids in patients with SDB may result in respiratory depression. In an unmonitored setting, it may lead to life-threatening respiratory events. More studies are required to evaluate the effective management and prevention of respiratory depression in patients with SDB. This review summarizes the current state of knowledge relating to the pathophysiology of respiratory depression by opioids and opioid-related respiratory depression and appraises the association between opioids and SDB.

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Pathophysiology of respiratory depression by opioids

Opioid epidemic

Drugs acting on μ-opioid receptors (MOR) are widely used as analgesics or as drugs of abuse. In addition to their analgesic and euphoric properties, MOR drugs also affect cardiorespiratory activity and can induce life-threatening respiratory arrest and death. Medications acting on MORs, such as morphine, fentanyl, oxycodone, and hydrocodone, are widely prescribed for acute and chronic pain. In the United States, there are over 250 million prescriptions per year for opioid analgesics [1]. In fact, opioid use and misuse increased 40-fold between 1996 and 2011 and are still increasing [1]. Although opioid medications are an essential part of pain treatment, the significant rise in prescriptions and usage is associated with an increase in the number of hospitalizations and deaths related to opioids. Indeed, there is a clear association between the increased rate of opioid prescriptions and the occurrence of adverse effects, aberrant abuse, and unintentional deaths. The increase in opioid poisoning has led to an opioid epidemic in the United States, exceeding 20,000 victims every year [2]. The health burden associated with opioid misuses and overdoses is therefore considerable, and the pathophysiology underlying the life-threatening side effect of opioid-induced respiratory depression needs to be clarified. The objective of this review is to understand the pathophysiology of respiratory depression by opioids, evaluate the respiratory depression after anesthesia, and appraise the association between opioids and sleep-disordered breathing (SDB). SDB includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and obesity hypoventilation syndrome (OHS). We hope to raise awareness related to the sedating properties of MOR analgesics and the risks associated with sedation and respiratory depression.

Opioid analgesia

The opioid system, which comprises endogenous peptides that bind to μ, δ, and κ-opioid receptors, mediates both endogenous and exogenous opioid-mediated analgesia [3]. The widely used opioid analgesics induce analgesia mainly through their action on MORs expressed in neural circuits involved in nociception. These circuits include cortical, subcortical, and brainstem areas and spinal circuits [4]. Because MORs are widely expressed throughout the nervous system, they not only inhibit nociceptive circuits but also circuits regulating autonomic functions such as cardiovascular and respiratory functions.

Side effects associated with opioid analgesics

MOR medications induce side effects such as hypoventilation [5], constipation, addiction, sedation, and changes in blood pressure and cardiac function [6]. These side effects, especially sedation and cardio-respiratory depression, severely reduce the effective use of opioids because of the risks associated with the inhibition of autonomic functions. In chronic opioid users, these risks are even higher because patients develop tolerance and require more opioids to reach effective levels of analgesia, which further increases the risk of respiratory depression by opioid analgesics [7].

Opioid-induced respiratory depression

One of the main side effects associated with MOR analgesics is hypoventilation, which is characterized by a reduction in the respiratory rate [5] and a decrease in airflow [8]. In addition, MOR analgesics potentiate sleep apnea. Morphine can significantly reduce respiratory rate even at mild therapeutic dosages [9]. When morphine is used at a higher dosage or when highly potent MOR drugs such as fentanyl are used, they can induce severe respiratory depression and/or can completely stop breathing if not treated with the MOR antagonist naloxone. In addition to its effects on respiratory rate, the MOR analgesic morphine decreases the ventilatory response to carbon dioxide [10], therefore suggesting that morphine dampens chemosensitivity in addition to directly affect respiratory rate. The severity of opioid-induced respiratory depression, however, depends on the type of MOR medications,

the dosage used, the state of arousal of the patient (sleep or awake), and the concomitant administration of other respiratory depressant drugs such as sedatives [11]. In this study, we review some of the factors and the underlying mechanisms contributing to the severity of respiratory depression by MOR analgesics.

Factors contributing to respiratory depression by opioids

One striking observation when opioids are administered to patients is that breathing may be stable when the patient is awake but could rapidly fail when the patient falls asleep. This observation raises the concept that the severity of respiratory depression is linked to states of brain arousal (i.e., sleep, sedation, drowsiness, or anesthesia). Indeed, breathing is tightly regulated by states of brain arousal because considerable differences in ventilation are observed between wakefulness and sleep. Reductions in air flow or CO_2 chemosensitivity during sleep can indeed lead to SDB such as OSA and/or CSA, respectively. The same concept applies to opioid-induced respiratory depression, which is regulated by sleep–wake mechanisms [12]. Fentanyl or morphine, for instance, significantly increases CSAs during slow-wave sleep [12], suggesting that there are state-dependent mechanisms regulating the severity of respiratory depression. To test this concept, we performed a study in children who received a small dose of morphine and were recorded overnight by using polysomnography [9]. We found that morphine reduces high-frequency electrocortical activity (Fig. 1), which indicates drowsiness and sedation. This is consistent with the potent sedative properties of opioids characterized by the reduction of motor control, loss of attention, and sleep architecture changes [13]. We also found that

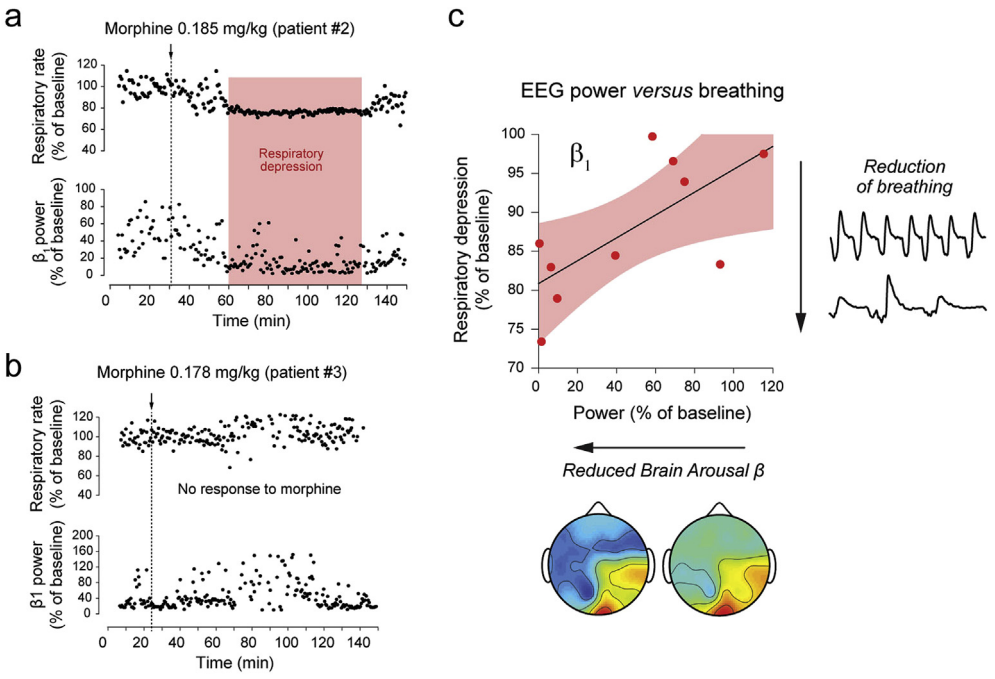

Fig. 1. Relationship between the sedating properties of the opioid morphine and the severity of respiratory depression. Morphine administration in a young patient decreases high-frequency β (20–30 Hz) electrocortical power and respiratory rate (a). In another patient, with already reduced high-frequency electrocortical activity, a similar dose of morphine had no effect on electrocortical activity and respiratory rate (b). In 11 patients, there was a significant relationship between the reduction in β high-frequency electrocortical power and the severity of respiratory depression (c), therefore suggesting that the severity of respiratory depression is associated with the reduction in electrocortical power induced by morphine. Used with permission from Montandon G et al. Anesthesiology. 2016; 125: 889–903 [9].

when patients exhibit a high level of cortical arousal before morphine administration, morphine produced electrocortical changes consistent with sedation, and this was accompanied by respiratory depression (Fig. 1). According to the same concept, a reduction in brain arousal by sedatives, anesthetics, or alcohol would also increase the risk of respiratory depression and associated overdoses by MOR drugs. Taken together, these findings indicate a powerful effect of cortical arousal state *per se* in the severity of respiratory rate depression produced by opioid analgesics.

Neural circuits involved in respiratory depression by opioids

Respiratory circuits sensitive to opioids

By binding to MORs, opioid drugs inhibit the neuronal activity of many central nervous system structures. MORs are widely expressed in the central nervous system, and their activation inhibits several physiological functions. Using brain imaging, the cortical and subcortical centers, involved in the volitional control of breathing and inhibited by the MOR ligand remifentanil, have been identified [14]. Remifentanil decreases blood oxygen level-dependent (BOLD) fMRI activity in the left dorsoventral prefrontal cortex, anterior cingulate, cerebellum, and periaqueductal gray (Fig. 2). Data using BOLD imaging are, however, limited because opioids directly affect cerebrovascular and hemodynamic control. Interestingly, the periaqueductal gray is involved in nociception [4], modulates arousal, and controls respiratory activity [15]. The periaqueductal gray may, therefore, constitute a hub between cortical arousal, sedation, and respiratory rate depression by opioid analgesics.

Brainstem circuits regulating breathing and MORs

The respiratory network located in the brainstem rhythmically activates respiratory muscles and generates breathing, but the contribution of the various parts of this circuit to respiratory depression by opioids is unknown in humans. The roles of the brainstem structures involved in respiratory depression have been extensively investigated using different animal models, but no clear consensus has yet been achieved. In decerebrated dogs, application of the MOR agonist DAMGO to the parabrachial/Kölliker–Fuse complex, a pontine structure regulating arousal and breathing (Fig. 2), depresses breathing [16], but its contribution to respiratory rate suppression by opioids is controversial [17]. Indeed, opioid-related changes in these pontine structures may be due to indirect effects of opioids on respiratory pattern and/or upper airway activity [18]. In a more caudal region of the brainstem, the rostral ventromedial medulla (Fig. 2) may mediate respiratory depression [19] and opioid analgesia [4]. In addition, application of MOR ligands to the medullary raphe (Fig. 2), two brainstem structures that are sensitive to CO_2, reduces the respiratory responses to CO_2 [20]. Moreover, opioids increase the occurrence of OSA [12,21], therefore suggesting that upper airway motor control is also impaired by opioids [22]. Overall, these data suggest that opioid analgesics impair several brainstem circuits important in the control of breathing and may explain hypoventilation associated with MOR analgesics.

Medullary circuits and MOR drugs

Although these circuits may be modulated by MOR analgesics, the main region of the medulla that generates breathing is the ventrolateral medulla [23]. Application of MOR agonists to the ventrolateral medulla depresses breathing [24]. When isolated *in vitro*, the ventrolateral medulla is inhibited by opioids [25,26]. At the core of the medulla is the preBötzinger (preBötC), a neural site essential for the generation of rhythmic breathing in animals [27,28] and humans [29]. The preBötC is highly sensitive to opioids [28] and mediates an important component of respiratory depression by opioid analgesics [30]. In this region, neurons expressing neurokinin-1 receptors are preferentially inhibited by MOR ligands [30]. Interestingly, neurokinin-1 receptors are the cognate receptors for substance P, an important peptide in nociceptive circuits. Despite these studies, the role of the preBötC in mediating opioid-induced respiratory depression remains controversial [17]. Other studies have shown that the ventrolateral medulla does not respond to opioids in larger animal models [31]. In conclusion, these

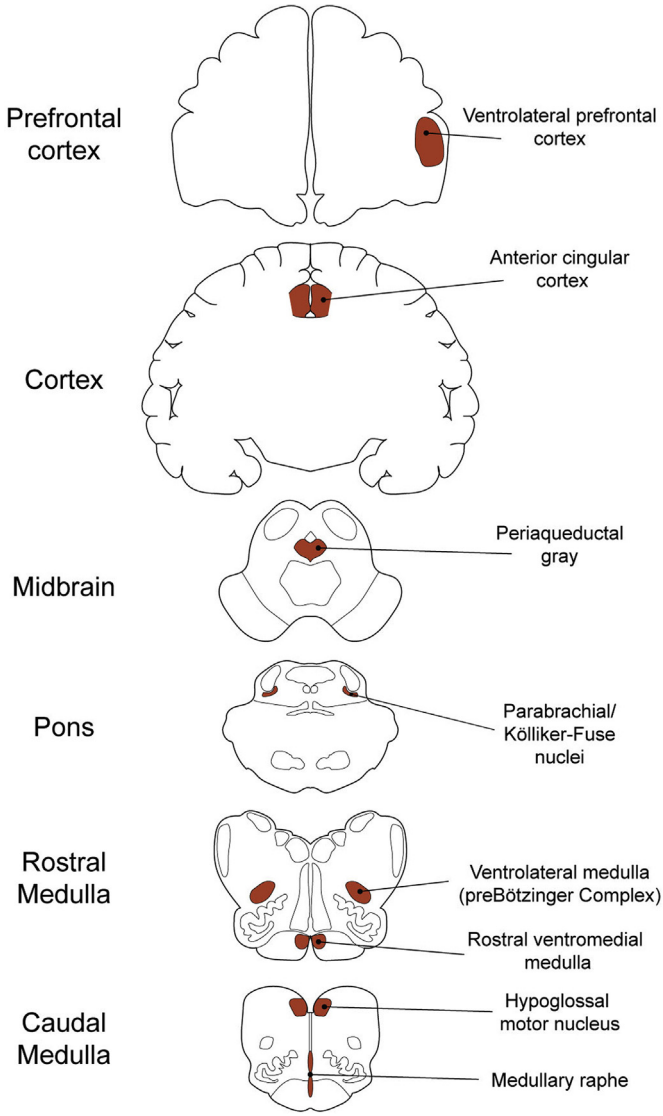

Fig. 2. Neural circuits sensitive to MOR analgesics and regulating opioid-induced respiratory depression. Coronal views of brain structures sensitive to MOR analgesics and regulating breathing. The ventrolateral prefrontal cortex, the anterior cingular cortex, and the periaqueductal gray are activated during remifentanil administration and volitional breathing. The parabrachial/Kölliker–Fuse nuclei are sensitive to MOR analgesics. In the medulla, the preBötzinger Complex (preBötC), the rostral ventromedial medulla, the medullary raphe, and the hypoglossal motor nucleus are sensitive to MOR analgesics and may contribute to opioid-induced respiratory depression. This map was constructed using animal and human studies.

studies show that the core circuits regulating breathing are sensitive to MOR drugs and that they mediate important components of opioid-induced respiratory depression.

Cellular mechanisms regulating MOR inhibition

MORs are G-protein-coupled receptors that activate pertussis toxin-sensitive G-proteins such as $\beta\gamma$ G-proteins and several second messengers to inhibit neuronal activity. These G-proteins elicit

potassium currents due to the coupling between Gβγ and G-protein-gated inwardly rectifying potassium (GIRK) channels [32]. MORs, therefore, hyperpolarize excitable cells, and GIRK channels also contribute to MOR inhibition of respiratory circuits [33], which suggests new avenues of research to develop potential therapeutic approaches targeting the GIRK channel pathway and prevent respiratory depression by opioids.

Potential preventive therapies for opioid-induced respiratory depression

To prevent respiratory depression and reduce hospitalization due to overdoses associated with opioids in this high-risk group, avoidance of opioids and development of new therapies should be considered. When feasible, continuous regional anesthesia using a catheter may be considered. This may limit or avoid the use of opioid medications during the perioperative period. There are three different strategies that could lead to the development of preventive treatments for respiratory depression without reducing opioid analgesia. First, the use of the MOR antagonist naloxone to reverse the effects of opioids is not feasible as a preventive treatment because it also eliminates the beneficial analgesic effects of opioids. (i) Stimulation of the respiratory network by targeting an excitatory neurotransmitter system important for breathing has proven to be a potential strategy. Ampakines, which are allosteric modulators of a type of glutamate receptors, increase ventilation and prevent opioid-induced respiratory depression in rats [34] and humans [35]. Their efficacy at higher opioid concentrations is, however, unknown. Drugs acting on 5-HT_{4a} receptor agonists are also potential respiratory stimulants [26], but their capacity to reverse respiratory depression without affecting analgesia is controversial [36]. (ii) New opioid compounds acting on MORs with potent analgesic properties but presenting reduced respiratory depression are also of great interest [37] but may not be able to replace existing pain treatments, which are often complex and require a combination of analgesics. (iii) Inhibition of a second messenger mediating MOR inhibition of respiratory circuits may also be a potential strategy. Because most opioid analgesics are highly selective for MORs with limited off-target effects on other opioid receptor types, targeting the endogenous mechanism mediating MOR inhibition may be able to prevent respiratory depression. New pharmaceutical compounds may, however, be developed in the future to selectively target second messengers only involved in respiratory depression.

Respiratory depression during phase I recovery

The immediate postoperative period, Phase I recovery, is notable for dynamic changes in physiological parameters as the effects of anesthesia dissipate. During this period, patients require continuous monitoring and must have access to immediate therapies to address any potentially harmful or life-threatening conditions. In the United States, postsurgical patients undergo Phase I recovery in the postanesthesia care unit (PACU), which is a specialized area that provides anesthesia-specific intensive care unit (ICU)-level care. Postsurgical patients are held in the PACU until vital organ system functions normalize and are then deemed to be safe for discharge to lower acuity levels of care (e.g., postsurgical ward and outpatient area) where they undergo the second phase of recovery, i.e., Phase II recovery.

Assessment of recovery from anesthesia

Typically, the recovery of organ system functions in the immediate postanesthesia period is assessed by the return of consciousness, motor strength, normalization of blood pressure, and recovery of respiratory function [38]. At most institutions, a return of respiratory function is defined by patients' ability to (i) maintain an airway without assistance or cough on command and (ii) maintain oxyhemoglobin saturation within a preoperative parameter. In the contemporary era, these criteria to evaluate pulmonary function may be inadequate to determine the risk for postoperative respiratory complications [39–41]. The basis for currently used criteria were defined in the 1970s [38]. Since then, there have been substantial changes in the prevalence of respiratory diseases and perioperative management that theoretically increase the risk for postoperative hypercapnic respiratory failure.

Pulmonary disease and OSA as risks for postoperative respiratory depression

It is believed that with increased rates in obesity and with increased population longevity, the prevalence of SDB conditions, specifically OSA, may have increased (however, epidemiological studies on this topic suffer methodological limitations, preventing a definitive estimation of OSA temporal prevalence changes) [42]. OSA is known to be very common but often an undiagnosed condition among surgical patients [43]. In addition, the perioperative administration of opioid analgesics has increased in response to the standards set by the Joint Commission [44,45]. Both OSA and perioperative opioids are recognized as important risk factors for postoperative hypercapnic respiratory failure. Moreover, many postoperative patients are administered supplemental oxygen, which effectively negates the use of a pulse oximeter in identifying depressed respiratory effort until very high levels of arterial carbon dioxide are reached [46]. Therefore, a discharge assessment criterion that relies on oxyhemoglobin saturation can lead to a false sense of security.

Postoperative hypercapnic respiratory failure is a serious adverse event that can lead to severe morbidity or death [47]. Recent evidence suggests that more than 20% of postsurgical patients have prolonged episodes of hypoxemia, of which 95% may go undetected when standard postoperative monitoring is used [48]. In response, the American Society of Anesthesiologists (ASA) issued practice guidelines calling for preoperative evaluation for OSA [49]. Formal overnight polysomnography is required for definitive OSA diagnosis but is impractical for widespread preoperative assessment [40]. Alternative screening for OSA with overnight pulse oximetry [50] or assessment tools like STOP-Bang [51] have been proposed, but these measures have diagnostic limitations [40]. The ASA guidelines also recommend that the perioperative management be adjusted for patients with known OSA or in those who are considered at risk. However, it is estimated that 20% of adult surgical patients are at high risk for OSA [43], making it impractical to triage all these patients to higher levels of postoperative care. With regard to the increased doses of perioperative opioid analgesic administration, safety and regulatory organizations have called for increased monitoring of patients requiring postoperative opioids [49]. Although emerging technology may accurately monitor patients for postoperative respiratory depression, many of these modalities are still impractical for widespread use.

Assessment of adverse respiratory events in post-anesthetic care unit

To better assess the risk for postoperative hypercapnic respiratory adverse events, Gali et al. introduced a distinctive, two-phase evaluation process that combined preoperative assessment for OSA with nursing respiratory assessment during Phase I recovery [52]. During Phase I recovery, registered nurses continuously monitored patients during three 30-min periods for four different specific events of respiratory depression. These respiratory-specific events are (i) bradypnea, (ii) apnea, (iii) hypoxemia, and (iv) "pain-sedation mismatch" (i.e., high pain score reported in the presence of high sedation score) (Table 1) [39,53]. Patients with "pain-sedation mismatch" may be at increased risk for respiratory complications if given additional analgesics after discharge from the recovery room [52]. Any patient who develops a respiratory-specific event during any two 30-min periods in PACU is considered to have "recurrent respiratory-specific events" [52]. It is recommended that patients with a

Table 1
Mayo Clinic criteria for respiratory-specific depressive episodes in the PACU [39].

Respiratory event	Definition
Hypoventilation	<8 respirations/min (3 episodes needed for yes)
Apnea	≥10 s (only 1 episode needed for yes)
Desaturation	Pulse oximetry < 90% or preoperative saturation (3 episodes for a yes)
Pain/sedation mismatch	RASS score −2 through −5 and pain score >5 (1 episode needed for a yes)

Modified with permission form Gali B et al. Anesthesiology. 2009; 110: 869–77 [39].
Patients are screened for respiratory-specific depressive episodes during Phase I recovery for 30-min evaluations. If a patient has any events in two or more of the three evaluation periods, the patient is considered to have experienced recurrent events [39].
Abbreviation: PACU: Postanesthesia Care Unit; RASS: Richmond Agitation-Sedation Scale [53].

positive OSA screening and recurrent respiratory-specific events are either fitted with noninvasive positive pressure ventilation devices [i.e., continuous positive airway pressure (CPAP) or Bilevel positive airway pressure (BPAP)] and/or admitted to a unit with advanced monitoring capabilities (e.g., ICU, a ward with pulse oximetry with telemetry capabilities) [54]. Patients witnessed to have recurrent respiratory-specific events had higher rates of postoperative respiratory complications than those who did not exhibit signs of respiratory depression during Phase I recovery [39,52,55]. One study categorized patients into four groups on the basis of an OSA screening and the occurrence of respiratory events during Phase I recovery. Respiratory complications occurring after PACU discharge was 3.5-fold greater in patients with a positive OSA screening and 21-fold greater in those who had respiratory-specific events, with the highest risk for complications in patients with both a positive screen and recurrent events during Phase I recovery (Fig. 3) [39]. Another study that examined emergent naloxone administration to treat respiratory depression or opioid-induced oversedation after discharge from the PACU found that patients who had a single episode of respiratory depression in the PACU were at fivefold increased risk for subsequent administration of naloxone following PACU discharge [55]. A case-matched control study examining the outcomes of patients administered naloxone in the PACU for respiratory depression found those patients were at increased risk for postoperative adverse events [56]. The subset of patients administered naloxone and discharged from the PACU to the ICU had similar rates of complications as the controls, but the other subset of patients discharged to standard postoperative wards were at increased risk [56]. These studies, albeit from a single institution, suggest that episodes of respiratory depression during Phase I recovery can be useful in tailoring postoperative care for specific patients [54]. The current practice at the Mayo Clinic, Rochester, MN, for patients who meet Phase I discharge criteria but experienced recurrent respiratory events is to apply continuous pulse oximetry and admit the patient to telemetry bed.

Risk factors for postoperative respiratory depression

Several risk factors have been associated with respiratory depression in the PACU. The most important variable is the presence of OSA. In a study by Gali et al., more patients with a positive OSA screening had a respiratory event than those without a positive screen (45% vs. 35%, P = 0.043). Among patients undergoing elective total joint arthroplasty surgery under general anesthesia, a history of positive screen for OSA was found to be associated with respiratory depression during Phase I recovery

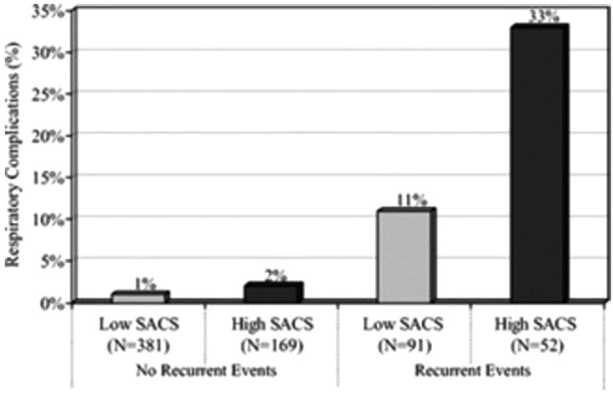

Fig. 3. The percent of surgical patients who experienced postoperative respiratory complications as a function of preoperative assessment for OSA and episodes of respiratory depression during Phase I recovery [39]. The frequency of postoperative respiratory events is displayed according to the four patient groups defined by the combination of sleep apnea clinical score (SACS) (low/high) and recurrent postanesthesia care unit (PACU) events (no/yes). From a multiple logistic regression analysis, which included SACS group and recurrent PACU events as explanatory variables, the likelihood of postoperative respiratory events was found to be significantly associated with high SACS (odds ratio = 3.5, P = 0.001) and recurrent PACU events (odds ratio = 21.0, P < 0.001). Used with permission from: Gali B et al. Anesthesiology. 2009; 110: 869–77 [39].

[57]. Several components of the anesthetic management have been associated with respiratory depression including increased doses of perioperative opioids, the use of sedating-nonopioid medications such as midazolam and gabapentin, and the use of more soluble anesthetic volatile agents such as isoflurane [57,58]. Changes in perioperative management that decreased the administration of such medications were associated with decline of respiratory depression in the PACU [57,58]. However, it is not known whether a reduction in respiratory events *vis-à-vis* changes in anesthetic management would equate to lower rate of postoperative complications.

Postoperative monitoring strategies: pulse oximetry and other modalities for assessment of respiratory depression

In most contemporary practices, patients hospitalized in standard wards undergo intermittent evaluations of vital signs [59]. However, with regard to detecting opioid-induced respiratory depression, this practice is considered to have only low-moderate sensitivity, specificity, and reliability. Traditional estimates of the incidence of opioid-induced respiratory depression suggest a rate of less than 1%, but these estimates may not be accurate because they rely on variable definitions of respiratory depression (hypoxemia vs hypopnea) or on retrospective data [60].

Continuous pulse oximetry is considered superior to intermittent vital sign checks for the detection of opioid-induced respiratory failure. In patients without supplemental oxygen, this modality is considered to have high sensitivity and reliability, moderate to high specificity, and fast response time. The application of supplemental oxygen reduces sensitivity and specificity to moderate and response time to slow, but the reliability is still considered to be high. Using continuous pulse oximetry, a prospective study from the Cleveland Clinic of noncardiac surgical patients found that 21% of them had oxyhemoglobin saturation (SpO_2) of 90% for an average of $\geq$10 min/h and 8% had for an average of $\geq$20 min/h, whereas 8% had $SpO_2 < 85\%$ for $\geq$5 min/h [48]. Further, 3% of postsurgical patients had $SpO_2 < 80\%$ for $\geq$30 min [48]. In contrast, intermittent vital sign assessments only identified hypoxemia in 5% of patients and missed 90% of hypoxemic episodes where SpO_2 was <90% for at least an hour [48]. A smaller study of 178 postsurgical patients who self-administered opioids by using a patient-controlled analgesic device found that 12% developed hypoxemia ($SpO_2 < 90\%$) and 41% developed bradypnea (<10 breaths per minute for >3 min) [61]. One possible mechanism as to why intermittent vital sign checks are inferior to continuous pulse oximetry was suggested by the observation that SpO_2 values were 6.5% greater with manual measurement than with automated measurements [62]. This observation suggests that sedated patients may become aroused in response to manual vital sign measurements; thus, opioid-induced respiratory depression is masked.

The introduction of continuous pulse oximetry with telemetry may have positive impact on patient care [59]. Taenzer et al. [59] described the impact of the introduction to postsurgical ward a system that utilized continuous pulse oximetry with the capability of sending notifications to nursing staff through a wireless pager. They observed that rescue events (defined as the activation of a medical rescue team) decreased from 3.4 to 1.2 per 1000 patient discharges, and ICU transfers from 5.6 to 2.9 per 1000 patient days, while there was no change in these outcomes in two similar wards where this surveillance system was not introduced [59].

However, consensus is lacking as to what degree of oxyhemoglobin desaturation (or duration of this "low level" of desaturation) constitutes clinically relevant hypoxemia from opioid-induced respiratory depression [63]. Further, reliance on hypoxemia to identify opioid-induced respiratory depression can be problematic, especially in the setting of supplemental oxygen. This was demonstrated by Fu et al. [46] who examined the effects of hypoventilation and varying degrees of inspired oxygen (FiO_2) on oxyhemoglobin saturation. At normal levels of inspired oxygen, hypoventilation was readily manifested by the development of hypoxemia [46]. However, slight increases in the percentage of inspired oxygen delayed the development of hypoxemia in the setting of profound respiratory depression [46]. The common practice of application of supplemental oxygen has a detrimental effect on the sensitivity of pulse oximetry and diminishes its value to detect early signs of opioid-induced respiratory depression. Technologies to assess ventilation such as bedside capnography, acoustic monitoring of respiration, and transthoracic impedance plethysmography have been developed and assessed for practical widespread utilization. Such novel monitors that directly measure the respiratory drive could

prove superior to pulse oximetry as hypoxemia is only a surrogate variable for depressed respiratory drive.

Another intermittent assessment that may be valuable in identifying patients at risk for opioid-induced respiratory depression is sedation scores. Data from the Anesthesia Closed Claims Project database on postoperative opioid-induced respiratory depression found that 62% of cases had nursing evaluations before the event that noted patient somnolence [47]. Increased appreciation by healthcare staff that opioid-induced somnolence could be an early warning sign for impending hypercapnic respiratory arrests might improve the value of intermittent assessments.

Timing of postoperative respiratory depression

Given the limitations of current monitoring technology, improved understanding of when patients are at increased risk for hypercapnic respiratory arrests would help tailor postoperative monitoring. A review of emergent naloxone administration to treat opioid-induced respiratory depression or over-sedation in postsurgical patients admitted to standard wards found that 58% of administrations occurred within 12 h of PACU dismissal and 88% within the first 24 h (Fig. 4) [55]. Similarly, the Anesthesia Closed Claims Project analysis of postoperative opioid-induced respiratory depressive events found that 88% occurred within the first 24 h and 12% within the first two postoperative hours [47]. Ramachandran et al.'s [64] audit of their postoperative critical events found that 34% events occurred within the first six postoperative hours and 81% during the first day; Taylor et al. [65] similarly found that 56.5% events occurred within 12 h and 77.4% within the first day. The consistency of these reports suggests the first few hours following Phase I discharge represent a period of high risk and an opportunity to target monitoring resources.

Respiratory depression after neuraxial opioids

A well-known exception to these observations of the timing of hypercapnic respiratory arrests is the administration of opioids to the neuraxial space. The timing of respiratory depression in these cases is

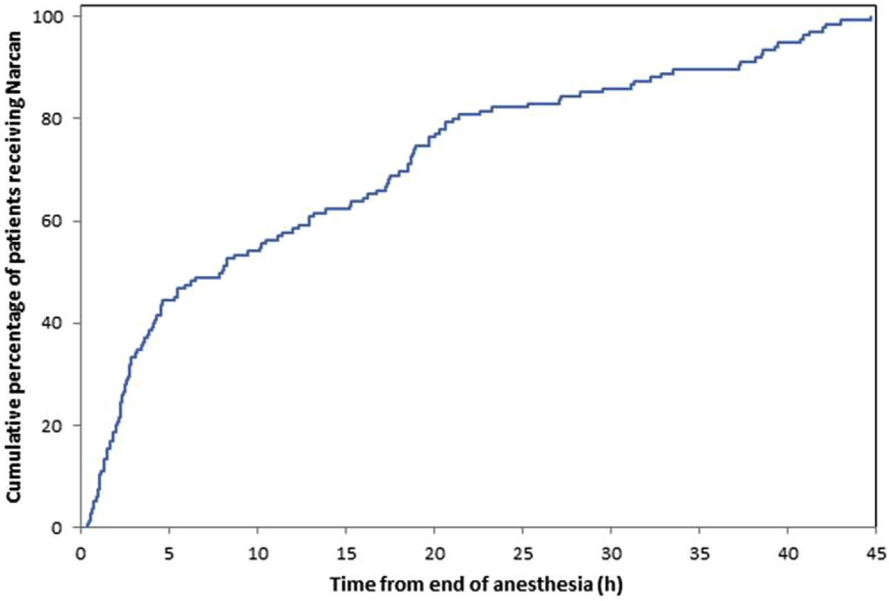

Fig. 4. Cumulative frequency of time after discharge from anesthesia care to naloxone administration. Used with permission form Weingarten TN et al. Anesth Analg. 2015; 121: 422–9 [55].

complex and related to the hydrophilicity of the opioid and location of the injection. Intrathecal administration of the hydrophilic opioid, morphine, has a typical onset of respiratory drive at 2–4 h, peak effect of 5–10 h, and resolution by 20 h. Epidural administration of morphine produces a biphasic pattern with initial absorption by epidural veins, causing effect at 2 h, followed by cephalad spread through the cerebral spinal fluid, causing depression at 8 h with effects lasting to 24 h following injection. Lipophilic opioids rapidly diffuse from the neuroaxial space and undergo systemic absorption. This results in earlier development of respiratory depression, with peak effect approximately 2 h after administration and resolution by 8 h. The optimal period of observation for patients administered neuroaxial opioid analgesia is outlined by the 2009 guidelines from the ASA Task Force on Neuraxial Opioids [66].

Opioids and SDB

SDB is a chronic breathing disorder ranging from uncomplicated snoring to OSA, CSA, and OHS. OSA is characterized by upper airway obstruction, resulting in intermittent hypoxemia and recurrent episodes of sleep arousal. In the general adult population, its prevalence ranges from 9% to 25% [67], but many are not diagnosed and not treated, increasing their risk of perioperative complications [43]. The prevalence of OSA is even greater in bariatric patients and can exceed 70% [68].

Unlike OSA, CSA is a cluster of conditions that represent decreased respiratory drive resulting in hypoventilation during sleep. CSA can be associated with other comorbid conditions (e.g., congestive heart failure and other neurologic diseases) but can also be caused by medications. Chronic opioid users are at increased risk of developing CSA with a mean prevalence of 24% (range 14–60%) [69].

The term OHS comprises a combination of obesity (BMI >30 kg/m^2) and daytime hypercapnia ($PaCO_2$ >45 mmHg) in the absence of an alternative explanation (i.e., neuromuscular, mechanical, or metabolic) for hypoventilation. The prevalence is approximately 0.15–0.6% in the general population and up to 50% in those with BMI >50 kg/m^2 [70]. A 10–20% of OSA patients may have OHS.

Joint Commission has declared that there has been an increase in perioperative opioid administration and a higher incidence of opioid induced respiratory depression. Overall, the morbidity and mortality associated with opioids have increased [44,45]. Because of well-established connection between opioid use and SDB [71,72], concerns have been raised that administrating opioids to patients with coexisting SDB may worsen SDB. Approximately 70–85% of the patients on opioids have some degree of SDB postoperatively [69]. Elderly patients with OSA and higher 72 h total dose of opioids are both risk factors for worsening of apneas and hypopneas postoperatively, whereas male patients and general anesthesia are also risk factors for worsening CSA postoperatively [73].

Preoperative screening

The following questionnaires have been evaluated and validated for identifying patients at risk of OSA in surgical population: STOP-Bang [74], Berlin [75], ASA checklist [75], and perioperative sleep apnea prediction score [76]. The inclusion of preoperative serum bicarbonate level may improve the predictive accuracy of the screening instrument [77]. Serum bicarbonate is an important marker for identifying daytime hypercapnia, and levels above 27 mmol/L are suggested to predict OHS [78].

The STOP-Bang Questionnaire is the most validated screening questionnaire for high-risk OSA patients during the perioperative period [74]. It consists of eight dichotomous (yes/no) items linked to the clinical features of sleep apnea. The total score ranges from 0 to 8. Patients can be classified for OSA risk based on their respective scores. Patient with STOP-Bang scores 5–8 have a high possibility of having moderate to severe OSA [79]. Conversely, patients with STOP-Bang scores 0–2 are less likely to have OSA [74].

OSA and perioperative complications

In surgical population, patients with known or suspected OSA are associated with an increased risk of perioperative complications [80]. OSA patients have increased sensitivity to anesthetics, sedatives, and opioids, leading to impaired ventilatory responsiveness to hypercapnia and hypoxemia. However,

when obese patients diagnosed with OSA and managed accordingly, the severity of OSA was not associated with the rate of perioperative complications [81].

Pain perception in patients with OSA

Opioid-based perioperative management of pain can be challenging in OSA patients as both pain processing and sensitivity to opioids are altered [82]. Certain pathophysiological characteristics of the disease (e.g., chronic intermittent hypoxemia, sleep disruption, and altered inflammatory response) can enhance the perception of resting pain by increasing the expression of hyperalgesic markers or by acting on central pain modulators [83]. For example, a decrease in oxyhemoglobin saturation from 92% to 75% can double the odds of perceiving pain [84]. Chronic intermittent hypoxemia also increases the number of μ-opioid receptors resulting in increased sensitivity to respiratory effects of opioids [85].

The evidence regarding the association between intermittent hypoxemia, pain perception, and opioid analgesic effects are limited (Table 2) [82]. In a prospective observational study, children with OSA undergoing tonsillectomy received less opioid but had increased incidence of opioid-related respiratory events [86,87]. In other studies of OSA patients, intermittent hypoxemia and increased serum hypoxemic markers and pro-inflammatory mediators were associated with enhanced pain perception [88] and increased opioid sensitivity [89,90]. Intermittent hypoxemia and the degree of preoperative SpO_2 nadir may influence postoperative opioid requirements [91]. CPAP can mitigate sleep disruption and intermittent hypoxemia, which may decrease inflammatory products and sensitivity to pain [92].

Effects of opioids on OSA phenotypes

OSA is a complex multifactorial disease with distinct phenotypes, and this may account for differing sensitivities to opioids among different subgroups [93]. The main physiological determinants encompassing various OSA phenotypes include (i) the propensity to wake up from respiratory stimulus during sleep, (ii) the ability of upper airway dilator muscles to respond to pharyngeal obstruction during sleep, and (iii) the inherent stability of the respiratory control system.

Some OSA patients have a high threshold for arousal, which implies a lower propensity to arouse from sleep because of hypoxemia. Opioids and other sedating medications can delay arousal, which may precipitate an “arousal arrest” leading to death [94]. Unfortunately, there is no conventional way to assess arousal thresholds preoperatively. The Anesthesia Patient Safety Foundation has recommended continuous monitoring of postoperative patients on opioids with high-resolution pulse oximetry and possibly capnography to detect early oxyhemoglobin desaturation. The use of regional anesthesia and multimodal analgesia may be beneficial in selected OSA patients [95].

Table 2
Literature evidence for the association between intermittent hypoxia and pain perception and/or opioid analgesic effect [82].

Investigations	Exposure	Outcomes	
		Pain perception	Opioid analgesic effect
Experimental			
Smith, 2009 [83]	OSA	Decreased	–
Khalid, 2011 [92]	OSA	Increased	–
Doufas, 2013 [89]	Nadir SaO_2	–	Increased
Prospective			
Brown, 2006 [88]	Nadir SaO_2	–	Increased
Sadhasivam, 2012 [86]	OSA	Increased	Decreased
Sanders, 2006 [87]	RDI	–	Decreased
Retrospective			
Brown, 2004 [91]	Nadir SaO_2		Increased
Doufas, 2013 [84]	Nadir SaO_2	Increased	–
Turan, 2015 [90]	Time at SaO_2 <90%	–	Increased

Modified with permission form Lam KK et al. Curr Opin Anaesthesiol. 2016; 29: 134–40. [82].

Another important variable in the phenotypic description of OSA is the response of upper airway dilator muscles to pharyngeal obstruction during sleep [30]. Pharyngeal abductors are modulated by three mechanisms: (i) central respiratory drive (increasing $PaCO_2$ and declining PaO_2), (ii) negative pressure reflexes during inspiration, and (iii) cortical arousal drive. During airway obstruction, the increasing $PaCO_2$, declining PaO_2, and the negative airway pressure restore the airway patency by gradually increasing the contraction of the pharyngeal dilators. The opioid-induced decreased central respiratory drive to hypoxemia and hypercapnia could decrease the neural output to upper airway dilator muscles resulting in airway collapsibility [96].

Some OSA patients have a propensity to develop a cyclical breathing pattern oscillating between obstructive breathing events (sleep) and arousal (wakefulness), without reaching a stable pattern of breathing. This instability in ventilatory control is defined by a phenomenon called "high loop gain" [97]. High loop gain is characterized by an augmented ventilatory response to hypoxemia and hypercapnia. The hyperventilation culminates in hypocapnia and decreased respiratory drive. This can result in decreased tone of the upper airway dilator muscles that receive the central neural output leading to upper airway obstruction. Further, hypocapnia can also precipitate central apnea, which subsequently leads to hypoxemia or hypercapnia, perpetuating the cycle of instability leading to periodic breathing [93].

Ventilatory control is highly sensitive to changes in carbon dioxide pressure during non-slow-wave sleep or non-rapid eye movement (REM) sleep [98]. Even a minor hypocapnia in non-REM sleep can precipitate central apneas. Opioids increase the non-REM sleep and decrease slow-wave sleep. This prolonged non-REM sleep can precipitate episodes of ventilatory instability and thereby central apnea in patients with OSA [98].

Chronic opioid therapy and CSA

In patients on chronic opioid therapy, the presence of risk factors such as male gender, older age, history of stroke, brain tumor, and/or congestive heart failure can exacerbate CSA. At-risk patients may develop opioid-induced impaired ventilatory drive leading to CSA [60]. The balance between hypoxic and hypercapnic ventilatory drive may be altered in patients on chronic opioid therapy such that the hypoxic drive to breathing may recover, while the hypercapnic drive remains depressed. Characteristically, patients on opioids develop a breathing pattern manifested by episodes of hypoventilation followed by increased ventilation in response to hypoxemia [99]. In addition, patients on chronic opioid therapy often develop borderline hypercapnia ($PaCO_2 > 45$ mmHg).

Chronic opioid therapy in patients with sleep-disordered breathing

The disadvantages of long-term opioid therapy to treat chronic pain are being increasingly recognized. This is especially true for patients with SDB. The Centers for Disease Control and Prevention guidelines for non-cancer chronic pain recommend that if opioids are indicated, treatment should be initiated with immediate release medications rather than extended release medications [100]. The immediate release medications have lower risk for overdose and respiratory depression. In contrast, extended release medications should be reserved for patients with severe pain who failed the initial treatment with immediate release medications.

In the setting of opioid therapy, it is important to consider the possibility of SDB. Treatment of underlying obstructive components of SDB is the logical basis for the use of CPAP. However, in patients with primarily CSA, CPAP can be ineffective and may aggravate CSA [69]. Devices that permit independent adjustment of inspiratory and expiratory pressures such as BPAP can be used to treat the central and obstructive components of SDB. A recent systematic review reported the effectiveness of BPAP in eliminating CSA in 62% of patients on chronic opioids [101]. ASV provides the variable inspiratory support on a breath-by-breath basis, above the expiratory pressure, to regulate ventilation and prevent hypocapnia-induced central apneas. The current literature supports the use of ASV for the treatment of CSA associated with chronic opioid use, and it is found to successfully treat CSA in patients unresponsive to CPAP. The studies supporting the use of ASV demonstrated a significant reduction in

AHI and central apnea index; however, they failed to show the impact of ASV on patient symptoms, quality of life, and long-term health outcomes [102].

Summary

Although opioids are the mainstay of pain management, they can be associated with hazardous respiratory depression. Postoperative opioid-induced respiratory depression can lead to hypercapnic respiratory failure, leading to serious morbidity or death. Opioids and sedatives in the presence of SDB may indicate increased vulnerability to respiratory depression. Identifying patients at risk can allow for modifications of perioperative management. Observations of respiratory depression during Phase I recovery can be used to further refine the identification of higher risk patients. Intermittent vital sign evaluations may be inadequate for the contemporary era. Continuous pulse oximetry with telemetry features has been shown to reduce the need for rescue events and ICU transfers. It must be appreciated that measurement of oxyhemoglobin saturation by pulse oximetry provides a crude measure of ventilatory drive, especially with the administration of supplemental oxygen. In certain high-risk patients, opioid reduction or an opioid-free anesthesia may not be possible due to severe postoperative pain. To prevent "failure to rescue" and adverse outcome, vigilant monitoring should be considered if opioids are administered. We should be aware that chronic opioid therapy is often associated with CSA, the diagnosis and management of which can be challenging.

Practice points

- Identifying surgical patients with high risk of sleep apnea may help to risk stratify the perioperative management of these patients.
- The inclusion of preoperative serum bicarbonate level to STOP-Bang scores may improve the predictive accuracy of identifying high-risk patients with SDB.
- During Phase I recovery, high-risk OSA patients should be monitored for respiratory-specific adverse events such as bradypnea, apnea, desaturation, and sedation-analgesia mismatch.
- Continuous monitoring is considered superior to intermittent vital sign checks for the detection of opioid-induced respiratory depression.
- Increased opioid-induced somnolence could be an early warning sign for impending hypercapnic respiratory arrests.

Research agenda

- Research is needed to identify specific phenotypes of OSA that are prone to respiratory depression during the perioperative period.
- Studies are required to evaluate the effectiveness of continuous pulse oximetry and capnography on patient outcomes.
- Efforts are needed to improve the CPAP compliance during the perioperative period.

Conflict of interest statement

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Opioid-free anesthesia opioid side effects: Tolerance and hyperalgesia

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Opioids are the most potent drugs used to control severe pain. However, neuroadaptation prevents opioids' ability to provide long-term analgesia and produces opposite effects, i.e., enhancement of existent pain and facilitation of chronic pain development. Neuroadaptation to opioids use results in the development of two interrelated phenomena: tolerance and "opioid-induced hyperalgesia" (OIH). Tolerance, a pharmacologic concept, and OIH, a clinical syndrome, have been mostly observed under experimental conditions in animals and in human volunteers. In contrast, their occurrence and relevance in clinical practice remain debated. In perioperative setting, intraoperative administration of high doses of opioids increases postoperative opioid requirements and worsens pain scores (acute tolerance or perioperative OIH). Further, preoperative chronic opioid intake and postoperative long-term use of opioid analgesics beyond the normal healing period have a negative effect on surgical outcome. Conversely, observations of improved patient's recovery after opioid-sparing anesthesia techniques stand as an indirect evidence that perioperative opioid administration deserves caution. To date, perioperative OIH has rarely been objectively assessed by psychophysics tests in patients. A direct relationship between the presence of perioperative OIH and patient outcome is missing and certainly deserves further studies.

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Introduction

A major increase in the use of opioids analgesics for pain control has emerged during the last 20 years [1]. The widespread use of opioids to relieve acute pain (after surgery and trauma)—now considered as "the fifth vital sign"—and the more liberal use of opioids to relieve chronic non-cancer pain have unmasked the perverse effects of these analgesics. In acute pain setting, well-known adverse effects (nausea-vomiting, dizziness, and pruritus) may delay recovery and even harm the patients (deep sedation and respiratory depression). In the context of chronic use, major social issues (abuse, misuse, and unintentional deaths from overdoses) have appeared [1]. Despite that, opioids remain the most potent drugs used to control severe pain. However, neuroadaptation prevents opioids' ability to provide long-term analgesia and produces opposite effects, i.e., enhancement of existent pain and facilitation of chronic pain development [2]. Neuroadaptation to opioids use yields to the development of tolerance and to a phenomenon called "opioid-induced hyperalgesia."

Opioid tolerance and opioid-induced hyperalgesia: rethinking definition, context and perioperative implications

Opioid tolerance and opioid-induced hyperalgesia (OIH) are interrelated phenomena that contribute to pain worsening during opioid administration. Confusion between them may lead to inadequate treatment of the patients [2,3]. While opioid tolerance may be solved by increasing the doses of opioid, OIH is be controlled by tapering the doses of opioid administered.

Tolerance is described as a pharmacological effect, a state of adaptation, in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time [4]. Opioid tolerance is a multidimensional phenomenon as tolerance occurs not only to analgesia but also to nausea, sedation, respiratory depression, and other central nervous system depressive effects of opioids. The progressive lack of response to opioid administration can be explained by a "*within-system adaptation process,*" where the drug elicits an opposite reaction within the same system in which the drug elicits its primary action [2]. This neuroadaptative response will progressively neutralize the drug's effect [Table 1].

OIH refers to increased pain sensitivity due to opioid use. "Hyperalgesia" has been, for a long time, referred to as an increased response to a stimulus that was normally painful. According to a more recent view, hyperalgesia, i.e., increased pain sensitivity, refers to an umbrella term including allodynia, decreased pain threshold, and increased response to suprathreshold stimulation [5]. Moreover, it is mandatory that the paradoxical phenomenon of OIH develops during opioid administration [6]. In practice, the main problem that remains is the definition of OIH and its detection [Table 2]. OIH has often been observed after the administration of opioids (most of the time, after the termination of ultra-short-acting opioid remifentanil infusion), questioning the cause of hyperalgesia: acute tolerance

Table 1
Mechanisms underlying neuroadaptation to opioid use.

Opioid intake simultaneously induces a potent analgesic effect, which masks the concomitant development of the phenomena of	
Opioid Tolerance explained by "Within-system" adaptation theory	**Opioid-induced Hyperalgesia** explained by "Between-system" adaptation theory
Opioid receptors desensitization - internalization - down-regulation - phosphorylation or heterodimerization with other receptors (e.g., chemokine receptors)	Recruitment of opponent neuronal circuits - NMDA - Dynorphins and BDNF - CCK - Neuro-inflammation (interleukin, TOLL-R4)
Opioid tolerance may occur first [45]	OIH might occur after longer time use and higher doses of opioids [45] OIH is a contributor to the development of opioid tolerance [10]

From Rivat and Ballantyne [2] and Simonnet and Rivat [10].

Table 2
Clinical expression of OIH syndrome.

The following symptoms are observed during ongoing opioid administration: 1) Increase in pain intensity over time 2) Diffuse pain or spreading of pain to other locations than the initial painful site 3) Increase in pain sensation, i.e., hyperalgesia and allodynia, to certain external stimuli (such as heat, mechanical pressure, and touch). Other medical conditions such as clinical or pharmacological opioid withdrawal, evidence of underlying disease progression, and evidence of opioid tolerance tested clinically by decreased pain in response to an adequate opioid rescue dose have been excluded.

Adapted from Eisenberg, Suzan & Pud [6]; Katz et al. [9].

or perhaps opioid withdrawal? A recent commentary [3] mentioned increased opioid requirements and worsened pain scores in patients who were exposed to high doses of intraoperative opioids as "perioperative OIH or acute tolerance." In the case of long-term opioid use, OIH might not be rare and might develop during the administration of low and high doses of opioid [7]. OIH typically presents as a rapidly developing tolerance to opioid analgesic effect associated with a change in pain pattern (allodynia, diffuse pain, and central nervous system hyperexcitability such as myoclonic seizures). It is worth noting that hypersensitivity related to opioid administration has rarely been objectively assessed by the application of psychophysics measurements, i.e., quantitative sensory testing (QST), either in perioperative conditions [8] or in chronic pain setting [9]. Hyperalgesia simultaneously occurs with opioid administration but is often masked by the more powerful analgesic effect of the drug [10]. The paradoxical hypersensitivity induced by opioid use may be explained by the "*between-system adaptation*" concept where the recruitment of different neuronal circuits, i.e., specific pronociceptive processes, opposes the analgesic effect of the drug [2] [Table 1].

To summarize, tolerance (a pharmacologic concept) and OIH (a clinical syndrome) have been mostly observed under experimental conditions both in animals and in human volunteers. In contrast, their occurrence and their relevance in clinical practice remain debated [4,5]. The link often observed between tolerance and hyperalgesia seems to suggest that OIH is an important contributor to the development of tolerance [10]. In this study, we review the current knowledge regarding perioperative tolerance and hyperalgesia in the context of acute and chronic opioid administration. Direct evidence and indirect proofs of OIH and their perioperative implications will be considered.

Perioperative opioid tolerance and hyperalgesia: intraoperative opioid administration in opioid-naive patients

Observations in relation with common intraoperative opioids use

Fentanyl and sufentanil, two potent synthetic μ-receptor agonists, are the most often used opioids in the perioperative setting. In experimental conditions, in healthy rats, repeated doses of fentanyl induce a biphasic response, with the analgesic effect followed by a dose-dependent lowering of pain thresholds, indicating the development of hyperalgesia. Moreover, in the same animal model but under inflammatory conditions induced by a carrageenan injection, fentanyl dose-dependently prolonged and enhanced the long-lasting hyperalgesia caused by the inflammatory lesion [11]. In an animal model of bone fracture, Minville et al. showed that while sufentanil produced an analgesic effect early after its administration, it enhanced pain responses to both mechanical and thermal stimuli for up to 4 days [12]. Similar observations have occurred in human volunteers regarding the effect of intravenous fentanyl on pain ratings (electrical stimulation and cold pressor test) and area of pinprick hyperalgesia secondary to intradermal electrical stimulation. The volunteers who received a high fentanyl dose ($10\ \mu g \cdot kg^{-1}$ vs. $1\ \mu g \cdot kg^{-1}$) reported lower pain scores, both during and 4.5–6 h after the infusion. Very interestingly, the same patients also presented with significantly larger areas of hyperalgesia 4.5–6 h after the infusion [13]. In perioperative conditions, the administration of intravenous fentanyl increased morphine consumption up to 12 h after hysterectomy performed under spinal anesthesia,

which could point to acute tolerance development [14]. Similarly, Chia et al. compared pain scores and postoperative fentanyl consumption after hysterectomy and found increases in both outcomes after high-dose (15 $\mu g \cdot kg^{-1}$) vs. low-dose (1 $\mu g \cdot kg^{-1}$) intraoperative fentanyl [15]. In another randomized study, heart surgery patients anesthetized using a high-dose (40–70 $\mu g \cdot kg^{-1}$ followed by 5–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$) vs. low-dose (2 $\mu g \cdot kg^{-1}$ followed by 1–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) fentanyl regimen not only consumed significantly more morphine but also displayed significantly lower mechanical and heat pain threshold on the forearm up to 3 days after surgery. This suggests the development of both acute tolerance and OIH [16]. Devulder reported a case of diffuse pain developing after intrathecal injection of 25 μg of sufentanil (an admittedly very high dose) in a patient with pre-existing neuropathic pain [17]. In a retrospective study, Aubrun et al. found an association between a high dose (>0.6 μg/kg) of intraoperative intravenous sufentanil and the incidence of severe pain in the postanesthesia care unit [18]. More recently, in a randomized trial, Fechner et al. tested the effects on pain scores, morphine consumption, and hyperalgesia area after cardiac surgery of two different sufentanil concentration targets (0.4 $ng \cdot mL^{-1}$ vs. 0.8 $ng \cdot mL^{-1}$) [19]. On the day of the surgery (but not later), patients in the high-dose group (1.03 ± 0.08 $\mu g \cdot kg^{-1} \cdot h$) reported higher pain scores during inspiration and consumed significantly more morphine than those in the low-dose group (0.55 ± 0.04 $\mu g \cdot kg^{-1} \cdot h$), which suggest the presence of acute opioid tolerance. All patients developed primary and secondary hyperalgesia in the days following surgery, but without differences between the groups. Despite their widespread use, fundamental and clinical data on the development of tolerance or hyperalgesia following fentanyl or sufentanil administration in the perioperative period remain scarce.

Remifentanil, whose unique pharmacokinetic properties combines a fast onset of action with a predictable and rapid recovery independent of the infusion duration, is frequently used in total intravenous anesthetic regimen [20]. For over a decade, however, numerous animal, human volunteer and clinical studies have suggested that the use of remifentanil is associated with the development of acute tolerance and OIH [20]. In human volunteers, the potential of remifentanil to increase the area of mechanical hyperalgesia induced by electrical stimulation or topical capsaicin has been demonstrated [20].

In 2014, Fletcher and Martinez [8] published a meta-analysis on postoperative OIH. They included 19 prospective studies comparing pain scores, morphine consumption, and hyperalgesia after high- vs. low-dose remifentanil or placebo in adult patients undergoing surgery. The authors concluded that high intraoperative doses of remifentanil are associated with significant increases in acute pain intensity and increased morphine use during the first 24 h after surgery. Data pooled from four studies showed the development of hyperalgesia in the high-dose remifentanil group [8]. Using the same search terms, we found five more recent prospective studies comparing high and lower doses of intraoperative remifentanil infusion [Table 3]. For remifentanil, the opioid for which we have the most evidence for OIH and acute tolerance, the cumulative intraoperative dose seems to be important. Fletcher and Martinez demonstrated that higher doses of remifentanil increased pain scores, morphine consumption, and area of hyperalgesia but could not define a cut-off value [8]. In a more recent review, however, Angst suggested a threshold of 50 $\mu g \cdot kg^{-1}$ for acute tolerance and 40 $\mu g \cdot kg^{-1}$ for remifentanil-induced hyperalgesia [20]. The impact of the way the remifentanil infusion is stopped at the end of surgery has recently come into investigation. In a randomized, double-blinded, placebo-controlled, crossover study, Comelon et al. compared cold- and heat-induced pain scores in healthy volunteers receiving a remifentanil infusion (target concentration 2.5 $ng \cdot mL^{-1}$). Cold pain scores were higher than those at baseline after both abrupt and gradual withdrawal, indicating OIH development. Heat pain scores, however, were only higher than baseline after abrupt withdrawal and not after gradual withdrawal. The authors concluded that the gradual withdrawal of remifentanil protected from the development of OIH to heat-induced pain [23]. This concept was tested in a clinical setting by Han et al. They investigated whether stepwise tapering of remifentanil at the end of thyroid surgery would influence pain scores during the first postoperative 24 h. All patients received desflurane and high-dose remifentanil (0.30 $\mu g \cdot kg^{-1} \cdot min^{-1}$) anesthesia. In half the patients, this dose was continued until the end of surgery. In the other half, the anesthetist in charge began tapering remifentanil 30 min before the end of surgery. While the total remifentanil dose was similar between the groups, pain scores were significantly lower in the latter group, 30 min and 2 h (30 [10–60] vs. 40 [20–80], $P = 0.018$) after surgery. As the investigators did not measure pain sensitivity, no conclusion can be drawn regarding hyperalgesia [24].

Table 3
Recent prospective studies comparing low- and high-dose remifentanil in surgical patients.

	Number of patients	Type of surgery	Anesthesia protocol	Intervention	Outcome measured	Results	Comments
Treskatsch et al. [62]	30	Lower abdominal surgery	Sevoflurane, no nitrous oxide	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Pain NRS 0, 1, 2, 3, 4, and 6 h. PCA iv morphine 6 h. PONV.	No difference between groups.	High dose still relatively low. Small number of patients. Hyperalgesia not measured.
Kim et al. [63]	126	Breast surgery	Propofol TIVA, no nitrous oxide	Remifentanil 5 ng·mL vs. 10 ng·mL	Pain VAS 0, 30 min, 6 h, and 24 h. PONV 0, 30 m, 6 h, and 24 h.	No difference between groups.	Pain only secondary endpoint. Low dose could be considered high dose. Hyperalgesia not measured.
Zhang et al. [64]	60	Thyroidectomy	Propofol TIVA, no nitrous oxide	Remifentanil 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Pain VAS 20, 45, 60, 75, and 120 min and 18 −24 h. Mechanical pain threshold preoperative, 2 h and 18–24 h. IV morphine 24 h.	Pain scores (only at 30 min) reduced in HD group. Reduced mechanical pain threshold at 2 and 18 −24 h.	Clinical significance unclear (only difference in pain at 30 min could conceivably be explained by higher residual plasma concentrations). Lowered mechanical pain threshold in both groups.
Yamashita et al. [65]	30	Gynecological surgery	Sevoflurane, no nitrous oxide	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Cumulative epidural local anesthetic/ fentanyl consumption at 48 h after surgery. NRS at 1, 3, 6, 12, 24, and 48 h.	Cumulative amount of local anesthetic significantly greater in the HD group, no difference in pain scores.	Small number of patients.
Koo et al. [66]	120	Pancreas surgery	Sevoflurane, no nitrous oxide	Remifentanil 1 ng·mL vs. 4 ng·mL	Cumulative morphine consumption at 1, 3, 6, 12, 24, and 48 h. NRS at 1, 3, 6, 12, 24, and 48 h.	No difference between groups.	High dose still relatively low. Hyperalgesia not measured.

NRS: numerical pain rating; VAS: visual analog scale; PONV: postoperative nausea and vomiting; PCA: patient-controlled analgesia; HD: high-dose.

Evidence for and clinical relevance of OIH in perioperative patients

On the one hand, the effect of an intraoperative administration of opioid, and specifically the use of ultra-short opioid such as remifentanil, certainly deserves attention because pain after surgery remains poorly controlled. Intraoperative use of high doses of opioids and short-duration opioids may inadvertently cause higher acute postoperative pain, which in turn induces a need of greater postoperative analgesic consumption and perhaps could lead to long-term analgesics use [1]. On the other hand, a few clinical studies have highlighted the capacity of opioids to increase the area of secondary hyperalgesia surrounding the surgical wound. In their landmark paper on patients undergoing major abdominal surgery, Joly et al. demonstrated that the area of mechanical hyperalgesia was significantly bigger if patients had received a high (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) vs. a low (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dose of intraoperative remifentanil. Pain scores—and surprisingly, pressure pain thresholds—were not different between the groups [25]. Similarly, reducing the total remifentanil dose using a target-controlled infusion as opposed to a continuous infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ markedly decreased the extent of mechanical hyperalgesia around the wound up to 4 days after cardiac surgery [26]. Song et al. randomized thyroidectomy patients to a high- (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and low-dose (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) remifentanil anesthesia regimen and found a greater decrease in the peri-incisional mechanical pain thresholds in patients in the high-dose group up to 48 h postoperatively [27]. Similar results have been reported after gynecological and urologic surgeries [28]. Furthermore, opioids also seem to be able to induce or increase hyperalgesia in parts of the body that have not been operated, e.g., remifentanil after dental surgery [29] and fentanyl after cardiac surgery [16].

The clinical relevance of enhanced hyperalgesia, specifically secondary hyperalgesia, in the acute postoperative period is still debated, but several studies showed an association between its extent and the development of chronic pain after various procedures [30], e.g., abdominal, iliac crest harvest, or thoracic surgery [31]. Moreover, the use of remifentanil is dose-dependently associated with the risk of persistent pain after cardiac surgery [32]. As chronic pain after surgery is a major clinical problem—affecting between 10% and 50% of patients, depending on the type of surgery and significantly worsening quality of life of those afflicted—its prevention by limiting the use of intraoperative opioids deserves future research [33]. Here it is mandatory to note that only a minority measured pain threshold or extent of hyperalgesia, which makes it impossible to differentiate tolerance from OIH [5]. Moreover, pain ratings and hyperalgesia do not always go hand in hand, as was nicely demonstrated in a study on healthy volunteers by Mauremann et al., where subjects receiving a high dose of fentanyl reported with decreased pain intensity but increased area of hyperalgesia [13]. Clinical studies have shown similar findings, like in the elegant study by Schmidt et al., where patients without significant postoperative pain at the incision site had markedly lower pressure pain tolerance thresholds at the palmar carpus of the right hand if they had received a high remifentanil dose during surgery [29]. Other studies that reported both outcomes found the same results after thyroidectomy [22], abdominal [25], and thoracic surgery [26,31]. As mentioned previously, the importance of postoperative hyperalgesia is increasingly recognized as a risk factor for the development of chronic pain.

Perioperative opioid tolerance and hyperalgesia: impact of chronic opioid intake

Chronic opioid intake in the perioperative period concerns a non-negligible number of patients. On the one hand, preoperative opioid consumption seriously complicates perioperative management. Clinical studies involving in- and out-patients report that 50–60% of the patients present with pain during the preoperative visit, with up to 38% of them taking some opioid analgesics to relieve their pain, generally musculo-skeletal pain [34,35]. Perioperative management of these patients is often challenging with increased postoperative opioids consumption (i.e., tolerance) [34,36]. Further, despite higher opioids use, patients also report more severe postoperative pain scores, which might be taken as a sign of OIH [36,37]. According to the concept of pain trajectories, patients with chronic pain resolve their postoperative pain more slowly after surgery than patients without preoperative pain [37]. Moreover, preoperative opioid intake further increases postoperative pain scores [38] and may place patients at higher risk to develop chronic postsurgical pain compared to patients with chronic pain who do not take preoperative opioids [38].

On the other hand, long-term postoperative opioids intake also negatively impacts patient-reported outcome measures, being usually associated with poor satisfaction and functional status [39]. Patients consuming preoperative opioids are at higher risk for long-term postoperative opioid intake. The literature also reports a 3–7% incidence of prolonged opioid use after surgery among patients who were not preoperative users. The epidemic problem of opioid consumption in the US reveals that prescription opioids have become regarded as "a gateway drug" to heroin [1]. Numerous patients continue to use postoperative opioid analgesics far beyond the normal healing period [1,40].

To summarize, chronic opioid intake in the perioperative period stands as a major problem. The issue is not the use of opioids to relieve severe postoperative pain. The question is to what extent perioperative management of opioid analgesics can interfere with patient's recovery.

Chronic opioid intake: is tolerance an overestimated phenomenon?

A systematic review about patients taking long-term opioids (oral, transdermal, or intrathecal use) to alleviate chronic noncancer pain demonstrated that 12–22% discontinued treatment due to adverse effects, while 6–10% stopped opioid intake due to lack of efficacy [41]. Several reasons can contribute to opioid treatment failure including the development of tolerance and hyperalgesia, which both interfere with opioids' ability to provide long-term analgesia. It is generally assumed that the development of tolerance to the analgesic effect takes time. Among patients under long-term extended release opioids (i.e., median duration of treatment: 311 days), more than 30% never change their opioid dose, and for others, changes are modest [42]. Dose escalation during chronic opioid treatment and increased postoperative opioid consumption in those patients might not be the most adequate measure for opioid tolerance because other causes might be involved such as underlying disease progression, existence of pre-existing pain, anxiety, and depressive mental state. In contrast, a small study including patients with chronic low back pain has demonstrated the development of analgesic tolerance after only 1 month intake of an average dose of 75 mg (range 30–120 mg) morphine per day [43]. The patients also developed hyperalgesia assessed by cold pressor test within 1 month of morphine treatment. That questions the relationship between opioid tolerance and OIH. It is commonly admitted that OIH is a major contributor to the development of analgesic tolerance. Chu et al., studying patients with chronic low back pain, found that opioid tolerance may develop in the absence of concomitant OIH [44]. In their study, 42% of the patients taking an average dose of 78 mg morphine per day for 1 month, with a positive therapeutic benefit on pain and function, developed analgesic tolerance to a remifentanil infusion without evident basal OIH. These results suggest that "with-in system" adaptation may first occur to oppose analgesia and may be accompanied by OIH after longer term opioid therapy or perhaps higher daily dose of opioid intake [44]. Before closing the discussion about opioid tolerance, it is mandatory to underline that differential tolerance may put patients at significant risk [3]. For example, while tolerance to the gastrointestinal side effects develops more slowly and to a lesser degree, no tolerance develops to the respiratory depressant effects of opioids, and therefore, patients on chronic opioids remain highly sensitive to additional opioids administration [please refer to other chapter: chapter 3].

Chronic opioid intake: is opioid-induced hyperalgesia an underestimated phenomenon?

As generally believed, OIH only develops after long-lasting opioid use and with high doses of opioid intake. By definition (Table 2), increased pain sensitivity should develop during opioid administration [6]. In a previous evidence-based structured review, Fishbain [45] questioned the evidence of OIH in humans and highlighted several confounders. Today, it must be acknowledged that the prevalence of clinical OIH during chronic opioid treatment remains unknown. A hyperalgesic state has often been observed on former opioid abusers under the methadone maintenance therapy, but these reports remain subject to caution because opioid addicts personality may affect QST [45]. Moreover, the major problem regarding the diagnosis of clinical OIH relies on the lack of consensus regarding which psychophysics test (QST) might be the most appropriate. The systematic review by Katz et al. [9], including 14 RCTs conducted in patients with chronic pain, indicated that most of the sensory modalities tested to date have failed to demonstrate opioid hypersensitivity. Different findings with different pain

modalities (i.e., heat pain, cold pain, pressure pain, etc.) do not necessarily imply inconsistency but rather demonstrate that opioids modulate the different nociceptive systems in different ways [45]. A recent study assessing OIH in community-dwelling adults with chronic pain found that long-term opioid use (average 60 mg morphine equivalent dose (MED) per day; IQR: 30–120 mg) was associated with hyperalgesia demonstrated by altered heat pain perception [46]. Moreover, the capacity of opioids to modulate endogenous pain processes (Table 1) may contribute to the development of OIH. Assessment of endogenous pain processes, either inhibitory or excitatory ones, requires the application of specific QST, also called "dynamic" tests, such as conditioned pain modulation (CPM) or temporal summation (TS) in contrast with "standard" psychophysics tests such as pain threshold and tolerance [47]. Here it is worth noting that dynamic QST have demonstrated interesting predictive values for both severe acute postoperative pain and development of persistent pain after surgery [47]. Opioid dose and treatment duration negatively affect inhibitory pain processes, as assessed by the CPM test [48]. In addition, excitatory processes are also boosted as temporal summation of second pain, which is enhanced in patients with chronic pain under opioid treatment (daily dose > 75 mg MED) [49]. Hina et al. [34] found that 50% of opioid-treated patients (average MED 42 ± 25 mg per day) scheduled for orthopedic surgery presented with hyperalgesia including positive TS. Going one step further, the clinical relevance of QST, which assess only one pain modality, e.g., heat, cold, pressure, etc., can be questionned. To date, very few studies have utilized a standardized "clinically relevant" stimulus (i.e., a "multimodal" stimulus that can induce some tissue lesion) as the nociceptive stimulus to assess OIH in patients [50,51]. Two studies tested a subcutaneous lidocaine injection prior to an interventional therapeutic procedure in patients with chronic pain. Subjects taking more than 30 mg MED per day reported higher preinjection pain score. Postinjection pain intensity and unpleasantness, however, were greater in patients taking more than 90 mg MED per day [50]. Not only the dose but also the duration of opioid treatment seemed to correlate with pain and unpleasantness scores. Unpleasantness experience might be an indicator of pain tolerance and might reflect OIH effect on pain processing (modulatory endogenous processes and cognitive and emotional components) better than it does on nociceptive transmission [50].

Hyperalgesia simultaneously occurs with opioid administration [10] but is effectively masked by the powerful analgesic effects of the drug. A study has investigated the relationship between analgesic effect and hyperalgesic effect of chronic hydromorphone treatment in patients suffering from neuropathic pain [52]. The authors found that OIH negatively correlated with the analgesic effect of hydromorphone. In addition, opioid dose was directly correlated with the extent of OIH and reversely correlated with the magnitude of clinical analgesia [52]. This study indicates the necessity to assess the individual patient. A similar conclusion has been made by Katz et al. [9] in their systematic review: there is clearly a need for further studies to identify the proportion of patients developing OIH during chronic opioid treatment. For example, 55% of patients with neuropathic pain under hydromorphone treatment presented with heat hypersensitivity [52], and 50% of patients with preoperative pain taking opioids before orthopedic surgery expressed positive TS and hypersensitivity [34]. Individual factors play a major role in the development of clinical OIH, including genetic [8] and pharmacogenetic factors (e.g., expression of the M3-glucuronide metabolite, which possess hyperalgesic properties) [45].

According to the available literature, OIH may develop after both low and high doses of opioid intake, irrespective of the opioid [45], and even after short-term use (only 1 month) [43]. Thereby, in practice, OIH represents an individual phenomenon that is probably underestimated, because not objectively assessed. More importantly, no study has clearly established a link between the presence of preoperative OIH and patient outcome. The literature, however, seems to show that chronic opioid intake may contribute to pain persistence. For patients who receive methadone maintenance treatment, the prevalence of a severe chronic pain condition reaches 37%, higher than in the general population (around 20%). Further, the incidence of severe chronic pain seems to correlate with the dose and the duration of substitutive treatment [53]. Another example includes patients with chronic headache who consume large amounts of analgesics including opioid derivates [54]. Opioid-overuse headache may share some mechanisms involved in OIH and specifically pain exacerbation related to the pro-inflammatory effect of opioids on glial cells (Table 1). Such observations question the long-term sensitization (also called "latent opioid sensitization") caused by opioid use [2] where continued pain on long-term opioid therapy might not be related to the original injury, i.e., surgery or

trauma, but to continuous opioid intake. Once again, very few studies have considered the problem. Treister et al. [55] have questioned the reversibility of OIH. Their results seem to show that altered pain perception is a reversible phenomenon, but one that may require a long period of abstinence to reset. A recent report highlighted withdrawal pain as a barrier to opioid cessation. In this report [56], "withdrawal-associated injury site pain," previously healed sites, and pain-free injury sites temporarily became painful again during opioid withdrawal, and this experience was a barrier to opioid intake cessation for some patients [56].

Indirect proofs of OIH in perioperative patients

Although direct evidence of perioperative OIH is scarce, the existence of indirect proofs cannot be ignored. In other words, perioperative situations where opioid use has been reduced seem to demonstrate an effective, if not better, outcome for the patients. Chapman et al. have compared the quality of postoperative pain management in the US and European institutions after orthopedic surgery [57]. At day 1, the mean worst pain was lower for European patients than for US patients [5.4 (SD 2.5) vs. 7.4 (SD 2.7)] ($p < 0.0001$). Europeans also reported significantly less emotional discomfort and less interference of pain with rehabilitation, although 70.2% European patients received opioid analgesics on the ward vs. 98.3% US patients. The point here is not to develop drugs and/or techniques that help spare perioperative opioid consumption. Several drugs commonly used in perioperative anesthesia as "analgesic adjuvants"—among others ketamine, pregabalin, magnesium and nitrous oxide—attenuate the development of OIH and hence should be considered as "antihyperalgesic adjuvants." Failure to account for their use might explain some discrepant results regarding the existence of OIH in current practice [8].

One step further, avoidance of any intraoperative opioid administration, also referred as "Opioid-Free Anesthesia (OFA)," is not only feasible but does not seem to cause enhanced postoperative pain and suffering like in an earlier study, which demonstrated that sevoflurane alone provided better recovery than propofol and fentanyl for day-care surgery [58]. More recently, in a large retrospective study, Jo et al. analyzed 2582 patients undergoing thyroidectomy who had received intraoperative remifentanil and found that they reported significantly worse pain scores (6.73 [95% CI 6.65–6.80] vs. 5.08 [95% CI 4.97–5.19]) on the day of surgery than patients matched on baseline age, gender, height, weight, and type of operation whose anesthesia was maintained with volatile anesthetics alone [21]. Using a similar method, Sanfilippo et al. found significantly worse pain scores (5.1 ± 2.1 vs. 4.3 ± 2.1) on the first postoperative day [22]. Beta-adrenergic antagonists, e.g., esmolol, used as analgesic adjuvants decrease postoperative pain and analgesic consumption [59]. In some cases, esmolol was even used as an alternative to intraoperative opioid administration and provided improved immediate recovery. The real benefit of opioid-free (and even "opioid-less") anesthesia on longer term outcome after surgery is highly difficult to assess, although the reduction of acute postoperative pain by itself facilitates rehabilitation and thereby may contribute to enhance recovery. The use of general anesthesia as a risk factor for chronic postsurgical pain after hip and knee arthroplasties in contrast with loco-regional techniques deserves to be questioned as general anesthesia techniques certainly involve the administration of opioids, perhaps at a high dose, while the use of a loco-regional technique permits opioid-sparing anesthesia [60]. Finally, recent reports have begun to mention the benefit of preoperative weaning of opioid use on outcome after joint arthroplasty [61].

Conclusion

Opioid analgesics are the most potent drugs used to control severe pain. However, neuroadaptation prevents opioids' ability to provide long-term analgesia and even produces opposite effects, i.e., enhancement of existent pain and facilitation of chronic pain development. Neuroadaptation to opioids use yields to the development of two interrelated phenomena: tolerance and "opioid-induced hyperalgesia" (OIH). Tolerance, a pharmacologic concept, and OIH, a clinical syndrome, have been mostly observed under experimental conditions in animals and in human volunteers. In contrast, their occurrence and relevance in clinical practice remains debated. However, in perioperative setting, not only intraoperative but also pre – and postoperative opioid use negatively affects surgical recovery.

Conversely, opioid-sparing techniques (also called "opioid-less" and "opioid-free" anesthesia) are raising increasingly more interest because they are generally associated with improved patient outcome. They may be considered an indirect proof that perioperative opioid administration deserves reflexion and should not anymore remain the most comfortable choice of health care providers. This is particularly important when perioperative pain management remains suboptimal and chronic post-surgical pain prevention is considered as an indicator of the quality of perioperative health cares. No doubt, perioperative OIH and its impact on patient outcomes deserve further well-designed studies.

Practice points

- Intraoperative administration of high doses of opioids increases postoperative pain scores, morphine consumption, hyperalgesia, and possibly the risk of persistent pain after surgery. If intraoperative opioids are needed, they should be used at the lowest possible dose.
- Chronic opioid intake in the perioperative period negatively affects postoperative recovery; thereby, both pre- and postoperative intake beyond the healing period represents a major problem and should be tightly controlled.
- There is increasingly more indirect evidence that opioid-sparing techniques of anesthesia (intraoperative opioid-free or opioid-less anesthesia, preoperative weaning of opioid treatment) are associated with improved patient outcome.

Research agenda

- The impact of intraoperative opioid (especially other than remifentanil) administration on the development of hyperalgesia and chronic pain after surgery should be further investigated.
- In patients under long-term opioid treatment (pre- or postoperative therapy), OIH may represent an individual phenomenon, which is probably underestimated, because rarely objectively assessed. Further studies are mandatory to make an objective link between the presence of pre- and postoperative OIH and patient outcome.

Conflict of interest statement

None.

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Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature

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Opioids are widely used in clinical anesthesia. However, side effects include postoperative nausea and vomiting, shivering, ileus, and urine retention and are specifically discussed here.
From the available evidence, it appears that the use of opioids is strongly associated with impaired gastrointestinal motility. Therefore, to prevent postoperative ileus, the use of opioids should be minimized and opioids should be replaced by other drugs. With regard to the risk of postoperative urinary retention, one problem is the lack of standardized definition. Nevertheless, the use of opioids is clearly an important risk factor. Postoperative nausea and vomiting have high incidences. Even if the mechanisms are partially understood, opioid-sparing strategies have been shown to decrease its incidence. Finally, the problem of postoperative shivering has been, at least partially, solved by the avoidance of (high doses) remifentanil and the use of alpha-2 agonists.
In conclusion, postoperative urinary retention, postoperative ileus, nausea and vomiting, and shivering are complex problems seen

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after surgery. Management is possible, but prevention is possible with the avoidance of high doses of intraoperative opioids, conjointly to opioid-sparing techniques.

Introduction

Opioids are widely used in clinical anesthesia and emergency medicine. Opioids decrease pain by their action in the peripheral nervous system, spinal cord, and brain and are agonists for the classical mu, kappa, and delta opioid receptors. The administration of opioids affects multiple organ systems such the cardiovascular-, respiratory-, endocrinological-, renal and urodynamic-, neurological and gastrointestinal systems. However, the use of opioids can cause a variety of side effects, and therefore, proper dosing and monitoring of these side effects are important. In this review, the opioid side effects such as postoperative nausea and vomiting (PONV), shivering, ileus, and urine retention are discussed.

Opioids and postoperative ileus

Postoperative ileus is a commonly seen complication after gastrointestinal, pelvic, and several nonabdominal surgical procedures. One definition of postoperative ileus is the cessation of bowel motility after surgical intervention and clinically characterized by pain, abdominal distension, the inability to oral intake, nausea and vomiting, and a delay in normal bowel function [1–3]. However, there is no single definition of what is generally accepted the best practice, and therefore, because of a lack of a consensual definition, the incidence of postoperative ileus varies among different publications. The incidence of postoperative ileus is between 10% and 30% of the patients undergoing abdominal surgery and more specific 17% following colectomy [2–4]. The incidence of postoperative ileus in other procedures such as cardiac or orthopedic procedures is reported to be approximately 10% [2–4]. Moreover, postoperative ileus is associated with increased length of hospital stay by several days, hospital costs, and 30-day readmission rates [1–5].

The pathophysiology of postoperative ileus is complex and multifactorial [1–3]. The stress response as a result from surgery results in a short period of intestinal paralysis where after this gastrointestinal function recovers slowly. The small bowel and stomach recover after 0–24 h and 48–72 h, respectively [1–3]. The mechanism of postoperative ileus is a complex process where inflammatory, fluid and electrolyte, pharmacological, and neurogenic factors interact. Several risk factors such as increased age, male gender, low preoperative albumin, long duration of surgery, previous abdominal surgery, emergency surgery, and acute and chronic opioid use are associated with developing postoperative ileus [1–6]. The use of opioids is strongly associated with impaired gastrointestinal motility, and subsequently, postoperative ileus and patients with ileus were associated with higher opioid consumption than patients without ileus [1–6]. Opioids have a dose-dependent inhibitory effect on the intestinal motility [1–6]. Several opioid receptor types such as kappa, mu, and delta have been identified in the intestinal tract [7,8]. Kappa- and mu-receptor agonists regulate cholinergic transmission in the mesenteric plexus. All three receptor subtypes of opioid receptors have been identified on neurons of submucosal and myenteric plexuses [7,8]. In humans, mu opioid receptors are present on immune cells, submucosal and myenteric neurons in the lamina propria [7,8]. Apart from opioids being responsible for affecting gastrointestinal motility, opioids may also influence ion and fluid transport and create an antisecretory effect [1–8]. The inhibitory effects on the gastrointestinal tract of opioids are seen after intravenous, intramuscular, and epidural administration of opioids [2–6,9]. The pharmacological treatment of postoperative ileus consists of two main approaches: treatment with laxatives and prokinetic drugs; however, treatment of postoperative ileus is beyond the scope of this review [3,5]. Furthermore, postoperative ileus is strongly associated with increased healthcare costs [3,4]. A large study showed a prolonged hospital stay of 11.5 vs. 5.5 days and an increase of the cost per case, USD 18.877 vs USD 9460, respectively [1,10]. Therefore, to prevent postoperative ileus, the use of

opioids should be minimized, and opioids should be replaced by other drugs, which prevents surgical stress in patients, which is described in other sections of the review.

Opioids and postoperative urinary retention

Maintaining micturition postoperatively can be challenging as the inability of the latter results in urinary retention. Postoperative urinary retention is frequently seen post surgery and anesthesia, and its overall incidence is 2.1% [11,12]. However, because of a lack of standardized, well-defined criteria and definition of postoperative urinary retention, the incidence reported in the literature may vary from 2.1% to 70% [11–13]. Impaired or the impossibility of micturition postoperatively is associated with delayed outcome and increased costs and should be prevented [14]. In clinical practice, three methods have been used to diagnose postoperative: clinical examination, bladder catheterization, and ultrasound assessment [11–13]. The perioperative risk factors for postoperative urinary retention are age and gender, type and duration of surgery, comorbidities, drugs, intravenous fluids, and effects of anesthesia and analgesia [11–13]. The use of opioids is an important risk factor in developing postoperative urinary retention, and opioid administration has a dose-dependent effect on the incidence of postoperative urinary retention [9,11–17].

The normal bladder has a capacity of approximately of 400–600 ml and an urge to void around 60% of its volume [11–13]. A spinal reflex is initiated by afferent signals from the receptors in the bladder, and a detrusor contraction and micturition are initiated by parasympathetic efferent signals. The effects of opioids on renal function and urodynamics are well described [11–17]. A decrease in electrolyte excretion and antidiuresis may result from mu-receptor activation as kappa-receptor activation produces diuresis. Data suggest that opioids do not alter renal function [16]. However, the exact mechanism of the development of urinary retention is not well understood. Intrathecal morphine in rats results in inhibition spontaneous bladder contractions and an increase in bladder capacity. (ref) In dogs, intrathecally administered fentanyl causes relaxation of the internal urethral sphincter. In humans, urinary retention after intrathecally administered morphine results from the inhibition of the parasympathetic activity, which results in relaxation of the detrusor [11–17].

The route of opioid administration is important with regard to the incidence of postoperative urinary retention. Intrathecal morphine has an incidence of 42–80% reported in the literature [11–17]. However, other routes of morphine administration in equivalent doses, such as intravenous or intramuscular administration, showed less frequent urinary retention [11–17].

Spinal opioids such as morphine and sufentanil cause dose-dependent suppression of the detrusor contractility and subsequently a decrease in sensation of urge. However, not all intrathecally administered opioids act similarly with regard to urinary retention. In a study in which the urodynamic effects of three opioids were compared, intravenous morphine, fentanyl, and nalbuphine resulted in a delayed micturition but detrusor contractility was only decreased after the administration of fentanyl and nalbuphine [16]. However, in another study, sufentanil and morphine resulted in a dose-dependent decrease in detrusor contractility. The onset time and duration of the effects of opioids on micturition show a large variability. The recovery times of a normal bladder function were 14 and 20 h after 0.1 or 0.3 mg of morphine and 5 and 8 h after 10 or 30 μg of sufentanil, respectively [16]. The onset time and duration of the effects of opioids on micturition shows a large variability. In healthy human volunteers, inhibition of the bladder as a result of intrathecal morphine and sufentanil occurred within 1 h and lasted up to 24 h. However, the recovery time of the bladder functions was shorter with sufentanil than with morphine [11–17].

Epidural anesthesia with local anesthetics alone is also associated with urinary retention postoperatively [9]. When the local anesthetics are combined with opioids, the incidence of urinary retention is increased. Detrusor strengths are decreased after 5–15 min after epidural morphine 4 mg and last for up to 15 h [11]. Furthermore, postoperative urinary retention is also related to the level of epidural anesthesia. Opioids administered at the lumbar epidural level are associated with a higher incidence of urinary retention than those administered at the thoracic level [11].

Additional medication to reduce pain such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the incidence of postoperative urinary retention as a result of opioid-reducing

effects compared to cases in which opioids were used. Opioids reducing effects of additional drugs to suppress surgical stress may lead to a lower incidence of postoperative urinary retention [11–13].

Postoperative urinary retention is caused by multiple anesthetic and nonanesthetic factors. However, the administration of opioids is associated with a high incidence of postoperative urinary retention. The true incidence of postoperative urinary retention is unknown because of a lack of defining criteria. Opioid-induced postoperative urinary retention should be prevented as this is associated with delayed outcome and should be evaluated in large prospective clinical trials.

Nausea and vomiting

PONV have high incidences after surgery. Series report proportions as high as more than 50% for nausea and more than 20% for vomiting [18]. Some authors suggest that, regarding the great discomfort to the patients, demands could be first from the patients [19].

Apart from discomfort due to nausea, pain due to vomiting and other consequences can occur, such as raised arterial pressure, intracranial and intraocular pressures, risk of aspiration, postsurgical bleeding, and leak of sutures. The mechanisms for this are clearly multifactorial, involving multiple limbic, cortical, and vestibular inputs to the nucleus tractus solitarius [19]. As a consequence of these multifactorial mechanisms, it is difficult to identify precisely the predominant cause(s) of opioid-induced PONV. However, some pathways have been proposed as logically associated with opioid-related nausea and vomiting. Among these, enhanced vestibular sensitivity (by a direct stimulation of mu-receptor in the epithelium), direct effects chemoreceptor trigger zones (seen even with low doses of opioids), and delayed gastric emptying are suspected to be of major importance [20].

Interventions to manage PONV include, between others, setrons and corticosteroids. However, none of the medications used for are devoid of side effects, including headache, sedation, QT prolongation, and/or increased total cost.

A possible way to prevent these is identification and avoidance of risk factors, if possible. Recognized risk factors include female gender, nonsmoker, previous PONV/motion sickness, and opioid use (intra and postoperative) [21]. With regard to nonmodifiable risk factors, pharmacological prevention can be employed (i.e., avoidance of halogenated gases in favor of propofol infusion, droperidol, corticosteroid, and/or setrons use). Fortunately, some risk factors such as opioid use are highly controllable. Indeed, as opioids influence the risk of PONV in a dose-dependent manner, dose matters [18]. A recent publication showed that prophylaxis with ondansetron and dexamethasone is more effective in preventing PONV when combined with opioid-free total intravenous anesthesia than combined with balanced anesthesia using inhalation and fentanyl [22]. This could be seen also as prevention for another cause of discomfort, postoperative shivering (POS).

Postoperative shivering

Indeed, high doses of short-acting opioids, especially remifentanil, are a well-known risk factor of POS, with an incidence of up to 60% and a relative risk of approximately 2% for remifentanil [23,24]. Possible consequences include increased oxygen consumption and associated cardiovascular complications such as myocardial ischemia. The type of opioids seems to have an influence, with a possible higher risk with remifentanil [24].

The pathophysiology of POS has not been well established. It has been proposed that POS is a sign of adrenergic activation associated with acute opioid withdrawal (secondary to acute tolerance). Indeed, short-acting opioids such as remifentanil are associated with acute tolerance and hyperalgesia, especially when higher doses are used. Nevertheless, even if an increased incidence of POS is seen with the use of higher remifentanil doses, its incidence is also seen with low doses [24].

Even if it has been suggested that central glutamatergic system (e.g. N-methyl-D-asparate, NMDA receptors) may mediate this phenomenon, ketamine effect is still discussed [25,26]. With regard to the pharmacological prevention of POS, clonidine has proven efficacy [27], probably both by direct and indirect effects (i.e., reduction of opioid use). Logically, opioid less, of a fortiori, opioid-free anesthesia, may be a valuable option to prevent this postoperative complication.

Conclusion: a plea for a decrease in opioid use

Postoperative urinary retention, postoperative ileus, nausea and vomiting, and shivering are complex problems seen after surgery. Management is possible and can be done early to avoid discomfort, morbidity, and prolonged length of hospital stay. A significant proportion of this problem can be prevented as it is related to intraoperative opioids, at least when alternatives are available. Logically, for this objective, the avoidance of high doses of intraoperative opioids should be first recommended, conjointly to opioid-sparing techniques. When possible (e.g., in an experienced team), opioid-free anesthesia is an option to avoid intraoperative opioid-related problems.

Practice points

1. To prevent postoperative ileus, the use of opioids should be minimized.
2. Other drugs than opioids can be used to prevent patients from surgical stress.
3. Aim for identification of risk factors and preventive strategies to avoid PONV.
4. Use the lowest dose of opioids possible to prevent opioid-induced postoperative urinary retention.
5. The use of high dose(s) short-acting opioids should be avoided to prevent POS.

Research agenda

1. Postoperative ileus is associated with a delayed healthcare outcome and increased costs. Further research is needed to understand the pathophysiology, improve preventive strategies, and treat this postoperative complication.
2. Opioid-induced postoperative urinary retention is associated with delayed outcome and should be evaluated in large prospective clinical trials.
3. PONV results in patient's discomfort and delayed outcome. The predominant causes of opioid-induced PONV should be identified in clinical research to improve treatment and outcome.
4. The awareness of the incidence and consequences of POS, which is caused by the use of high doses of short-acting opioids should be increased.

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Authors' contributions

HDB and PF designed the study. HDB, OD and PF collected, selected and performed the analyses, the interpretation, prepared the manuscript and approved the final version.

Conflict of interest

None.

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Additives used to reduce perioperative opioid consumption 1: Alpha2-agonists☆

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Because of their significant side effects, especially in obese patients, the routine perioperative use of opioids has been questioned recently. Alpha$_2$-agonists are drugs with a considerable analgesic potency with the potential to reduce opioid consumption. Alpha$_2$-agonists bind to alpha$_2$-adrenergic receptors in the CNS and peripherally. They inhibit the central sympathetic outflow, resulting in an attenuation of blood pressure and heart rate and in a sparing effect on anaesthetics and analgesics. In the postoperative period alpha$_2$-agonists provide an analgesic effect without respiratory depression and other known opioid side effects. Intraoperatively, a complete replacement of the synthetic opioid fentanyl by the alpha$_2$-agonist dexmedetomidine has been demonstrated. Although alpha$_2$-agonists have a sedative action, recovery times are not prolonged compared to those of opioids. Cardiovascular side effects such as bradycardia and hypotension have to be observed and treated.

Introduction

Although opioids are a mainstay of anaesthetic practice and their employment seems indispensable, the routine use of this group of analgesics has been questioned recently. Synthetic opioids were introduced into the anaesthetic armamentarium during the late 1960s. Because of the hypnotics available at that time and the massive lack of potent analgesics there was a strong medical need for

☆ In memoriam of a good friend, Riku Aantaa, MD.

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these drugs. The administration of opioids helped to administer a stable anaesthesia even in severely ill patients. However, during the following years, it became evident that opioids also exert significant side effects such as respiratory depression, nausea and vomiting, delirium, hypothermia, hyperalgesia, constipation, and more subtle effects such as impairment of the immune function.

To reduce the adverse effects not only of opioids but of other potent analgesics too, a multimodal analgesia consisting of the combination of different analgesics has been suggested, especially in fast track surgery and is now employed widely [1,2]. With the advent of drugs with considerable analgesic potency during the last years, it may even be conceivable to almost replace opioids in their routine use during and after anaesthesia.

Thus, our current thinking about anaesthesia as a set combination of hypnotics, opioids and muscle relaxants has to be rethought and may be revised.

Historic perspective

One group of drugs that may be employed to reduce the use of opioids in anaesthesia are alpha$_2$-adrenergic agonists or short alpha$_2$-agonists. The prototype of this group, clonidine, was developed during the 1960s, which was about the same time when synthetic opioids were introduced to clinical anaesthesia. However, clonidine was first developed as a vasoconstrictor and decongestant for flu patients at the pharmaceutical laboratory of Boehringer Ingelheim. During that phase, clonidine was administered to a secretary who suffered from a bad cold. Dr. Stähle, the leading chemist, reported what happened: 'However, there was some surprise and embarrassment when the lady fell asleep for 24 h. She also developed a rather low blood pressure, a marked bradycardia and dryness of the mouth. The dose amounted – as determined later – to the equivalent of approximately 20 tablets of Catapres' [3]. Thus, the typical actions and adverse effects of alpha$_2$-agonist were clearly established: sedation, low blood pressure, bradycardia and inhibition of salivation and a remarkable margin of safety. Following this experience, clonidine was successfully introduced in 1966 as an antihypertensive albeit with an undesirable sedative effect. It was only at the end of the 1980s that the potential of clonidine for clinical anaesthesia was realised, and it was first used as an adjunct during anaesthesia. It was reported that the administration of clonidine reduced both sedative/hypnotic and analgesic requirements. A few years later another, more specific alpha$_2$-agonist was tested for the first time for the use in anaesthesia. Starting in veterinary medicine, the dextro enantiomer of medetomidine, dexmedetomidine, proved to possess even more potent effects than clonidine.

Pharmacology of alpha$_2$-agonists

Clonidine and dexmedetomidine are imidazolines that bind to both adrenergic and imidazoline receptors. Whereas clonidine has a relatively slow onset of about 30 min and a long elimination half-life of 9–12 h, dexmedetomidine has a faster onset and an elimination half-life of about 2 h [4,5]. In addition, dexmedetomidine is much more selective for the alpha$_2$-adrenergic receptor than clonidine (1660 vs 220 alpha$_2$- to alpha$_1$-selectivity for dexmedetomidine and clonidine, respectively) [6,7]. Clonidine is a partial agonist at alpha$_2$-adrenergic receptors, while binding of dexmedetomidine exerts full agonist properties. Alpha$_2$-adrenergic receptors are classified according to either pharmacological or genetic profiles. Pharmacologically, they are divided into Alpha$_{2A}$-, Alpha$_{2B}$- and Alpha$_{2C}$-receptors. According to the localisation of their respective genes, the genetic classes comprise Alpha$_2$C10-, Alpha$_2$C4- and Alpha$_2$C2-receptors [8,9].

Binding of an agonist at the alpha$_2$-adrenergic receptor leads to an activation of inhibitory G-proteins and a decrease in cAMP; however, other pathways have also been described [8,10,11]. The main effect of alpha$_2$-agonists, the sympatholysis leading to sedation and low blood pressure, is mostly mediated through alpha$_{2A}$-receptors. Alpha$_{2B}$-receptors mediate the transitory increase in blood pressure because of a direct vasoconstrictive effect [12]. High densities of alpha$_2$-adrenoceptors are found in the central nervous system mainly in noradrenergic nuclei such as the nucleus coeruleus. Alpha$_2$-adrenergic receptors are an integral part of the neuronal pathways of natural sleep [13]. However, depending on its dose, the alpha$_2$-agonist dexmedetomidine not only induces a sleep-like sedation in fully arousable patients but may also induce an anaesthesia-like state [14]. Because these actions are mediated through

an effect on a single type of receptor, there exist potent antagonists, which may counteract the sedative/hypnotic effect of alpha$_2$-agonists within seconds [15]. However, none of these antagonists is clinically available at present. Experimentally, subtype specific compounds with more specific actions have been described recently; yet, it is currently not clear if and when these compounds will be approved for clinical use.

Alpha$_2$-agonist mediated analgesia has been suggested to be closely related to opiate and adenosine receptors. Alpha$_2$-receptors and A1-adenosine receptors show cross-tolerance and dependence with μ-opioid receptors. The underlying mechanism of this relationship has been attributed to the common inhibitory G-protein pathways [16–18]. The principal site of action for alpha$_2$-agonist mediated analgesia appears to be spinal and not the brain, although dexmedetomidine can readily cross the blood-brain-barrier because of its high lipophilicity.

Pain during anaesthesia?

Sedated, anaesthetised or comatose patients are not able to report pain. Unfortunately, there is currently no generally accepted method for the determination and quantification of the strength of pain during anaesthesia. However, it was demonstrated in patients in the intensive care unit that signs of pain such as grimacing, tachycardia or high blood pressure exist even in unconscious or comatose patients and that these signs may be attenuated by administration of analgesics [19]. Similar parameters for the indirect determination of pain have been found during anaesthesia [20]. For example, haemodynamic changes reflect the involvement of the autonomous nervous system as part of pain processing in the unconscious. More specifically, pain may be determined by the detection of an excitation of the sympathetic nervous system. Although analgesics reduce sympathoexcitation most likely through a reduction of pain, one has to be aware that other drugs that block or attenuate the sympathetic response to pain such as beta-blockers may have a similar stabilizing effect although they do not exert an antinociceptive action. This is important to comprehend the action of alpha$_2$-agonists. Because they inhibit sympathetic outflow in the central nervous system; blood pressure and heart rate are reduced even in patients not experiencing pain. Thus, the sympathoinhibition of alpha$_2$-agonists during an operation may indicate a level of antinociception that is not existent. At present, there is no way to solve this dilemma. However, one may argue that this question is irrelevant because unconscious (and amnestic) patients are not able to report intraoperative pain in the postoperative period [21].

Alpha$_2$-agonist mediated analgesia, polymorphisms

In volunteers, dexmedetomidine exerted a potent analgesic action comparable to that of synthetic opioids [7]. Clinically, alpha$_2$-agonists have been demonstrated to possess analgesic properties postoperatively and to attenuate opioid-induced hyperalgesia [22].

Co-administration of alpha$_2$-agonists and opioids leads to an opioid sparing effect that is more pronounced for dexmedetomidine compared to clonidine and appears to be dose related. Initially, the analgesic effects of alpha$_2$-agonists were expected to occur generally. During the recent years, however, there have been reports on polymorphisms at alpha$_2$-adrenoceptors, leading to a reduction in analgesic efficacy in certain populations [23].

Clinical use of alpha$_2$-agonist during opioid free anaesthesia

Morbidly obese patients are at particular risk in the perioperative period and present a challenge in anaesthetic management during the perioperative period. Morbid obesity is associated with impaired function of respiratory muscles, diminished functional residual capacity, increased oxygen consumption, an increased work of breathing, increased upper airway resistance, an increased incidence of obstructive sleep apnoea syndrome and hypoventilation induced pulmonary hypertension leading to right heart failure [24–26]. Opioid induced respiratory depression may lead to prolonged mechanical ventilation in the postoperative period to avoid postoperative hypoxaemia [27].

The abandonment of opioids may be of great benefit in morbidly obese patients, but this benefit is certainly not limited to this group of patients. Because of the lack of respiratory depression compared to opioids, alpha$_2$-agonists have not only been employed in the intra- and postoperative phase but for induction of anaesthesia, too. In 2005, a first case report was published on the successful use of dexmedetomidine for the anaesthetic management of a morbidly obese patient weighing 433 kg [24].

An early report by Aho et al. in patients undergoing abdominal hysterectomy analysed the usefulness of dexmedetomidine for maintenance of anaesthesia. Dexmedetomidine did not completely abolish the need for isoflurane but diminished its requirements by more than 90% [14]. In 5 out of 10 patients, it was not necessary to supplement any isoflurane. Thus, dexmedetomidine was able to exert an anaesthetic action by itself with no reports of intraoperative recall. The same group of investigators also demonstrated a potent analgesic and opioid sparing effect of dexmedetomidine in the postoperative period [28]. Dexmedetomidine was as effective as i.v. oxycodone. Another study demonstrated a more than 60% reduction in postoperative opioid consumption in presence of dexmedetomidine [29].

Dexmedetomidine can also be used intraoperatively to completely replace an opioid. In a pilot study, in bariatric patients, it was shown that dexmedetomidine leads to lower blood pressure and heart rates, while decreasing desflurane requirements. Postoperatively, dexmedetomidine provided lower pain scores and less use of morphine rescue medication than the fentanyl group. Thus, in bariatric patients, it is possible to completely replace potent opioids such as fentanyl, possibly leading to less respiratory depression and less obstructive sleep apnoea complications [25]. In addition, in a larger study also in a bariatric population ($n = 124$), it was shown that patients treated with propofol, dexmedetomidine and ketamine instead of a volatile anaesthetic and fentanyl developed less PONV (-17.3%) with a number needed to treat (NNT) of 6 [30].

In bariatric surgery, it was demonstrated that the use of alpha$_2$-agonists leads to a reduction in postoperative opioid consumption, less respiratory depression, shorter PACU stay, less use of antiemetics and a favourable cardiovascular stability [31]. Interestingly, there was no clear dose-related effect when doses of 0.2 μg/kg/h up to 0.8 μg/kg/h of dexmedetomidine were studied. In contrast, a recent double-blind randomised study in patients undergoing hysterectomy showed a dose-dependent opioid-sparing effect of dexmedetomidine even at low doses [32]. Addition of 0.05 μg/kg/h dexmedetomidine to 0.02 μg/kg/h sufentanil did not result in an increase in side effects compared to 0.02 μg/kg/h dexmedetomidine added to the same dose of sufentanil. The higher dose of dexmedetomidine resulted in a 25% reduction of sufentanil consumption [32,33]. These findings may indicate the existence of a ceiling effect in the opioid sparing action at least of dexmedetomidine.

In a meta-analysis of the effects of systemic administration of alpha$_2$-agonists on perioperative morphine consumption and pain intensity, it was clearly demonstrated that alpha$_2$-agonist exert an opioid-sparing effect up to 24 h postoperatively and a decrease in the intensity of postoperative pain. The degree of morphine sparing was greater than that of acetaminophen, but weaker than that of ketamine or non-steroidal anti-inflammatory agents. A similar ranking of effects was observed with the reduction in postoperative nausea. Alpha$_2$-agonists also decreased the occurrence of postoperative nausea with a NNT of approximately 9 [34]. This effect is somewhat weaker than that of other established antiemetics, which typically show a NNT of 3–5 [35]. Although the basis of the anti-nausea effect of alpha$_2$-agonists is not known, it has been suggested that they possess an antiemetic efficacy by themselves, that they reduce opioid-induced PONV, or that they act through their sympatholytic effect as it was demonstrated that sympathoexcitation and catecholamine release increase PONV [36,37]. Another, more recent meta-analysis confirmed these findings for the alpha$_2$-agonist dexmedetomidine and reported lower postoperative pain intensity, less opioid consumption, and a reduction in opioid-related adverse events when dexmedetomidine was administered systemically [38]. Opioid-related pruritus occurred less often in patients treated with dexmedetomidine (NNT = 6) [39]. The analgesic effect of dexmedetomidine appears to depend on the kind of surgery performed and to be increased with a more intense dosing regimen [38]. Another meta-analysis found the opioid-sparing effect of dexmedetomidine to be distinct and to be stronger than that of non-opioid analgesics [39].

As always, meta-analyses are only as good as the underlying source studies. Because of an increased risk of publication bias, it is not recommended to evaluate analyses that include less than 10 studies [40]. Unfortunately, this was the case for the meta-analyses evaluating the effects of alpha$_2$-agonists on

pain, where only up to five studies were available depending on the exact question studied. Accordingly, the results of the meta-analyses available up to now have to be met with caution.

Inadequate acute postoperative pain control is one of the strongest predictors for the occurrence of chronic pain [41]. Although administration of alpha$_2$-agonists results in an antihyperalgesic effect, their role in treating chronic pain remains to be defined [42,43].

Side effects and caveats

Alpha$_2$-adrenoceptor agonists exert a transient peripheral vasoconstriction with a subsequent sympatholysis. It was demonstrated in various experimental and clinical settings that the reduction in sympathetic drive by alpha$_2$-agonists reduces blood pressure and heart rate below baseline values. Many clinical studies found less haemodynamic alteration, less myocardial ischaemia, lower anaesthetic requirements, and a more stable perioperative course when alpha$_2$-agonists were administered. This increase in perioperative stability leads David Longnecker to ask: 'Alpine anaesthesia. Can pretreatment with clonidine decrease the peaks and valleys?' [44]. Michael Roizen even questioned in a following editorial: 'Should we all have sympathectomy at birth? Or at least preoperatively?' [45]. The initial observations were confirmed in a study by Arthur Wallace et al. showing that perioperatively administered clonidine in patients at cardiac risk reduced perioperative myocardial ischaemia and postoperative death [46]. Meta-analyses provided more evidence of a beneficial effect of the perioperative administration of alpha$_2$-agonists on myocardial ischaemia and death [47–49]. However, in a meta-analysis, in patients undergoing non-cardiac surgery, it was suggested that perioperative administration of alpha$_2$-agonist increases the risk of hypotension and bradycardia [34]. This was confirmed by a recent large multicentre RCT demonstrating an increase in systemic hypotension and no effect on myocardial infarction in patients undergoing non-cardiac surgery indicating that haemodynamics need to be closely monitored when alpha$_2$-agonists are administered [50].

It has been believed that alpha$_2$-agonist induced sedation prolongs postoperative recovery times because of the inherent sedative action. However, when dexmedetomidine was used intraoperatively, there was a significant reduction in the time to extubation, indicating a faster return of protective reflexes and sufficient spontaneous ventilation [34]. The decreased times to recovery may be caused by the intraoperative opioid and anaesthetic sparing effects of dexmedetomidine.

Although alpha$_2$-agonists appear to exert many beneficial effects in the perioperative period and their analgesic efficacy allows for a complete abandonment of perioperative opioid administration, it should be reminded that alpha$_2$-agonists have not been approved for this application, and it is thus an off-label use.

Conclusions

With adequate dosing, dexmedetomidine in particular has been demonstrated to exert potent opioid sparing properties resulting in less respiratory depression and less PONV than a purely opioid based analgesia. However, there remains a lack of studies on the analgesic effect of alpha$_2$-agonists in the perioperative setting. To date, it remains unclear whether there is a clinical difference between the two substances mostly used, clonidine and dexmedetomidine, of which dexmedetomidine possesses a much higher specificity of the alpha$_2$-adrenoceptor. Optimal dosing strategies are lacking providing the best balance between perioperative analgesia, patient safety and quick recovery. Nonetheless, alpha$_2$-agonists appear to be one of the most tantalising arrows in the anaesthesiologist's quiver to reduce perioperative opioid consumption.

Summary

Because of their significant side effects, especially in obese patients, the routine perioperative use of opioids has been questioned recently. Alpha$_2$-agonists are drugs with considerable analgesic potency with the potential to almost replace opioids in the perioperative period. Binding of an agonist at alpha$_2$-adrenergic receptors leads to an activation of inhibitory G-proteins, and a decrease in cAMP among other pathways, leading to an attenuation of sympathetic outflow from the central nervous

system. Alpha$_2$-adrenoceptors are an integral part of the neuronal pathways of natural sleep. They not only induce a sleep-like sedation with fully arousable patients but can also mediate an anaesthesia-like state. In presence of alpha$_2$-agonists, the need of sedatives/hypnotics and analgesics is reduced by 40%–90% depending on dose and compound. The antinociceptive effect of alpha$_2$-agonists has been suggested to be related to opiate and adenosine receptors and common intracellular pathways. Clinically, alpha$_2$-agonists possess analgesic properties intra and postoperatively have anaesthetic and analgesic sparing effects, and attenuate postoperative opioid consumption. Respiratory depression is less frequent under alpha$_2$-agonists that, furthermore, have the potency to reduce opioid related side effects such as nausea and vomiting. Although the use of alpha$_2$-agonists has been shown to result in relatively steady haemodynamics, they may cause hypotension and bradycardia because of sympatholysis.

Practice points

- Currently used potent opioids have side effects such as respiratory depression, nausea and vomiting, delirium, hypothermia, hyperalgesia, constipation and impairment of immune function and others.
- Alpha$_2$-agonists have been used for the pre, intra and postoperative replacement of opioids.
- Clonidine and dexmedetomidine are currently the only clinically relevant alpha$_2$-agonists.
- Alpha$_2$-agonists cause sympatholysis, thus providing attenuation of blood pressure, heart rate and anaesthetic and analgesic sparing.
- Alpha$_2$-agonists provide postoperative analgesia with low risk for respiratory depression and a reduction in postoperative nausea and vomiting.
- Alpha$_2$-agonists are successfully used in bariatric surgery.

Research agenda

- The analgesic efficacy of the alpha$_2$-agonists clonidine and dexmedetomidine needs to be more exactly defined.
- The action of alpha$_2$-agonists on opioid-induced hyperalgesia and the development of chronic postoperative pain need to be looked at.
- Clonidine and dexmedetomidine need to be compared head to head.
- Dosing regimen need to be studied both for the intra and to postoperative period.
- The combination of intraoperative administration of short acting opioids such as remifentanil with a postoperative administration of alpha$_2$-agonists needs to be studied in different patient populations.
- Prevention and treatment of cardiovascular side effects need to be clearly established and absolute contraindications defined.
- The place of alpha$_2$-agonists in the field of opioid-free anaesthesia has to be defined.

Conflict of interest statement

Lecturer and Consultant to Orion Pharmaceuticals.

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Intravenous lidocaine

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Lidocaine has analgesic effect and antihyperalgesic and anti-inflammatory properties, which enable its use as a general anesthetic adjuvant. Lidocaine can reduce nociception and/or cardiovascular responses to surgical stress, postoperative pain, and/or analgesic requirements. However, its mechanisms of action remain unclear, despite its different known properties. Although the exact mechanism of action remains uncertain, initial bolus followed by a continuous lidocaine infusion has clear analgesic benefits. Lidocaine is one of the major drugs for opioid-reduced anesthesia or opioid-free anesthesia procedures. It clearly improves the postoperative outcomes with increased patient satisfaction. Such procedures should be included wisely in the enhanced recovery after surgery protocols. By using the recommended protocols, a high safety and efficacy of lidocaine can be achieved.

Introduction

Lidocaine (or 2-(diethylamino)-N-(2.6-dimethylphenyl)acetamide) is the main prototype of amino-amide local anesthetics (LAs). It has analgesic effect and antihyperalgesic and anti-inflammatory properties, which enable its use as a general anesthetic adjuvant. Lidocaine can reduce nociception and/or cardiovascular responses to surgical stress, postoperative pain, and/or analgesic requirements. However, its mechanisms of action remain unclear, despite its different known properties.

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Efficacy

Perioperative pain

From earliest randomized trials for abdominal surgery (from Rimbäck to de Oliviera) [1,2], various meta-analyses have confirmed the efficacy of intravenous (i.v.) lidocaine administration. From the earliest systematic review and meta-analysis [3–5] to the latest ones [6,7], it is interesting to note that existing reviews found similar results. These reviews demonstrate that patients undergoing any elective surgery under general anesthesia had a significant reduction of pain and/or opioid requirements during the first 24 postoperative hours.

Subgroup analysis suggested that the best benefit is for patients undergoing abdominal surgery (laparoscopic abdominal or open abdominal surgery) [6,7]. The effects on the gastrointestinal tract (decrease in postoperative ileus, shortening of both the time to first flatus and the time to first bowel movement, decrease in postoperative nausea and vomiting) are probably one of the major effects of lidocaine. Although it is still debated, it has been reported that lidocaine could shorten the length of hospital stay after abdominal surgery [8] or radical retropubic prostatectomy [9].

The analgesic effect of lidocaine has already been mentioned in some other aspects of anesthesia. The efficacy of lidocaine was reported in terms of decrease in pain intensity on the injection of propofol [10], decrease in the cardiovascular reaction to the tracheal intubation, and decrease in postoperative sore throat [11].

Comparison to the gold standard: the epidural

Epidural analgesia has been proposed as the criterion-standard analgesic for major abdominal surgery. Recent reviews have failed to find a significant difference between epidural and lidocaine infusion [12]. Because of its similar mechanisms of action, some authors called lidocaine infusion as “the poor man's epidural” [13] despite the fact that a continuous lidocaine i.v. infusion show, more or less, the same efficacy as that shown by an epidural administration of lidocaine for abdominal surgery [14–16].

Chronic pain

Lidocaine has several properties, which are particularly effective in the treatment of central and peripheral neuropathic pain [17,18]. In a neuropathic model (spinal nerve ligation), lidocaine infusion shows analgesic efficacy in three phases [19]. The first phase of ipsilateral relief is during the infusion with returning to the pre-infusion level within 30–60 min, followed by an intermediate phase with a transient improvement slightly later (360 min in the rat model), and the last phase of ipsilateral relief was observed from 24 h after infusion and sustained over the next 21 days. A recent review confirms the efficacy of lidocaine on the neuroinflammation response in perioperative pain and chronic neuropathic pain [20]. For the record, a long time ago, lidocaine was also proposed for the treatment of pancreatitis pain [21]. Its efficacy on some opioid-refractory pain was also reported [22].

Although it is not yet clearly demonstrated, lidocaine can be a potentially useful drug for the prevention of persistent postoperative pain (or chronic postoperative pain) [23,24].

Safety

Pharmacokinetic

Lidocaine is a weak base (cationic molecule with ionization constant pKa of 7.9) and poorly hydrosoluble. After i.v. administration, lidocaine is initially distributed to highly vascularized organs (i.e., the brain, kidneys, and heart), and then to less vascularized tissues (i.e., the skin, skeletal muscles, and adipose tissue). The volume of distribution is approximately 91 L.kg-1.

Around 60–80% of lidocaine is bound to plasma protein (albumin, mostly with α-1 acid glycoprotein, which increases postoperatively and specifically in elderly patients, and lipoprotein). An interesting experimental observation was that albumin administration could decrease brain extraction of lidocaine [25].

Furthermore, after i.v. lidocaine administration, 40% is temporarily extracted during first pass through the lungs [26]. This is partially due to a lower pH of the lungs than that of the plasma, but mainly due to metabolization of the drug by cytochrome P 450 (CYP) (particularly by CYP2D subfamily CYP2B1, CYP1A2, and/or other enzymes). This is the reason why lung trapping of lidocaine reduces the risk of intoxication in cases of accidental i.v. administration as compared to intra-arterial administration.

Around 90% of lidocaine undergoes hepatic metabolism (CYP3A4), with the production of active metabolites such as monoethylglycylxylidide, N-ethylglycine, and glycylxylidide [27]. During lidocaine continuous infusion, the accumulation of these metabolites may inhibit the biotransformation of lidocaine [28] and might have been implicated in some cases of intoxication. The clearance rate of lidocaine is approximately 0.85 L/kg/h.

Finally, lidocaine is eliminated by the kidney (10% of lidocaine is eliminated unchanged in the urine). The half-life of lidocaine is 1.5–2 h after a bolus lidocaine administration. The half-life could be prolonged approximately 3 h in obese patients. In continuous lidocaine infusion, the half-life could be prolonged by more than 3 h after 24 h administration to 6.9 h after 48 h of lidocaine administration [29]. Therefore, it is important to remember the risk of accumulation during continuous administration and to decrease the rate of lidocaine infusion with the time [30].

Drug–drug interactions

Ketamine usually used along with lidocaine for opioid-reduced (ORA) or opioid-free anesthesia (OFA) could prevent lidocaine-induced convulsion state. However, ketamine could impair cognitive function by enhancing neurotoxicity of lidocaine (particularly at the level of the hippocampus and amygdala) [31]. General anesthesia, probably by numerous drug–drug interactions, could increase the lidocaine plasma concentration and the amount of lidocaine in the brain [32]. This drug–drug interaction was experimentally reported when a beta blocker [33] or clonidine [34] was co-administered with lidocaine. The pharmacokinetic interactions could have considerable implications for clinical practice (i.e., decrease in the effective analgesic dose of lidocaine, thereby avoiding any undesirable effects). Conversely, the depth of anesthesia requires lower minimum alveolar concentration of volatile anesthetics or rate of propofol target-controlled infusion.

Receptors

Sodium channels

Like all LAs, lidocaine has little or no selectivity among different types of sodium (Na^+) channels [for review, see 35]. Typically, lidocaine blocks voltage-gated sodium channels (VGSCs or Na*v*) that induce the inhibition of (1) action potential propagation and (2) neuronal excitability. This mechanism is established for regional anesthesia. However, the underlying mechanism of action of i.v. lidocaine may be more complex than simply the blockade of peripheral impulses to the nerve.

With regard to the mechanisms of pain induction, it has been reported that tetrodotoxin (TTX)-sensitive Na^+ channels (Na*v*1.3 and Na*v*1.7) are activated after nerve injuries or inflammation. It has also been suggested that TTX-resistant Na^+ channels (Na*v*1.8 and Na*v*1.9) are especially important in neuropathy. In the case of naïve patients (or animal) with normal pain thresholds, the analgesic mechanisms of i.v. lidocaine have not yet clearly been described.

VGSCs are undoubtedly one of the sites of action of lidocaine. They are heteromeric integral membrane glycoproteins formed by association with α-subunits and regulatory β-subunits (β1–β4). Ten different mammalian α-subunits (Na*v*1.1–Na*v*1.9 and Na*x*)[see for review 36] are described. Briefly, Na*v*1.1, Na*v*1.2, Na*v*1.3, and Na*v*1.6 isoforms are mainly expressed in the central nervous system (CNS) (target of the antiepileptic drugs), and genetic deficiency induces seizures or decrease in the efficacy of LAs [37]. In contrast, Na*v*1.7, Na*v*1.8, and Na*v*1.9 are predominantly located in the peripheral nervous system (target of lidocaine and all LAs; genetic deficiency of these subunits induces pain or insensitivity).

Na*v*1.4 isoform is mainly expressed in the skeletal muscle (genetic deficiency induces myotonia), while Na*v*1.5 is the specific cardiac isoform (genetic deficiency induces arrhythmia). Interestingly, a Na*v*1.5 isoform has recently been reported to be expressed in the gastrointestinal tract [38]. This could be one explanation for the efficiency of the lidocaine in the quick recovery of intestinal transit. It is

interesting to note that in the irritable bowel syndrome due to mutations in the Na*v*1.5 isoform, the treatment with mexiletine, which exerts its pharmacological action through the blockade of VGSC, corrects digestive disorders; this result is similar to that observed with lidocaine administration [39].

The affinity of lidocaine for VGSC varies according to the conformation of the channels: the affinity is higher when the channel is open (i.e., active or inactive) and lower when it is closed (i.e., deactivated or at rest). However, at low concentrations, lidocaine induced only 50% of inhibition of the VGSC [40], which suggest another mechanism of action.

Other receptors

Moreover, increasing evidence has indicated that lidocaine affects other channels such as calcium (Ca^{2+}) channels, potassium (K^{+}) channels, and transient receptor potential channels. These other receptor sites are not located in the periphery, but in the brain or spinal cord.

Recently, the hyperpolarization-activated cyclic nucleotide (HCN) channels have been identified as one of the CNS targets of analgesic action of lidocaine (i.e., the thalamus, hippocampus, spinal cord, and dorsal root ganglion) [41]. Inhibition of HCN currents may downregulate the excitability of the spinal cord, thereby prolonging the efficacy of lidocaine to a larger extent than could be explained by its pharmacokinetics.

Lidocaine decreases post-synaptic depolarization mediated by N-methyl-D-aspartate (NMDA) receptors by inhibiting protein kinase C [42,43]. Lidocaine, and probably all ester-type LAs, inhibits the NMDA receptor (one of the major receptor channels for rapid excitatory neurotransmission) by various mechanisms [44,45]. Experimental data suggested that the site-of-action might be in close proximity, but is not identical to, that for magnesium (Mg^{2+}) and ketamine blockade [44,46].

The effects of lidocaine on G protein-coupled receptors have been described explaining its anti-inflammatory and anti-thrombotic actions [47]. These effects seem to be time-dependent [48].

Lidocaine interacts with different K^{+} channels [49]. At low concentrations, lidocaine suppresses the tonic firing pattern of tonic firing neurons by an interaction with voltage-gated K^{+} channels (whereas adapting firing neurons block was explained by the interaction with the VGSC) [40]. Lidocaine also acts on postsynaptic neurons to hyperpolarize the membrane. This mechanism could be explained by a facilitating effect on descending inhibitor system and increase in the release of noradrenaline or serotonin, which causes hyperpolarization by opening K+ channels [46].

Like cocaine, lidocaine increases the intracellular calcium (Ca^{2+}) concentration in the sensory cortex [50]. Modulation of Ca^{2+} currents in somatosensory neurons is one of the mechanisms underlying neuropathic pain [51]. Low voltage-activated T-type calcium channels (Ca*v*3.1, Ca*v*3.2, and Cav3.3) are involved in pain signaling. The Ca*v*3.2 subtype seems to be particularly involved in somatic neuropathic pain (nerve injuries, diabetes, and toxic chemotherapy) and in visceral pain (colonic hypersensitivity) [52].

Pharmacodynamic

Although the underlying mechanisms of action of i.v. lidocaine remain unclear, its pharmacodynamics efficacy is demonstrated. The optimal plasma concentration of lidocaine observed after i.v. administration (1–2 mg/kg) is largely under (below 5 μM/mL) the optimal concentration required to block peripheral nerve fiber impulses (i.e., 4–20 μM vs. 300–800 μM) [46]. This is why the analgesic effect of lidocaine could be explained by another mechanism (as described above) than that of the main theory of the Na^{+} channel blockade.

Similar discussion could be made on the risk of tumor recurrence and metastasis. It must be differentiated the local efficacy of lidocaine at high doses (i.e., direct cell toxicity) and the potential systemic effects at very low concentrations [53–56].

Systemic

Lidocaine is a class 1b antiarrhythmic drug with less pro-arrhythmic effects. This effect is due to the blockade of VGSC. Because lidocaine reduces intracellular Na^{+} and prevents Ca^{2+} overload, it has been recently reported experimentally to exert protective effect on cardiac function after myocardial ischemia [57] and could be involved in the reduction of infarct size [58].

Inflammation

We should separately discuss the antimicrobial effect reported only for the local administration of lidocaine (at high tissue lidocaine concentrations) from its systemic effects at low concentrations. Lidocaine has significant anti-inflammatory properties, including reduction of the *in vitro* and *in vivo* release of pro-inflammatory cytokines (e.g., interleukin-1β, TNF-α, nuclear factor-κB, and monocyte chemo-attractant protein-1) by reducing neutrophil activation [see for reviews 59–61]. The inhibitory effects of lidocaine on the priming process of polymorphonuclear neutrophils are more relevant than those observed with the amide LAs class [47]. This action does not seem to impair the healing process, as reported experimentally [62]. Any drug interaction in the healing process has not been described in the clinical review as a potential adverse effect [3–7].

In addition to its anti-inflammatory properties, it has been reported that lidocaine could increase the natural killer T-cell activity [55]. Lidocaine may have therapeutic benefit by attenuating vascular inflammation, which would minimize microvascular endothelium injury and inflammatory hyper-permeability [63]. Therefore, it is not surprising to find that this complex mechanism of lidocaine infusion has beneficial effects on the inflammatory cascade and the immune system as recently reported in retrospective evaluation of medical records of dogs with septic peritonitis that underwent laparotomy [64]. Systemic administration of lidocaine exerted a protective effect on cell-mediated immunity, which could reduce the occurrence of postoperative septic complications and tumor metastasis [65,66].

Blood–brain barrier

As described above, the main target of lidocaine is the CNS (i.e., the brain and the spinal cord); therefore, it must cross the pharmacologic blood–brain barrier (BBB, blood spinal cord barrier, and blood–nerve barrier for the peripheral nerves). Molecules must be transported by the active biological system through the BBB (for example, GLUT-1 transporter is an active transporter from plasma to the brain, and P-glycoprotein is highly active in extruding multitude of molecules). Therefore, it makes sense to think that there is some delay between the i.v. lidocaine administration and its action on the brain, spinal cord, and nerve [67]. Experimentally, a delay of around 15 min is reported to be required to achieve an equilibrium between plasma and extracellular brain space [68]. This similar delay was recently confirmed in human studies [69].

In some pathological situations, such as nerve injury (which might contribute to the development of neuropathic pain), a modification in the permeability of the BBB was reported [70]. It is possible to imagine, though it has never yet been studied, that the potential modification of the BBB permeability could modify the diffusion of lidocaine. Similarly, some drugs such as the one used under general anesthesia could also interfere with BBB permeability to lidocaine [71].

Toxicity

Perioral paresthesia, metallic taste, slurred speech, diplopia, light headedness, tinnitus, confusion, agitation, muscular spasms, and seizures have been reported when the lidocaine plasma concentration was higher than 5–8 μg/mL.

Under general anesthesia, cardiovascular toxicity (bradycardia, increase intervals, and widening QRS complex) could be the only one detectable signs of intoxication. This cardiac toxicity may be increased in cases of hypercapnia. However, at clinical doses of lidocaine infusion, more than its cardiac toxicity, the cardioprotective effect of lidocaine has been confirmed in a prospective randomized study with patients scheduled for coronary artery bypass graft [72].

Similarly, lower doses of lidocaine cause an increase in brain inspiratory activity, while very high doses result in ventilator depression [73].

Lidocaine-induced convulsions could be provoked by the activation of limbic structures such as the hippocampus and amygdala or from decrease in the cortical inhibitory neurons. At usual clinical concentrations, more than its anticonvulsant action, lidocaine may be an effective neuroprotective agent in treating early postoperative cognitive dysfunction [74]. This cerebral protection could be explained through many mechanisms (reduction of cerebral metabolic rate, reduction of ischemic excite-otoxin release, and deceleration of the ischemic transmembrane ion shift) but probably overall by its anti-inflammatory and anti-apoptotic properties. Clinically, lidocaine alone has very few effects on the bispectral index [75].

Protocol of administration

The recommended lidocaine doses in the perioperative period are 1–2 mg/kg as an initial bolus (as earlier as possible to anticipate the onset of action and to prevent propofol injection) followed by a continuous infusion of 1–2 mg/kg/h. For long surgical procedures, it could be wise to recommend progressive decrease in the rate of lidocaine continuous infusion (approximate reduction by 50% every 6 h). Clinically, based on its safety and efficacy, it was usually recommended to prolong the infusion of lidocaine for 24–48 h. However, two recent reviews and meta-analysis [7,76] reported no clear benefit to prolong the infusion beyond post anesthesia care unit (PACU). This prolonged effect could probably be due to the prolongation of the half-life of lidocaine and its metabolites as described above. Therefore, it could be recommended to stop the infusion of lidocaine at the end of the PACU stay. It is probably not recommended to add another LAs administration (infiltration or regional anesthesia) due to the risk of cumulative LAs toxicity.

In the OFA protocol, and because many of the drugs used in continuous infusion (anti-NMDA receptors, α-2 agonists receptors, anti-inflammatory drugs, magnesium sulfate, etc.) have a similar mechanism of action, or at least, a very close target, the doses may be slightly reduced. Similarly, because all these analgesic molecules have a sedative action, the target dose of the drugs used for anesthesia must be reduced (i.e., propofol or volatile agents) particularly in the case of close monitoring of depth of anesthesia and cardiovascular response.

Conclusion

Although the exact mechanism of action is not yet fully clear, continuous lidocaine infusion shows clear analgesic benefits, particularly in OFA or ORA procedures. It clearly improves the postoperative outcomes with increased patient satisfaction. Such procedure should be included wisely in the enhanced recovery after surgery protocols.

Practice points

- **A:** Lidocaine with initial bolus and continuous infusion has clear analgesic benefits, particularly for sparing opioids (opioid-reduced anesthesia) or for avoiding opioids (opioid-free anesthesia).
- **B:** On the basis of various meta-analyses, the recommended lidocaine doses in the perioperative period are 1–2 mg/kg as an initial bolus followed by a continuous infusion of 1–2 mg/kg/h. For long surgical procedures, it is recommended to progressively decrease the rate of lidocaine continuous infusion (approximate reduction by 50% every 6 h). Because there is no clear benefit to prolong the infusion, it is recommended to stop the infusion of lidocaine at the end of the post-anesthesia care unit stay.

Research agenda

- **A:** Further research is warranted to evaluate the safety in terms of pharmacokinetics, particularly when lidocaine is used in continuous infusion and with different possible interactions (drug–drug interactions and metabolic or genetic interactions).
- **B:** To evaluate the pharmacodynamics. The mechanism of action remains unclear and probably does not involve only blocking of the voltage-gated sodium channels.
- **C:** After the mechanism of action is clarified, it would be interesting to develop some tools for the monitoring of "pain" before, during, and after surgery.
- **D:** Dose-ranging studies could be useful to know the best protocol of administration for a specific patient during a specific surgery.

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Conflict of interest

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Stable anesthesia with alternative to opioids: Are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-analyses of randomized controlled trials

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Introduction: The role of ketamine and magnesium in improving postoperative pain and diminish opioid consumption has been largely described. Synthetic opioids are known to provide hemodynamic stability when given for major noncardiac surgery. Definitive evidence on the role of ketamine and/or magnesium on intraoperative hemodynamic control would support their potential as alternatives to opioids during surgery.
Methods: The available literature published on PubMed/Medline and EMBASE was reviewed systematically to perform meta-analyses of randomized controlled trials (RCTs) assessing the effect of ketamine and/or magnesium on hemodynamic response to surgery as the primary outcome.
Results: From 352 studies, we identified 19 RCTs, and after exclusion of eight studies (seven for inappropriate data reporting and one in non-English language), we analyzed 11 RCTs (five for ketamine and six for magnesium sulfate) including, in total, 371 patients, of whom 94 *vs.* 95 received ketamine *vs.* placebo and 147 *vs.* 145 received magnesium *vs.* placebo, respectively. Results show that in quantitative analyses, ketamine *vs.* placebo did not show a significant effect on heart rate (+0.71 bpm; 95% CI [−1.52 to

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+2.93], $P = 0.53$) but significantly reduced variability of blood pressure (−8.4 mmHg; 95% CI [−15.1 to −1.8], $P = 0.0005$). In contrast, magnesium *vs.* placebo reduced variability of heart rate (−3.7 bpm; 95% CI [−6.5 to 0.9], $P = 0.01$) without a significant effect on systemic blood pressure (+4.2 mmHg; 95% CI [−3.6 to +12.03], $P = 0.29$).

Conclusion: In conclusion, these meta-analyses of nine trials confirm that ketamine and magnesium, differently but consistently, reduce hemodynamic variability during surgery and may be seen as complementary not only for pain control but also to provide stable anesthesia. This study supports the use of those drugs to control the sympathetic response to surgery in the context of opioid-free anesthesia.

Introduction

The principle of opioid-free anesthesia proposes that surgery under anesthesia can be safely performed without the use of intraoperative opioids. The principle implies the use of alternative non-opioid pharmacologic and pharmacologic techniques to achieve appropriate intra- and postoperative analgesia.

One of the main benefits of the use of synthetic opioids is that they provide good hemodynamic stability when given in low-to-intermediate doses [1,2]. An adequate maintenance of intraoperative hemodynamics has a considerable effect on postoperative outcomes. Several studies indicate that intraoperative hemodynamic instability is associated with increased postoperative morbidity and perhaps mortality. Therefore, any strategy oriented to reduce or abolish the use of opioids should also minimize the sympathetic response triggered by the surgical insult.

Ketamine and magnesium have been largely described to improve postoperative pain control. The literature has consistently reported that both drugs provide effective postoperative analgesia and reduction in opioid consumption. A meta-analysis aggregating data from 2482 patients showed that intravenous ketamine reduces postoperative opioid use by 40% [3]. Similar results have been shown with the administration of intravenous magnesium [4,5].

The effects of magnesium and ketamine on the cardiovascular system have been extensively studied in different clinical scenarios. However, there are insufficient data to conclude that any of those two drugs are potential alternatives to opioids to control the hemodynamic response to surgery. The main aim of this study is to assess the role of intravenous ketamine and magnesium in maintaining the hemodynamic response to major noncardiac surgery. Specifically, we hypothesize that magnesium and ketamine provide better hemodynamic control than placebo. To test this hypothesis, we conducted a qualitative and quantitative analysis of randomized controlled trials (RCTs).

Methods

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [6], we screened the literature published in PubMed/Medline and the EMBASE database.

Information sources, eligibility criteria, and study selection

We screened the PubMed/Medline and EMBASE (until November 2016) database using the keywords (((“Magnesium”[Mesh]) OR (“Ketamine”[Mesh]) AND “Surgical Procedures, Operative”[Mesh]) AND “Hemodynamics”[Mesh]). We used the PICOS framework (patient, intervention, comparison,

outcome, and study design) as proposed in the PRISMA statement. We limited the results to RCTs involving adults (aged >18 years) who received intravenous ketamine or magnesium for noncardiac surgery under general anesthesia as a single intervention (*vs.* control) and assessing the effect of ketamine and/or magnesium on hemodynamics during a surgical procedure.

Data collection and extraction

After the selection of the studies, relevant information from the original papers was extracted and registered in the Cochrane Collaboration's tool. Only publications in English were included. Extracted information included authors, date of publication, study design, type of surgery, type of anesthesia (only general anesthesia was considered), and number of participants. In the case of multiple doses or comparisons, the lowest dose (*vs.* placebo) was considered. With regard to the hemodynamic values, only the nadir (e.g., the highest deviation from baseline) was considered. Extraction of data was obtained from numerical values or from graphical expression as available. Studies without appropriate data reporting (e.g., size effect in terms of mean response) were excluded from the quantitative analyses. Missing data were considered as such.

Risk of bias details

Sequence generation, allocation concealment, blinding of participants and personnel, incomplete data outcome, selective output reporting, and any potential sources of bias were analyzed. Funnel plots were used to analyze a potential publication bias, and no evidence of such bias was found.

Statistical analysis

The outcomes were isolated from the studies identified as described above. For continuous outcomes (mean differences), the fixed effect mean difference for continuous outcomes was considered only in the case of homogeneity ($I^2 < 40\%$). For these continuous outcomes, data are presented as mean, with their 95% confidence intervals. Heterogeneity was assessed by the I^2 statistics for each comparison. An $I^2 > 40\%$ was considered to reject the homogeneity of the comparison (and to accept heterogeneity hypothesis). For all the comparisons, a *P*-value<0.05 was considered as statistically significant. In cases of heterogeneity, random effect models were used. Sensitivity analyses and random effect models were used to confirm the robustness of these methods (data not shown). All the analyses were performed using the RevMan 5.3.5 software (the Cochrane Collaboration, Oxford, UK).

Results

From 130 studies, we identified 14 RCTs, and after exclusion of five studies (for inappropriate data reporting), we analyzed nine RCTs (four for ketamine and five for magnesium sulfate) including, in total, 371 patients (Figs. 1 and 2, Table 1).

Ketamine trials

A total of 248 studies were identified by our search. Of them, eight RCTs were eligible, but three of them were excluded for inappropriate data reporting. Five were included in the meta-analysis [7–11]. In total, 94 *vs.* 95 patients received ketamine *vs.* placebo, respectively. In the quantitative analysis, ketamine *vs.* placebo did not show a significant effect on heart rate (+0.71 bpm; 95% CI [−1.52 to +2.93], $P = 0.53$), but it significantly reduced variability of blood pressure (−8.4 mmHg; 95% CI [−15.1 to −1.8], $P = 0.0005$) (Figs. 3 and 4).

Magnesium trials

A total of 104 studies were identified, of which nine randomized trials met the inclusion criteria (all with intravenous magnesium sulfate). Four studies were excluded for inappropriate data reporting;

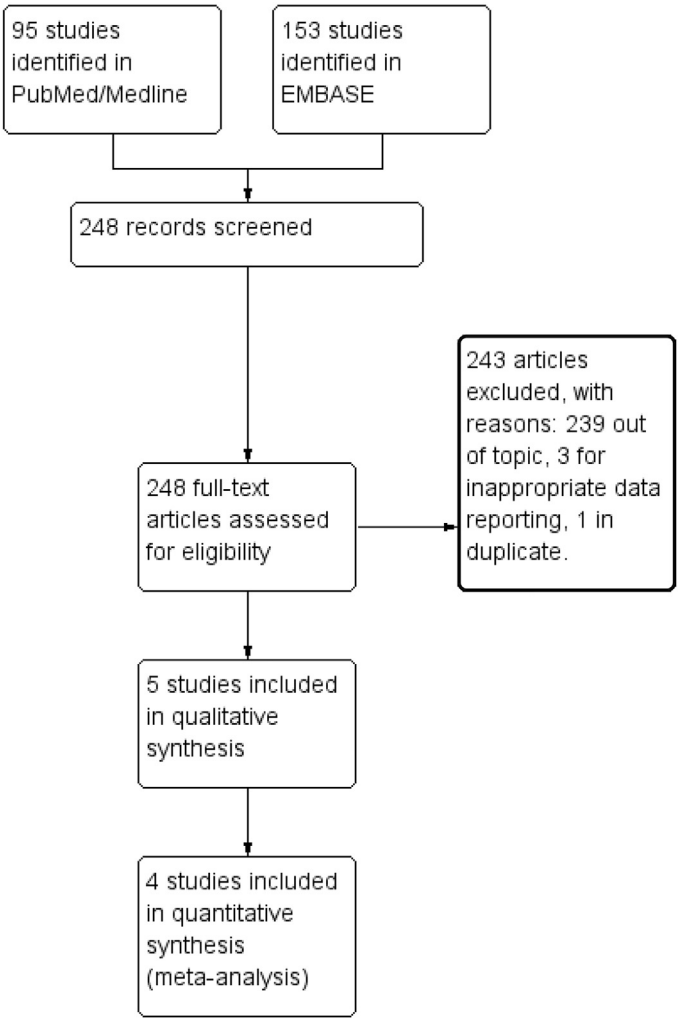

Fig. 1. PRISMA flow chart for ketamine trials on intraoperative hemodynamic stability.

thus, five trials were included in the meta-analysis [12–17]. A total of 147 *vs.* 145 patients were treated with magnesium *vs.* placebo, respectively. In contrast to ketamine, the use of magnesium significantly reduced variability of heart rate (−3.7 bpm; 95% CI [−6.5 to 0.9], $P = 0.01$) without a significant effect on systemic blood pressure (+4.2 mmHg; 95% CI [−3.6 to +12.03], $P = 0.29$) (Figs. 5 and 6).

Discussion

The present meta-analysis indicates that magnesium and ketamine given intravenously reduce hemodynamic variability during major noncardiac surgery. Specifically, low doses of ketamine decrease blood pressure variability, whereas magnesium provides stable heart rates in comparison to placebo. However, the clinical relevance of our findings is questionable as the magnitude of the effect on heart rate and blood pressure is modest.

Magnesium is a well-known antiarrhythmic drug that regulates voltage-dependent Na^+, K^+, and Ca^{2+} channels. As a result of its action on those channels, magnesium can prolong atrioventricular

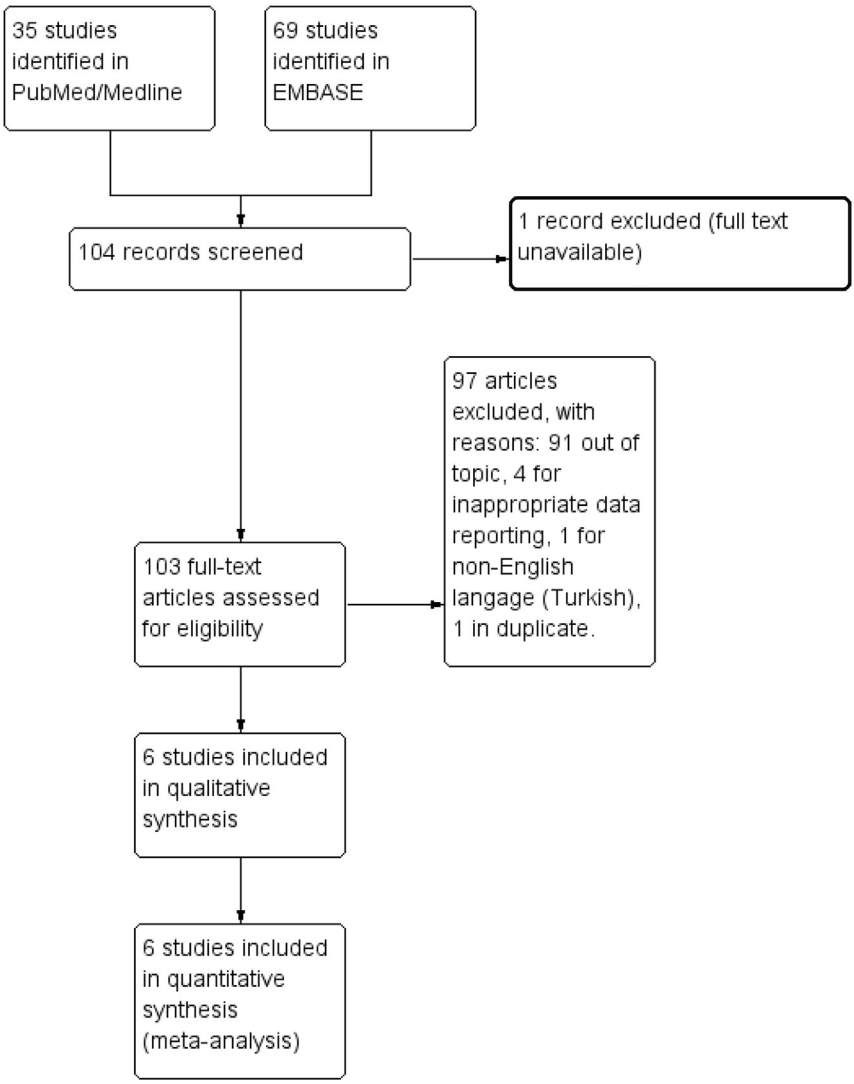

Fig. 2. PRISMA flow chart for magnesium trials on intraoperative hemodynamic stability.

nodal conduction times and PR and QRS durations [18]. Therefore, the observed effects of magnesium on the heart rate variability can be explained by its action on myocardial cell. However, we cannot rule out that the antinociceptive effects of magnesium might play a role in our findings. Adequate analgesia is typically associated with stable heart rates.

The observed effects of ketamine on blood pressure are more difficult to reconcile. Ketamine increases vascular tone by inducing the release of catecholamines; however, it can also induce vasodilation in small arteries by acting as Ca^{2+} channel blocker [19,20]. It is possible to speculate that at the doses used in the studies included in the meta-analysis, the sympathomimetic effects of ketamine are subtle; therefore, the observed maintenance in blood pressure is due to the action on the small vascular tree.

It can be argued that in the context of opioid-free anesthesia, the action of ketamine and magnesium simultaneously could be complementary to permit stable hemodynamics during anesthesia.

Table 1
Summary of the included studies in the meta-analyses. RCT: Randomized controlled trial. HR: Heart rate. BP: Blood pressurez.

First author/ year	Methods	Participants	Intervention	Outcomes
Agarwal 2001	RCT	Patients undergoing neurosurgery	Ketamine 0.5 mg/kg vs. placebo	HR, BP
Furuya 2001	RCT	Patients undergoing unspecified surgery	Ketamine 0.5 mg/kg + propofol 2 mg/kg vs. propofol 2 mg/kg	BP
Iwata 2010	RCT	Patients undergoing lung surgery	Ketamine 0.5 mg/kg vs. placebo	HR, BP
Satsumae 2001	RCT	Patients undergoing orthopedic surgery under tourniquet	Ketamine 0.25 mg/kg vs. placebo	HR, BP
Altan 2005	RCT	Patients undergoing spinal surgery	Magnesium sulfate 30 mg/kg followed by 10 mg/kg/h vs. placebo	HR, BP
Elsharnouby 2006	RCT	Patients undergoing endoscopic sinus surgery	Magnesium sulfate 40 mg/kg followed by 15 mg/kg vs. placebo	HR, BP
Jee 2009	RCT	Patients undergoing laparoscopic cholecystectomy	Magnesium sulfate 50 mg/kg vs. placebo	HR, BP
Oguzhan 2008	RCT	Patients undergoing lumbar disc surgery	Magnesium sulfate 30 mg/kg followed by 10 mg/kg/h vs. placebo	HR, BP
Ryu 2008	RCT	Patients undergoing gynecologic surgery under laparoscopy	Magnesium sulfate 50 mg/kg followed by 15 mg/kg/h vs. placebo	HR, BP

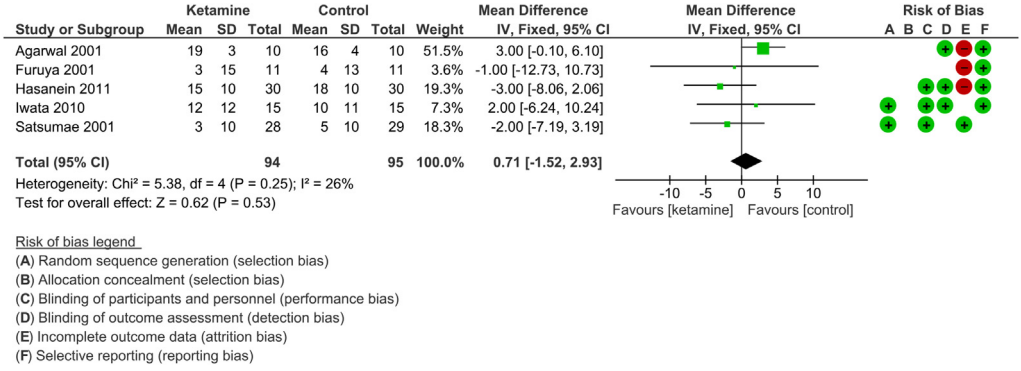

Fig. 3. Forest plot of comparison: Effect of ketamine on intraoperative variability of heart rate.

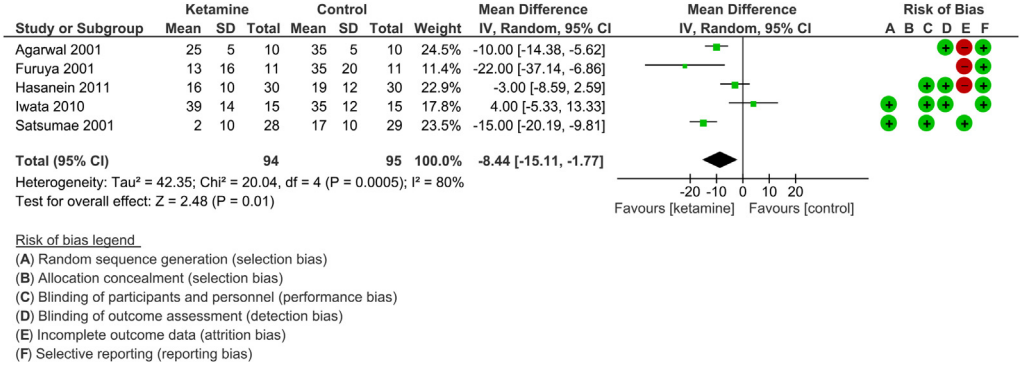

Fig. 4. Forest plot of comparison: Effect of ketamine on intraoperative variability of blood pressure.

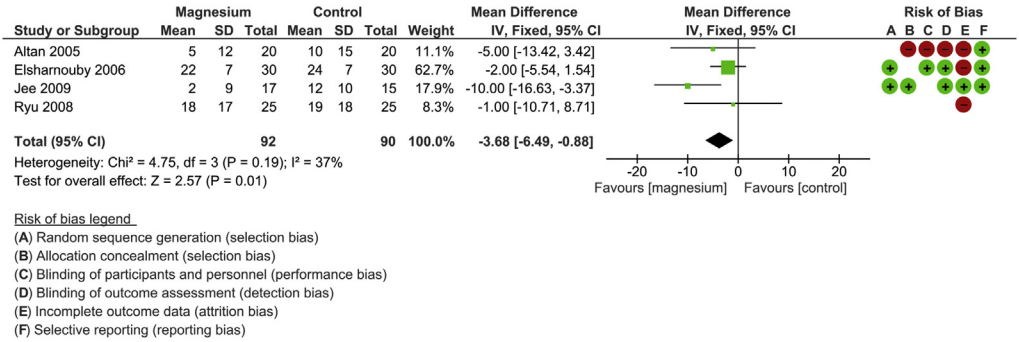

Fig. 5. Forest plot of comparison: Effect of magnesium sulfate on intraoperative variability of heart rate.

Furthermore, experiments on the association of these molecules may give us an important clue. Indeed, pretreatment with ketamine has demonstrated to improve the antinociceptive effect of magnesium [21]. Interestingly, the myocardial and endothelial cells express NMDA receptor [22,23]. Thus, a synergistic effect can be expected by the competitive blocking actions of drugs on the NMDA receptor in the cardiovascular system.

Our work has significant limitations. First, we focused our hypothesis on the impact that both drugs have on the hemodynamic response to surgery. Sympathetic activation in response to surgical trauma can be interpreted as a consequence of nociception. It can be argued that the concept of intraoperative pain (i.e., during the pharmacological coma associated with general anesthesia) is senseless because pain is a conscious experience. As previously mentioned, while ketamine can activate the sympathetic system when given at high doses, magnesium has the opposite effects. Therefore, our observations may only reflect the antinociceptive effect of both drugs and not their effect on the cardiovascular system.

Other limitations of our study include the various definitions (i.e., occurrence of hypotension) of these events, rendering the interpretation difficult, as reflected by the high heterogeneity, leading to the use of mostly random effect models. Moreover, the activation of the so-called (in the past) "pain matrix" is not anymore considered valid as the multimodal cortical representation elicited by painful stimuli is largely more complex and specific to the type of stimulation that can be seen during surgery [24]. Thus, not only pain cannot be assessed during general anesthesia but also cortical activation itself cannot be differentiated from pain because it might represent nonpainful sensorial modalities.

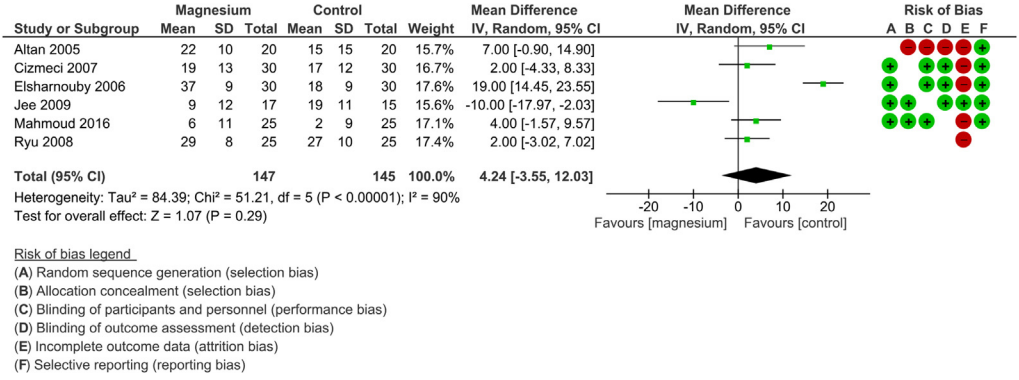

Fig. 6. Forest plot of comparison: Effect of magnesium sulfate on intraoperative variability of blood pressure.

Conclusion

In conclusion, the meta-analyses of nine trials confirm that ketamine and magnesium, differently but consistently, reduce hemodynamic variability during surgery. Therefore, the combination of both drugs may be seen as complementary not only to provide adequate pain control but also to maintain hemodynamic stability in the context of opioid-free anesthesia.

Practice points

- Ketamine and magnesium, differently but consistently, reduce hemodynamic variability during surgery and may be seen as complementary to provide stable anesthesia.

Research agenda

- The association of ketamine and magnesium to control the sympathetic response to surgery and to improve postoperative analgesia, in the context of opioid-free anesthesia, merits additional investigations.

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Authors contributions

PF designed the study. PF and JC, collected, selected and performed the analyses, the interpretation, prepared the manuscript and approved the final version.

Conflict of interest

None.

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8

Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks

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With increasing awareness of both short- and long-term problems associated with liberal perioperative opioid administration, the need for routinely and clinically feasible alternatives is greater than ever. Opioid-free anesthesia—previously reserved for bariatric surgery—is receiving increasing attention in mainstream anesthesia.
In this review, we present the truly multimodal concept of opioid-free anesthesia, which circumvents a number of opioid-related problems. For a concrete clinical perspective, we present in depth our opioid-free protocol for bariatric surgery.
However, clinicians must be aware of potential problems related to opioid-free anesthesia.

In August 2016, the Office of the US Surgeon General issued a letter and pocket card to 2.3 million medical professionals asking them to help address America's opioid epidemic. In a perspective article entitled “Ending the Opioid Epidemic – A Call to Action,” Dr. Murthy explained the reasons behind his unprecedented move [1]. One of the worrisome facts he pointed out was that the annual number of overdose deaths involving prescription and illicit opioids nearly quadrupled since 2000, in parallel

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with marked growth in the quantity of opioid pain relievers prescribed [2,3]. Although the campaign specifically addressed opioid prescription for chronic pain, the key lines on its "Turn the Tide Rx Pocket Card" should be kept in mind for analgesia in general: assess pain and function, consider whether non-opioid therapies are appropriate, talk to patients about treatment plan, evaluate risk of harm or misuse, and check when you use or prescribe opioids, start low and go slow.

Undoubtedly, there is consensus among caregivers and patients that adequate perioperative analgesia is paramount [4,5]. Acute postoperative pain is a major risk factor for developing chronic postoperative pain with all its potentially dire consequences [1,6,7]. The incidence of inadequately treated postoperative pain is at the same high levels as it was two decades ago [4,8]. Consequently, we as anesthesiologists are also challenged to look for alternative ways. In this article, we discuss opioid-free/opioid-minimal approaches and protocols in theory and practice. A protocol for an opioid-free perioperative regimen is presented, and potential associated dangers and limitations discussed. It is not the intention of this text to review all the non-opioid treatment protocols available, which have already been reviewed in detail elsewhere [9–11]. Nonetheless, we would like to emphasize perioperative pain protocols, as proposed from key opinion leaders [12].

Opioids can provoke severe side effects

Opioids still represent the mainstay of any perioperative analgesic treatment plan. However, opioids can provoke severe side effects. Some of these side effects such as postoperative nausea and vomiting (PONV) are obvious; some are of a more clandestine nature [13–15]. For example, both hyperalgesia and postoperative respiratory depression caused by opioids are of concern yet often go unnoticed [14,16]. Postoperative desaturation episodes are far more prevalent than generally appreciated [14], especially in patient groups with specific risk factors such as morbid obesity and obstructive sleep apnea [17,18]. Furthermore, undesirable side effects such as constipation, urinary retention, and drowsiness may significantly impede an otherwise uneventful postoperative course [19]. In times of ever more ERAS® (enhanced recovery after surgery) protocols emerging [20,21], the primary reliance on analgesic agents with such suboptimal side effect profiles seems outdated. Although an opioid (side effect)-free anesthesia and analgesia regimen long seemed elusive ("the Holy Grail") [22], newer truly multimodal protocols enable opioid-free (or at least opioid-sparing) anesthesia for certain types of operations [23].

Multimodal versus one product

Following the US Congressional "decade of pain control and research" [2001–2011] and pain being upgraded to "the fifth vital sign", pain therapy continues to be exceedingly disappointing [24], as illustrated by virtually unchanged rates of postoperative pain [8]. Some 3 out of 4 patients experience moderate, severe, or extreme pain [25]. At the same time, opioid prescription has reached all-time highs [1], although new and promising medications are largely missing [26,27]. Using the currently available options, what is the role multimodal anesthesia may play in providing satisfactory analgesia?

The concept of multimodal or balanced analgesia, generally attributed to Kehlet and Dahl, is now almost 25 years old and refers to attaining adequate analgesia through additive or synergistic effects of two or more analgesics, leading to reduction in doses and lower incidence of adverse effects from any particular medication [28]. Furthermore, a multimodal approach may potentially reduce central sensitization [6], one of the most underappreciated problems in the development of chronic pain [7,29]. Current guidelines also advocate a multimodal approach [30]. Intuitively, a "multimodal" approach triggering various stages of the pain pathway seems promising. Given the multitude of types of pain (e.g., neuropathic vs. nociceptive, malignant vs. non-malignant, acute vs. chronic/persistent pain, pain at rest vs. upon movement, etc.) and the number of sites potentially modifiable along the various neurochemical pathways, ranging from transduction, transmission, modulation, and perception, it should come as no surprise that pain therapy is not a "one-size-fits-all" solution [31]. Nonetheless, the results of multimodal analgesia have been disappointing [24].

How can the results of multimodal pain management be disappointing, given the plethora of meta-analyses within the last few years indicating effective analgesia and opioid reduction from various analgesic agents? There is such a wealth of literature that there are already reviews of meta-analyses [32]. Simple NSAIDs including acetaminophen have been proven effective, in meta-analyses, at reducing pain and/or sparing opioids in single doses [32], preemptively or preventively [33,34], and even more effectively in combination with one another [35]. The use of dipyrone (metamizole) may be a powerful and safe option [36]. α_2-Agonists also decrease pain and/or opioid consumption either as intravenous agents [37,38] or when applied to nerve blocks or neuraxial anesthesia [39]. Similarly, pregabalin/gabapentin in higher doses have been shown to be effective as perioperative adjuncts in reducing acute pain and/or opioid requirements [40], for preemptive analgesia [34], and in reducing the incidence of persistent or chronic pain [40]. Ketamine also has been shown to reduce pain as an adjunct to morphine [41], to confer preemptive analgesic benefits, and to reduce persistent post-operative pain in certain situations [42]. However, data on the preventive potential of ketamine on chronic pain are conflicting [43]. Finally, both intravenous lidocaine and magnesium have shown decreased pain scores and opioid requirements in the earlier postoperative period ($\leq$24 h), particularly in abdominal surgery [9,44].

A number of reasons may explain the disappointment in multimodal analgesia. First, "multimodal" may be quite minimal, potentially obscuring the full extent of benefits. For example, acetaminophen and an opioid fulfill the broader definition of the term, as illustrated by the (opioid-focused) WHO analgesic ladder [45]. Modern opioid-free concepts using a number of non-opioid analgesics [www.postoppain.org] may more suitably be called "multimodal." [46] Second, benefits that are currently well-established are not implemented, and appropriate structures may be missing [47]. In a recent analysis of nearly 800,000 patients in US hospitals undergoing below-knee amputation, open lobectomy, total knee arthroplasty, and open colectomy, the authors examined pain therapy on the day of surgery and thereafter [48]. On the day of surgery, approximately 97% of patients across the board received any opioid, but only 29.8% (colectomy) to 76.5% (total knee arthroplasty) received *any* non-opioid analgesic on the day of surgery! Even worse, only 3.7% (colectomy) to 44.7% (total knee arthroplasty) received *more than one* non-opioid analgesic on the day of surgery. This is particularly disappointing given the extreme underutilization of regional and local anesthesia [regional anesthesia 2.4% (below-knee amputation) to 25.2% (lobectomy)]. Other studies confirm these low rates of "multimodal" and truly multimodal analgesia and underscore structural/institutional inadequacies [49]. Third, surgery-specific protocols that are evidence-based, incorporate anesthesiological and surgical considerations, and include a risk-benefit analysis are required; not all interventions are the same. Studies and collaborations have begun to examine study-specific multimodal regimens for postoperative pain [31,46]. For example, the PROSPECT web-page (www.postoppain.org) provides a number of recommendations on what to do (and not to do) throughout the perioperative period, i.e. , preoperatively, intraoperatively, and postoperatively. Given that the observed effects in multimodal therapy often abate after an "early period," continuation of multimodal therapy into the postoperative period may prove beneficial. These recommendations frequently included non-pharmacological methods of analgesia, paracetamol, NSAIDs, and wound infiltration, i.e., a truly multimodal approach. However, the PROSPECT working group notes that a large part of the data available comes from unimodal interventions. This highlights the fourth point: scientific research and the scientific method. In their 2010 paper (before almost all of the previously mentioned meta-analyses were published), White and Kehlet reiterated their 2007 appeal that clinicians should "return to work!" [50] and conduct trials "rather than simply performing more meta-analysis and systematic reviews of the pain management literature." [47] However, comparing a complex multimodal therapy regimen to standard care may be contrary to a classical, step-by-step, scientific approach to causally determine effect. Furthermore, decreasing effect sizes (often measured by outcomes not highly relevant to clinical outcomes [50]) by adding a third or a fourth analgesic will greatly increase sample size, will potentially lead to underpowered analyses, may result in difficult-to-place "negative" studies, and may reduce transferability (e.g., external validity) [51,52]. But what does a comparison of acetaminophen vs. placebo mean for our patients? This analysis may be scientifically sound and embody the step-by-step approach, but are those the two clinical therapy options for colectomy (or almost any other procedure)? Acetaminophen or placebo? Fortunately, with the development of enhanced recovery

after surgery [ERAS® (http://erassociety.org/guidelines)] and opioid-free anesthesia protocols [53,54], steps toward comparing regimens with one another are emerging. That being said, for simpler day clinic or ambulatory procedures, a less extensive analgesic regimen may be appropriate. However, it should be kept in mind that analgesia for these procedures is also often insufficient [55].

Problems in using opioid-free anesthesia versus opioids

Although multiple regimens for an opioid-free/opioid-minimal perioperative analgesic management are possible, potential drawbacks or dangers have to be taken into account. While we have several thousand years of experience with opioids, we have less experience with the individual drugs used in opioid-free anesthesia, let alone their combinations. As the drug that clinicians may have the least experience with, we would like to emphasize some important caveats pertaining to dexmedetomidine administration. However, we are painfully aware that other, potentially more familiar, drugs also have drawbacks: the list of NSAIDs withdrawn from the market is impressively long, and NSAIDs may *inter alia* cause serious kidney damage [56] and anastomotic leakage [57].

Dexmedetomidine should be administered cautiously as several cardiovascular effects may occur. For example, dexmedetomidine should be given over at least 10 min as hypertensive episodes may otherwise be provoked [58]. Nonetheless, a generally hypotensive effect of dexmedetomidine (as well as clonidine) may be observed later as well [59,60]. In addition, bradycardia may commonly occur [61], and even cases of asystole have been reported [62]. Importantly, the use of dexmedetomidine is contraindicated in patients with higher degree AV-blocks. While there are certainly many benefits associated with the use of dexmedetomidine in the perioperative setting, caution is required. Let us remember the impact that liberal *de novo* use of perioperative β-blockers, undoubtedly with some similar hemodynamic properties as the α_2-agonists, have on patients' outcome: reduced risk of myocardial infarction but at the cost of increased risk of death, stroke, and clinically important hypotension [63,64]. In a further study, Devereaux et al. evaluated the effects of the α_2-agonist clonidine in patients undergoing non-cardiac surgery. They found that low-dose clonidine did not reduce the rate of death or myocardial infarction but increased the risk of clinically important hypotension and non-fatal cardiac arrest [59]. A cautious approach is advised with the use of α_2-agonists, especially in patients with severe cardiovascular disease.

Ideally, a multimodal drug combination causes greater analgesic effects and lesser side effects. However, this is not always the case, as pointed out in a study by Myhre et al., in which it was shown that the combination of a gabapentinoid and remifentanil caused additive analgesia but at the same time potentiated ventilatory depression and provoked some unwanted cognitive side effects [65]. Consequently, this study and the accompanying editorial remind us that a multimodal drug approach does not necessarily *per se* always reduce side effects [65]. Generally, data on adverse events related to combinations of non-opioids are sparse, and there is an urgent need for studies looking at benefit and potential harms of multimodal pain treatment [66].

Is it worth changing to opioid-free anesthesia?

The benefits of switching to opioid-free anesthesia are largely based on the avoidance of opioid-related adverse events. These benefits include benefits for the patient, benefits for hospital resources, and societal benefits. In a 2013 analysis of 300,000 patients, 12% of surgeries had opioid-related adverse events [19]. Patients with opioid-related adverse events had nearly twice the treatment costs, twice the length of stay, and a significantly higher readmission rate. Even after adjustment for a number of factors, treatment costs and length of stay remained significantly higher in this group [19]. Although the list of side effects is long, the two most common serious side effects are respiratory depression (3.3%) and ileus (6.1%) [19,67]. Further, similar to anesthesiologists being at a higher risk of opioid dependence on account of (occupational) exposure [68], patients given opioids and leaving the hospital with opioid prescriptions appear to be at a higher risk of opioid dependence [1]. Recent estimates for the “US epidemic” are 2 million dependent users and 12 million misusers for 2015 [1], a substantial socioeconomic burden. In addition, we know that perioperatively prescribed opioids also have a risk of misuse and abuse. In the setting of low-risk day surgery, recent research suggests that

patients prescribed opioids within 7 days of discharge are almost 50% more likely to still be receiving an opioid prescription at 1 year after surgery [69].

The final verdict is not in. However, the feasibility of opioid-free anesthesia has been demonstrated by a number of authors and protocols [23].

Low opioid dosing

Although it is possible to block autonomic hemodynamic reactions with high doses of opioids, this is a side effect-laden approach. Note that opioids are strong and rapidly acting autonomic blocking agents. However, they act so at a higher dose than required for analgesia. Thus, combining hypnotics (for anesthesia) and any of a number of autonomic blocking agents such as α_2-agonists [70], β-blockers [71], calcium antagonists [72], lidocaine [73], magnesium, or ketamine [74] could be an effective way of reducing or eliminating opioids [23]. From a philosophical perspective, it is uncertain what nociceptive firing during anesthesia really means for the patient and to what extent analgesics should be administered during anesthesia. Ethically, this is difficult to examine with the current standard of care, which explains a lack of studies in this area. Certainly adequate analgesia—through a multimodal approach—should be ensured during emergence from anesthesia. Preemptive or preventive analgesia with non-opioids [33,34], reduced surgical trauma through minimally invasive techniques, local wound infiltration, and non-opioid postoperative analgesia often suffice [23]. Furthermore, the hyperalgesic effect of opioids [15] and the role of secondary hyperalgesia on the development of chronic or persisting pain is one of the most underappreciated problems of (liberal) opioid administration [1,29,75].

Nonetheless, there may be situations in which some clinicians would generally administer some dose of opioid for immediate analgesic purposes (e.g., spinal anesthesia for Caesarian section) [76]. Although a number of other agents have been successfully used [77,78], their side effects, especially on the mother and child, may be limiting. However, even in these situations, an opioid reduction will probably be of benefit for the patient as the majority of opioid-induced side effects occur in a dose-dependent manner, and even single doses of opioids may cause hyperalgesia [23]. Interestingly, very low-dose fentanyl in rats has been shown to induce hyperalgesia but not analgesia [79].

In human studies, finding data with truly convincing clinical endpoints is challenging as postoperative opioid administration is often influenced by external factors, and the real clinical relevance of small differences in pain scores in the early postoperative period is uncertain. Furthermore, central sensitization such as secondary hyperalgesia is very rarely measured even in the experimental setting [7], and the antihyperalgesic properties of non-opioid analgesics is underexplored [78]. Finally, data on postoperative persistent/chronic pain associated with perioperative opioid dosing is rare [80,81] and potentially influenced by postoperative pain levels. Unfortunately, even factors such as clinical experience may be misguided in the context of the development of chronic pain as treating clinicians rarely follow-up on patient pain beyond the first few days [6]; this may be one of our collective "blind spots."

Nonetheless, a few general comments pertaining to perioperative opioid administration may be made. First, there seems little benefit to higher dose continuous remifentanil infusion (other than favorable pharmacokinetics and dynamics for the clinician) as it is fairly evident that hyperalgesia can result [15]. Reduction or avoidance of a longer acting μ-agonist may be more difficult. Higher doses of intrathecal and epidural fentanyl have also been shown to increase postoperative opioid requirements and/or have been associated with higher pain scores [76,82]. However, neither of these outcomes truly indicate central sensitization (e.g., hyperalgesia) [83] as commonly misconceived. In a cross-over experiment of experimental pain, we administered a high dose (10 μg/kg) and a low dose (1 μg/kg) of fentanyl to healthy volunteers and measured acute pain by the numeric rating scale (NRS) and hyperalgesia by pinprick test [13]. The higher dose showed a 30% greater area of hyperalgesia but also lower pain scores (0.8 units) some 5 h after fentanyl administration. This apparent dissonance of increased hyperalgesia (+30%) but better analgesia (−0.8 units) may be common to longer lasting μ-agonists (but not remifentanil). This solicits the question of the clinical relevance of hyperalgesia *per se*. It seems possible that persistent or chronic pain may ensue [29,75,80,81].

While remifentanil is relatively easy to avoid in most situations, hyperalgesia resulting from longer-lasting μ-agonists poses a potential problem. Which opioid should we use, if one is really required?

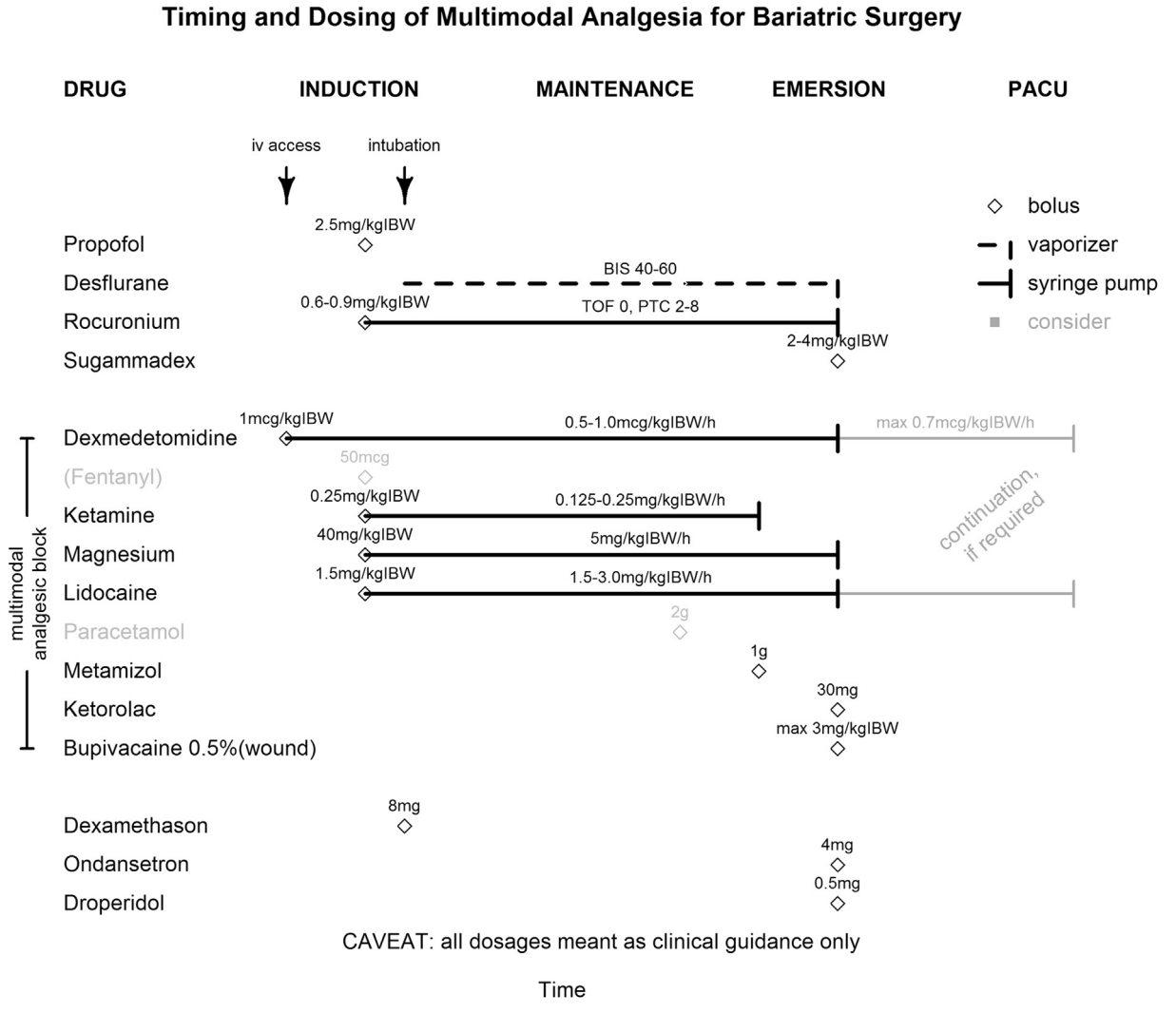

Fig. 1. Timing and dosing of multimodal analgesia for bariatric surgery.

Three things should be considered. First, the old adage "use as little as possible, but as much as necessary" will limit general use. Second, opioid selection is procedure specific and depends on the timing of nociception (e.g., remifentanil for short intense peaks, such as during craniotomy and pin placement). Third, clinician familiarity is important for patient safety. Hyperalgesia is probably a class effect, with the possible exceptions of racemic methadone [84,85] and μ-agonists-antagonists [86].

In summary, while completely opioid-free analgesia may not be (or may not be perceived to be) an option in all situations, a critical evaluation of opioid dosing and a full-fledged consideration of alternatives/adjuncts can and should take place in every patient.

Multimodal analgesia concept for bariatric surgery

Patients scheduled for gastric bypass surgery or sleeve gastrectomy often are enrolled in an opioid-free regimen at our institution. In this multimodal analgesic concept, several known and established non-opioid analgesic treatments are combined to eliminate (or at least minimize) opioid dosing [23]. In the case of laparoscopic bariatric surgery, this works remarkably well. Often it is even possible to totally abstain from opioids and still sufficiently block the autonomic nervous system reaction to painful stimuli. Several non-opioid drugs known for a (mild) analgesic effect are used [87]. These are, among others, dexmedetomidine, ketamine, lidocaine, and magnesium [9,73,88,89]. All these different agents are given as bolus doses at the start of anesthesia and are then continued at predefined rates (Fig. 1 schematically shows our perioperative protocol). Dexmedetomidine is best started as soon as an intravenous line is established and at least 10 min prior to induction (the bolus infusion is administered over the course of 10 min). As a result, by the time of induction, a good sedative effect and autonomic block is present, and any intubation stimulus is sufficiently blunted. Of note, this effect is somewhat slower with dexmedetomidine than with opioids. After preoxygenation, an induction dose of propofol is given (propofol 2.5 mg/kg IBW with additional bolus until loss of consciousness). As soon as the patient is unconscious, a bolus dose of ketamine is administered and neuromuscular blockade with rocuronium initiated. Importantly, given even the smallest suspicion of a difficult intubation, an awake fiberoptic intubation should be chosen. Once the patient is intubated, desflurane anesthesia is started, aiming for a Bispectral Index Scale (BIS®) value of 40–60. Dexmedetomidine and ketamine infusions are continued at predefined rates, and lidocaine and magnesium infusions are begun. Administering lidocaine prior to surgery as a bolus (1.5 mg/kg IBW) is also an option and may help further reduce a reaction to intubation. All infusions are then continued at predefined rates (or ranges) until the end of the intervention (or even beyond). The only exception is ketamine, which is stopped 30 min prior to the end to minimize any potential psychotomimetic side effects. PONV prophylaxis with dexamethasone (after induction) and ondansetron (prior to emersion) is given. Both these substance classes are known for some mild analgesia apart of their primary antiemetic action [90,91]. Dexamethasone has been shown to provoke hyperglycemia in obese patients with diminished glucose tolerance, so it is prudent to check glucose levels perioperatively [92]. In addition, classic analgesic medication such as acetaminophen and NSAIDs are administered at the end of the intervention. In this regimen, the use of acetaminophen may be limited as some studies have shown a loss of analgesic efficacy when acetaminophen and serotonin receptor antagonists were combined [90,93]. However, there are conflicting data on this, and larger trials are still needed to confirm a clinically meaningful interaction [94]. In sum, the analgesic protocol outlined above allows for opioid-free/opioid-minimal anesthesia in routine laparoscopic bariatric interventions. In our experience, patients treated according to this protocol have an astonishingly smooth recovery from surgery.

Dexmedetomidine for bariatric surgery

Dexmedetomidine is a highly selective α_2-agonist. It is approximately 8 times more specific to $\alpha 2$ adrenergic receptors than clonidine, and its elimination half-life is much shorter (2 h vs. 11.4 h) [95]. As early as 2002, Ramsay et al. presented the results of a study in morbidly obese patients testing the hypothesis that dexmedetomidine would improve postoperative pain management [58]. The authors had initially planned to include 80 patients in their study yet decided to stop the trial after the inclusion of only 25 patients because of the clear benefits of dexmedetomidine treatment. In addition to standard

care, the patients in this study randomly received an infusion of dexmedetomidine or saline 1 h prior to the end of the surgery. The study infusion was started at 0.5–0.7 μg/kg/h and adjusted intraoperatively according to the involved anesthesiologist. The study medication was continued postoperatively in the recovery room to keep the patient comfortable (maximal dose of 0.7 μg/kg/h dexmedetomidine). Additional analgesia was provided with 1- to 2-mg morphine boli. While there were no differences between the two groups in the time to extubation, the patients in the placebo group had significantly higher blood pressures and heart rates in the recovery room. At the same time, dexmedetomidine-treated patients received significantly less morphine. Further analysis revealed that all the patients in the placebo group required an airway intervention: all needed chin-lift post extubation, 62% needed a nasopharyngeal airway inserted, all had at least one episode of hypoxia (O_2 saturation below 90%), and 23% even needed reintubation. On the contrary, in the dexmedetomidine-treated group, none of the 12 patients required an airway intervention [58]. In 2006, this same bariatric surgery center had already treated over 2000 bariatric surgery patients. According to their experience, dexmedetomidine has been a significant factor in enabling over 85% of their patients to be discharged within 24 h of admission [96]. Furthermore, Ramsay concludes that dexmedetomidine seems to be ideal for the morbidly obese patient group because of its quality of analgesia and sedation while at the same time enhancing patient safety through lack of airway and ventilation compromise [58].

Hofer et al. reported similar experiences with the use of dexmedetomidine in a 433-kg morbidly obese patient with obstructive sleep apnea and pulmonary hypertension scheduled for Roux-en-Y gastric bypass [70]. The patient refused preoperative epidural placement. Thus, dexmedetomidine was chosen as primary analgesic for the intervention as the authors feared opioid associated perioperative respiratory depression. Immediately after anesthesia induction, a loading dose of intravenous dexmedetomidine 1.4 μg/kg (dosing weight based on an estimated lean body mass of 175 kg) was administered over 10 min, followed by a continuous infusion of 0.7 μg/kg/h. This rate was continued without cessation until the end of the first postoperative day. The authors describe an uneventful intraoperative course (low anesthetic requirements of isoflurane, 0.5 minimum alveolar concentration). No opioids were given prior to emergence. Upon awakening, the patient denied any pain and only complained of the endotracheal tube. Because of inadequate breathing patterns and the extreme obesity, the patient was transferred to the intensive care unit (ICU) for gradual weaning from mechanical ventilation, with uneventful extubation on the next morning. Interestingly, the patient exhibited lower opioid requirements during the first postoperative day while receiving dexmedetomidine (48 mg of morphine by PCA) as compared to the second postoperative day (148 mg of morphine by PCA) with similar pain scores.

In 2014, a further study on dexmedetomidine in bariatric surgery was published [97]. In this study, the authors compared a conventional arm (volatile anesthesia and opioids) with an opioid-free total intravenous anesthesia (TIVA) using propofol, ketamine, and dexmedetomidine. Patients in the TIVA group received propofol titrated to a BIS® level between 40 and 60, dexmedetomidine in a loading dose (0.5 μg/kg iv over 10 min), and with a continuous perfusion syringe thereafter (0.1–0.3 μg/kg/h). Additionally, prior to skin incision, 0.5 mg/kg ketamine was given. This study again proved the feasibility of an opioid-free anesthesia/analgesia concept in bariatric surgery. Furthermore, while the study team did not detect any difference between the two groups regarding pain levels and hydromorphone consumption during the recovery room period, both frequency and severity of PONV events were clearly reduced in the opioid-free TIVA arm (absolute risk reduction of 17.3%; number-needed-to-treat (NNT) = 6).

Use of dexmedetomidine in other situations and comparison with clonidine

The benefits of a dexmedetomidine infusion are not uniquely reserved for bariatric surgery. In various types of other procedures and patients, it has been shown that adding dexmedetomidine to a perioperative analgesic regimen can be advantageous [98]. A recent meta-analysis on the intraoperative use of dexmedetomidine also concluded that there is ample evidence for a postoperative analgesic effect [10]. Arain et al. found that the administration of dexmedetomidine before the end of a major inpatient surgery (initial loading dose of 1 μg/kg over 10 min, followed by 0.4 μg/kg/h for 4 h) reduced the early postoperative need for morphine by 66% [99]. Obviously, in a patient group in which

we particularly fear the side effects of opioids (i.e., postoperative hypoventilation, PONV), like in the morbidly obese or OSAS patients, this finding is especially relevant. Apart from its analgesic effect, dexmedetomidine also provides sedation, hypnosis, anxiolysis, and sympatholysis [11,37]. Most of the literature concerning dexmedetomidine addresses its sedative properties, particularly in the ICU setting [100]. It is possible that these sedative and anxiolytic properties contributed to the subjective better postoperative experience in some patients in the study by Arain et al. [99]. Because of the significant pharmacodynamic and pharmacokinetic differences of the α_2-agonists, the authors of a recent meta-analysis analyzed the influence of dexmedetomidine and clonidine on postoperative opioid consumption and pain intensity separately [37]. They found that both drugs given intraoperatively reduced postoperative morphine consumption. While dexmedetomidine treatment led to a significant decrease in opioid consumption from the 2nd postoperative hour until the 24th postoperative hour, clonidine had opioid-decreasing effects from the 12th until the 24th postoperative hour. In their analysis, morphine-sparing was more pronounced with dexmedetomidine than with clonidine: on average, 15 mg less morphine in the dexmedetomidine trials vs. only 4 mg morphine spared in the clonidine trials [37]. Both agents led to decreased pain intensity at 24 h (0.7 cm on the 10-cm VAS scale); however, at 48 h postoperatively, this pain-relieving effect was gone [37]. The authors could further show that the α_2-agonists reduced the incidence of early postoperative nausea: the NNT to prevent nausea with these agents was approximately 9. At the same time, they found no evidence that the treatment with α_2-agonists would delay recovery times.

Use of low opioid dose postoperatively as escape

Acute, insufficiently treated postoperative pain is not only traumatic for patients and frustrating for physicians but also a risk factor for the development of chronic pain and can increase postoperative morbidity [1,6]. As such, any discussion of chronic pain should also address acute postoperative pain. Severe postoperative pain may indicate the *temporary* need for an opioid, but it certainly indicates the need to reappraise the multimodal pain therapy. An underappreciated, effective, and quick-acting option is the use of local anesthetics [24]. The administration of an opioid and ketamine will buy time to optimize therapy (both pharmaceutical and non-pharmaceutical factors) and improve analgesia [41] and may reduce hyperalgesia [101]. Non-pharmaceutical options may be as simple as ensuring a warm environment (with facial warming) in slightly hypothermic patients. This has been shown to lead to significantly increased comfort scores and reduce self-administered analgesic agents [102].

If long-term opioid analgesia is perceived to be required, a combination of an opioid and NMDA-antagonist may be beneficial for the same reasons and should be administered with an antiemetic such as a serotonin 5-HT3 receptor antagonist, which also has some analgesic properties. An alternative in the absence of contraindications and provided that sufficient surveillance is available may be racemic methadone (the D-isomer is an NMDA-antagonist) [84].

As a concluding note, although not in the focus of this review, it is very important to be aware that psychological influences are an important outcome parameter on pain and especially the development of chronic postoperative pain. In our experience, it is crucial to be aware of psychological features and involve them in the therapeutic plan as well.

Summary

We would like to reiterate both the feasibility and necessity of truly multimodal, opioid-free analgesia in the perioperative period. For an increasing number of surgical procedures, total opioid-free or at least low-opioid anesthesia is possible and advisable. Several different protocols are available, should be employed, and will continue to be refined and applied to various interventions. The protocol we use in our center for bariatric surgery has been presented in detail.

Dr. Murthy's call – issued in August of 2016 – cannot be loud enough. A 2017 article in the New York Times stated that 2016 had the largest annual jump in drug-related deaths; fueled by the opioid crisis, drug-related deaths are now the leading cause of death among Americans under the age of 50 [103]. Recent studies have illustrated the skyrocketing prescription of opioids in the perioperative period in

the US [104,105]. In low-risk, opioid-naïve patients, approximately 70%–80% of patients filled prescriptions for an opioid postoperatively [104,105], and 13% of these continued to fill opioid prescriptions some 90–180 days later [104]. In another study in over 64,000 patients undergoing a mix of general surgical procedures, opioid-naïve patients required a median 15 days to discontinue postoperative opioid use [105]. It appears that the current opioid epidemic is in part based on the perioperative period and our indiscriminate administration of opioids. This is simply not acceptable.

Practice points

- Opioid-free anesthesia is feasible and confers many benefits.
- A truly multimodal approach using several analgesic agents may improve both short- and long-term outcomes.
- We, as perioperative physicians, should take on a leading role in halting the opioid epidemic.

Research agenda

- More and larger clinical trials exploring the efficacy of multimodal, opioid-free analgesic regimens are required.
- A better understanding of potential interactions among non-opioid analgesics is needed.
- Further research is warranted on understanding how analgesic drugs may affect hyperalgesia and persisting pain.

Conflicts of interest

None.

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Special indications for Opioid Free Anaesthesia and Analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery

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chronic obstructive behaviour
addictive
complex regional pain syndromes

Opioid-free anaesthesia (OFA) is a technique where no intra-operative systemic, neuraxial or intracavitary opioid is administered with the anaesthetic. Opioid-free analgesia similarly avoids opioids in the perioperative period.
There are many compelling reasons to avoid opioids in the surgical population.
A number of case reports and, increasingly, prospective studies from all over the world support its benefits, especially in the morbidly obese population with or without sleep apnoea.
A derivative technique is opioid sparing, where the same techniques are used but some opioid use is allowed.
This chapter is a review of the current knowledge regarding opioid-free or low-dose opioid anaesthetic and analgesic techniques for the following special populations: obesity, sleep apnoea,

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chronic obstructive pulmonary disease, complex regional pain syndromes, acute/chronic opioid addiction and cancer surgery.
Practical aspects include sympatholysis, analgesia and Minimum Alveolar Concentration (MAC) reduction with dexmedetomidine; analgesia with low-dose ketamine and co-anaesthesia; and sympatholysis with intravenous lignocaine.
Non-opioid adjuvants such as NSAIDS, paracetamol, magnesium, local anaesthetic infiltration and high-dose steroids are added in the perioperative period to further achieve co-analgesia.
Loco-regional anaesthesia and analgesia are also maximised.
It remains to be seen whether OFA and early postoperative analgesia, which similarly avoids opioids, can prevent the development of hyperalgesia and persistent postoperative pain syndromes.

Definition

Opioid-free anaesthesia (OFA) is a technique where no intraoperative systemic, neuraxial or intracavitary opioid is administered with the anaesthetic. Opioid-free *analgesia* similarly avoids opioids in the perioperative period.

For each component of the technique in Fig. 1, this chapter aims to guide readers to appraise the evidence base regarding OFA and assess its efficacy and safety.

This chapter also provides a clinical protocol to assist those who seek to use OFA in the operating room.

Morbid obesity and breathing-related sleep disorders (OSA)

The goals of avoiding opioids in the obese surgical population include the reduction or prevention of:

- Respiratory depression
- Central muscle rigidity

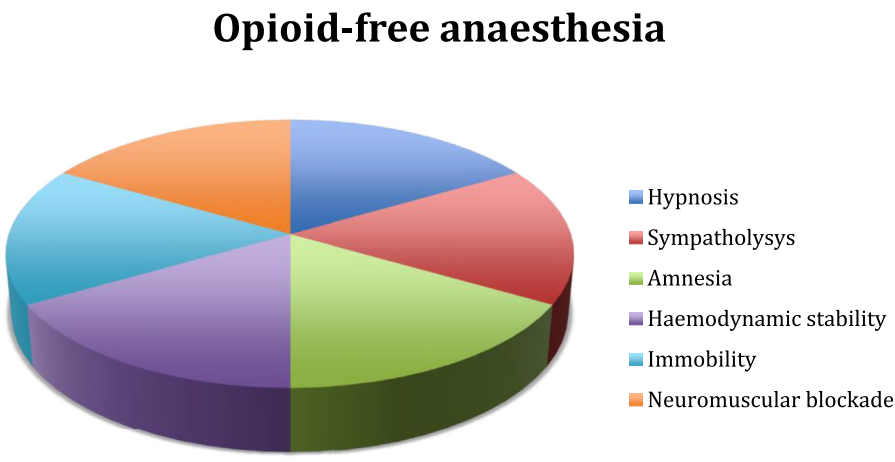

Fig. 1. Components of the OFA technique adapted from Mulier [1].

- Pharyngeal muscle weakness
- Obstructed breathing
- Negative inotropism
- Nausea, vomiting, ileus and constipation
- Urinary retention
- Tolerance and addiction
- Dizziness and
- Excessive somnolence.

It is highly desirable to avoid respiratory depressants in patients who are diagnosed with or suspected of having sleep-disordered breathing or obstructive sleep apnoea to reduce postoperative complications.

To address the opioid-related adverse events described above, the Sydney Institute of Obesity Surgery (SIOS) has adopted an OFA technique for the bariatric population irrespective of a diagnosis of sleep-disordered breathing. The technique instituted at the SIOS is modelled upon the experiences described by Mulier and De Kock and separately by Zieman–Gimmel [2].

Opioid-free and opioid minimisation techniques have also become a part of enhanced recovery after surgery protocols [3] for bariatric and other surgical interventions (Fig. 2).

The approach that the SIOS has adopted and that is detailed in this chapter is an example of a successful protocol (Fig. 3) that attempts to eliminate the 'opioid step' of the WHO ladder altogether. The OFA concept carries intra- and perioperative pain management beyond any of the steps in the analgesic ladder. It intends to create a new understanding of the physiological response to pain and opioids and includes expectation management to improve the level of safety and efficacy in the delivery of anaesthesia, especially for the morbidly obese and to enhance treatment outcomes.

The first two steps of the WHO analgesic ladder [5] emphasise the use of paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) before starting the use of opioids.

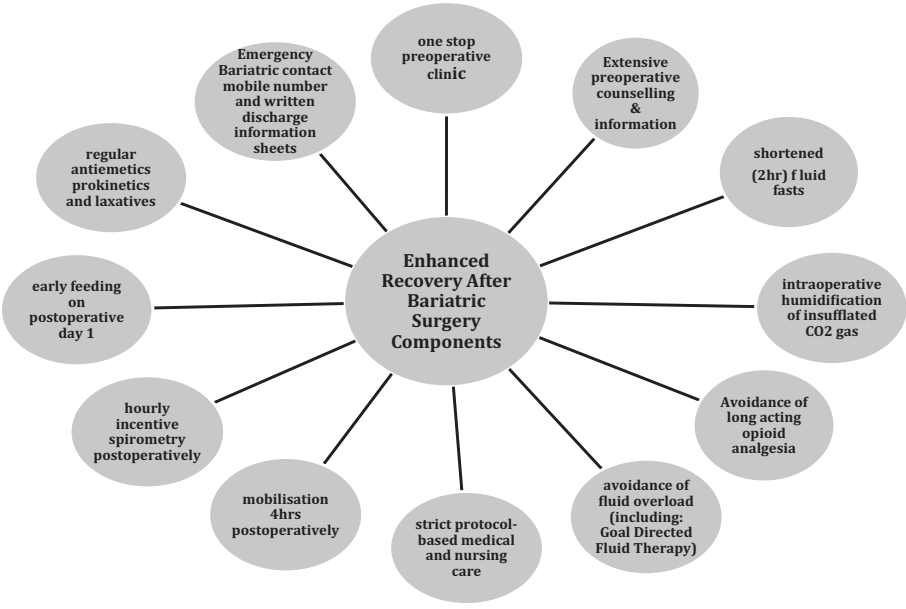

Fig. 2. Adapted from "components of enhanced recovery after bariatric surgery". Obesity Surgery. 2014; 24(5):753–758. https://doi.org/10.1007/s11695-013-1151-4, Awad S, Carter S, Purkayastha S et al. Enhanced Recovery After Bariatric Surgery (ERABS): Clinical Outcomes from a Tertiary Referral Bariatric Centre with open permission [4].

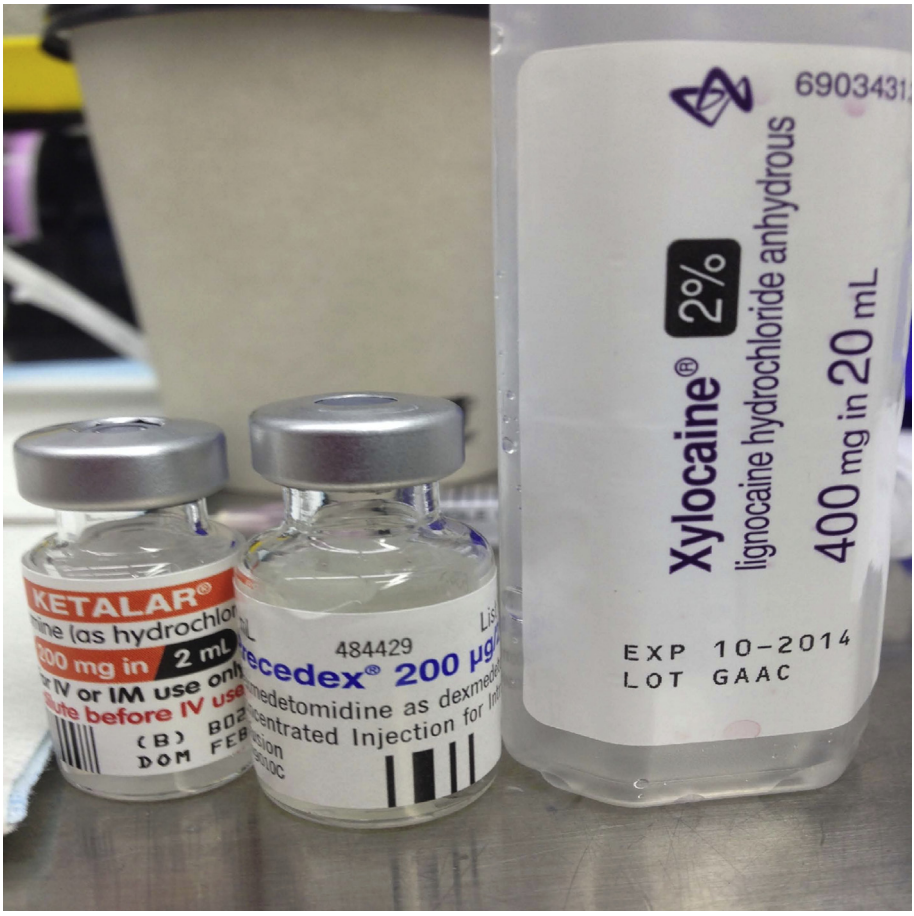

Fig. 3. Multimodal infusion (after Mulier). Dexmedetomidine: 10 μg/ml; Ketamine: 2.5 mg/ml; Lignocaine: 20 mg/ml.

In comparison, an opioid-free technique seeks to maximise the benefits of multiple analgesic adjuncts to achieve synergism of their different mechanisms of action.

Paracetamol (Acetaminophen)

Paracetamol is opioid sparing, effective and safe in the bariatric population [6]

Scheduled intravenous administration of this agent is indicated when the obese bariatric patient is nil by mouth in the early postoperative period rather than on a per-request basis.

NSAIDs

The Cox-2 drug parecoxib is a popular form of NSAID in Australia. It has a low side effect profile [7], particularly regarding gastric adverse events. It is approved by the Therapeutic Goods Administration [8] for use as a one-off dose perioperatively. Parecoxib may be substituted with any other NSAID, provided that the practitioner gives due consideration to bleeding risks and gastric mucosal integrity.

Magnesium

Magnesium acts as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) and has anti-inflammatory effects because it reduces plasma interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) levels in the postoperative setting [9].

A number of meta-analyses and RCTs within the past 5 years [10,11] have prompted a change regarding the efficacy of magnesium described in the important review of acute pain evidence by Schug and others [12].

While they previously disputed that magnesium had benefits, the 4th edition now reads.

> 'IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores'.

Recommended doses included a loading dose of 40–50 mg/kg ideal body weight (IBW), followed by a maintenance infusion of 10 mg/kg/h^2.

Clinicians who integrate magnesium as part of their OFA regime should be mindful of its potentiation of neuromuscular blocking agents and therefore should also pay careful attention to dosing regimens for the latter drugs. Quantitative monitoring of neuromuscular blockade is imperative.

Because of its vasodilating properties as a calcium channel antagonist, magnesium may also act as a hypotensive agent. The use of magnesium may be limited for this reason in a multimodal regimen that employs propofol or inhalational anaesthetic agents, alpha$_2$-agonists and the reverse Trendelenburg position frequently used in bariatric surgery.

Dexamethasone

Dexamethasone is a potent mineralo-glucocorticoid with proven efficacy [13] as an antiemetic for a variety of surgical procedures.

We have incorporated dexamethasone into our multimodal technique on the basis of De Oliveira's work and others where doses of >100 μg/kg in lean adults have clinically significant analgesic properties [14].

We also note that Bartlett [15] and others have cautioned against its routine use in an editorial, and they highlight patients who are diabetic and undergoing procedures (including bariatric) where anastomotic breakdown could be catastrophic.

The editorial generated controversy in subsequent correspondence, and we would await studies in clinical patients that demonstrate harm before we would review our practice.

Ketamine

Ketamine is another non-competitive antagonist of the n-methyl-D-aspartate receptor and is commonly used either as a small bolus of 0.25–0.5 mg/kg IBW or in a low-dose continuous infusion at 2–2.5 μg/kg/min.

Schug and others have summarised its benefits in APMSE4 [10] (Table 1) in both the general acute pain [16] population and bariatric patients [17].

Table 1
'Ketamine in acute pain' according to Schug [10].

- Reduces the incidence of chronic postsurgical pain
- Reduces opioid consumption
- Reduces time to first analgesic request
- Reduces postoperative nausea and vomiting compared to placebo
- Improves analgesia when combined with opioids
- Reduces the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use
- Reduces postoperative pain in opioid-tolerant patients
- Is especially useful when combined with magnesium

Table 2
Clonidine vs Dexmedetomidine.

Clonidine	Dexmedetomidine
Alpha 2 > Alpha 1	Alpha 2 > Alpha 1
220:1	1620:1
Partial agonist	Full agonist
Mildly lipophilic	Highly lipophilic
Reduces MAC by 50%	Reduces MAC by 90%
Plasma T1/2: 9–12 h	Plasma T1/2: 2–2.5 h
PB 50%	PB 94%
Elimination half-life: 8 h	Elimination half-life: 2 h
Distribution half-life: >10 min	Distribution half-life: 5 min
Inactivation at the locus coeruleus 'similar to normal sleep'	

Alpha-2 agonists Dexmedetomidine and Clonidine

The alpha$_2$-adrenoreceptor agonists represent a historical anomaly. They were pre-eminent in veterinary anaesthesia long before they became commonly used in human anaesthesia [18]. These drugs become difficult to use or unsuitable in the context of cardiovascular compromise. Noting the importance of accounting for interspecies variability known from veterinarian medicine, it is also important to appreciate the possibility of inter-patient variability. When using alpha$_2$-agonist-based techniques, careful haemodynamic and anaesthetic depth monitoring should be employed.

Over-sedation and haemodynamic compromise, specifically bradycardia and hypotension, are the main risks. Over-sedation can be avoided by timely cessation or tapering of maintenance infusions; bradycardia and hypotension often need to be treated with anticholinergic and vasoactive agents including ephedrine [19].

In the context of OFA, Schug and others in APMSE4 [10] conclude that:

Systemic alpha$_2$-agonists **reduce**
- Postoperative pain intensity
- Opioid consumption and
- Nausea

without prolonging recovery times [10].

The role of dexmedetomidine during opioid-free or opioid-sparing regimes in general surgical patients, the morbidly obese and, particularly, in sleep-disordered breathing patients is supported by a number of papers [20–24].

This has led to its inclusion in opioid-free regimens [25].

It is also worth noting the utility of dexmedetomidine in chronic obstructive pulmonary disease [20] patients.

Dexmedetomidine also preserves both sleep architecture [26] and airway patency [21].

Table 3
According to Palmer [47].

CRPS Prevention strategies and the anaesthetist
- Regional, sympathetic or epidural block or infusion
- Corticosteroids
- Non-steroidal anti-inflammatory drugs (NSAIDS) including COX-2 inhibitors
- Clonidine, ketamine or lignocaine infusions

(Reprinted from Aust Prescr 2015; 38:82–61 Jun 2015 https://doi.org/10.18773/austprescr.2015.029 with the permission from the author Ass Prof. Greta Palmer).

The pharmacokinetics of dexmedetomidine in the morbidly obese are believed to support its dosing under a LBM or IBW protocol [27,28].

At SIOS, we set the syringe driver at 100 kg for the simplicity of dosing.

A TCI program for dexmedetomidine has been published [29], but a 'smart' pump manufacturer has not yet adopted it.

Clonidine is also useful. However, its pharmacodynamic/pharmacokinetic profile may be undesirable [30] in the anaesthesia context because of its roller coaster effect on haemodynamics and prolonged sedation. Accordingly, we only recommend its use to top-up an inadequate sympatholytic state (Table 2).

Lignocaine (Lidocaine)

Lignocaine is a short-acting amide local anaesthetic agent. It is potent as a sodium channel blocker and has been shown to provide excellent analgesia when administered intravenously [31]. The evidence base supports lignocaine as an analgesic agent, an opioid-sparing agent, an anti-inflammatory and a co-anaesthetic [32]. It has particular benefit in the preservation and restoration of gastrointestinal function [33] and reduces the incidence of postoperative nausea and vomiting [34].

Just 3 years after it was synthesised and described for use as a local anaesthetic, the innovative use of lignocaine as a potent intravenous analgesic for labour pain, postoperative and cancer pain [35] was reported. Its use as a mainstay for the inpatient treatment of acute migraine was pioneered in Sydney, Australia, as early as the 1970s [36].

Grassi [37] has commented that the widespread use of systemic lignocaine for acute pain management is off-label but that it would be almost criminal to deny critical groups of patients (respiratory cripples, for example) its benefits.

Esmolol

This ultra short-acting cardio-selective beta 1 adrenergic blocker may be useful in attenuating unwanted sympathetic response during OFA [38].

Practicalities of OFA for bariatric surgery

Our own use of the multimodal mixture pioneered by Mulier [39] has been previously described [40].

We utilise a loading and maintenance intraoperative dose of dexmedetomidine/lignocaine/ketamine.

More recently, we combine this technique with TCI propofol (Schnider protocol) and have found that only moderate effect site target concentration (Cet) targets of 2.5–4.0 μg/ml are required if TBW is programmed as the weight scalar for the TCI [41].

Prior to induction of anaesthesia, a loading multimodal infusion based on 100 kg IBW is started at 20 ml/h equivalent to

- 2 μg/kg/h of dexmedetomidine
- 0.5 mg/kg/h of ketamine and
- 4 mg/kg/h of lignocaine

Patients are then induced with 2 mg/kg IBW of propofol and intubated with the aid of 1 mg/kg IBW rocuronium, after which maintenance with propofol TCI at 2.5–4 μg/ml effect site target concentration (Cet) is continued and neuromuscular blockade is maintained with 0.5 mg/kg/h (IBW) of rocuronium for the duration of pneumoperitoneum.

Routine antiemetic prophylaxis is administered with ondansetron, and dexamethasone is given in high dose both as an antiemetic and an adjunctive analgesic.

The loading multimodal infusion is continued until head-up position, peritoneal insufflation and placement of abdominal ports are complete.

The multimodal infusion is then progressively stepped down to 10 and 5 ml/h, equivalent to 1 and 0.5 μg/kg/h of dexmedetomidine, respectively.

To avoid delayed awakening and over-sedation, we interrupt the multimodal infusion 10–20 min prior to cessation of surgery [41]. Additional analgesia is provided with 1–2 g of intravenous paracetamol and 40 mg of parecoxib, together with intraperitoneal local anaesthetic and wound infiltration. At the end of surgery, complete reversal of neuromuscular blockade is performed, often using sugammadex as the preferred reversal agent.

The multimodal infusion is restarted upon arrival in the postanaesthesia care unit (PACU) at the lower rate, equivalent to 0.5 μg/kg/h of dexmedetomidine, where it is frequently the only analgesia required. In suitable patients, it may be used as a bridge to fentanyl PCA prior to ward transfer.

We are awaiting the evolution of nursing protocols prior to continuing an opioid-free technique for extended analgesia on the ward or high dependency unit.

Chronic postsurgical pain

Katz et al. [42] at Toronto General Hospital have introduced the concept of a Transitional Pain Service with the aim of preventing chronic postsurgical pain.

They describe how 'a multidisciplinary perioperative pain management plan is created prior to surgery'. In addition to surgical, logistic and behavioural components, the plan involves extended acute pain relief using all the non-opioid adjuncts discussed in this chapter including ketamine, alpha$_2$-agonists and lignocaine.

It is anticipated that if other groups follow the lead from Toronto, data collection from multicentre trials will unearth the outcome data that are necessary to select the interventions, which prevent the development of chronic postsurgical pain (Fig. 4).

Cancer surgery

Hontoir and Saxena et al. have shown statistically significant improvement in patient comfort after oncologic breast surgery prospectively with rigorous blinding and statistical analysis and using a clonidine/lignocaine/ketamine combination in the opioid-free group [43].

We therefore conclude that a well-conducted opioid-free technique such as the one we have described offers a clinical benefit to this group of patients, some of whom may suffer from obesity and sleep-disordered breathing.

As to the wide-ranging discussion on whether anaesthetic technique affects long-term outcome or recurrence after cancer surgery, there appears to be limited evidence.

Surgery, the processes of anaesthesia and individual anaesthetic agents have a complex effect on immunity, and each component may eventually prove to affect cancer outcome in its own way [44].

Basic cancer cell biology suggests that opioid analgesics inhibit both cellular and humoural immune function. It is conceivable that opioid avoidance therefore may improve cancer outcomes. However, definitive prospective data are not yet available.

Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is a painful debilitating condition in a limb. It is associated with abnormalities in skin; bone; and the autonomic, sensory and motor nerves [45]. The condition, once established, is extremely difficult to treat and causes severe disability.

Anaesthetists may therefore play a role in the primary or secondary prevention of CRPS. All the multimodal techniques described here under OFA may have a role; however, only limited evidence is available in the literature [46] (see Table 3).

Role of opioid-free/multimodal analgesia in the opioid-tolerant patient

As a consequence of the worldwide epidemic of substance use disorders, chronic non-cancer opioid therapies and the recognition of dependence as a result of opioids for acute pain in some patients,

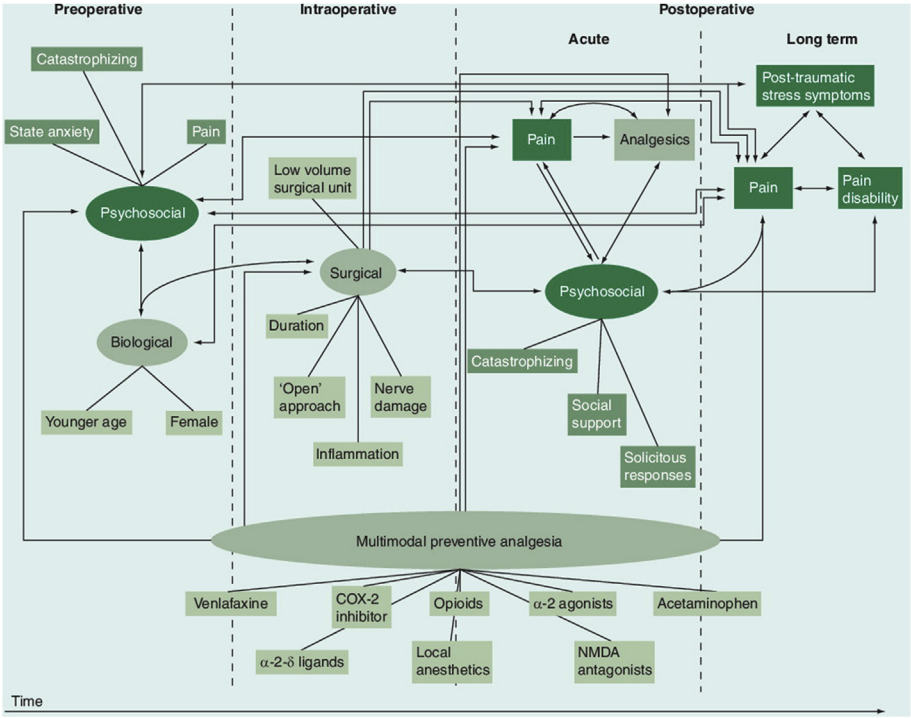

Fig. 4. Reprinted from J Pain Res. 2015 Oct 12; 8:695–702. https://doi.org/10.2147/JPR.S91924. eCollection 2015, 'The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain' with permission from Katz et al.).

anaesthetists will encounter opioid-tolerant patients presenting for surgical procedures on a regular basis. Management of the acute pain in opioid-tolerant patients includes their opioid maintenance dose and providing analgesia by opioid-reduced or opioid-free multimodal analgesia. Huxtable et al. have reviewed this topic [48] in detail, and their plan is reproduced with permission (Table 4).

In this group of patients, opioids will still form a substantial part of the inpatient management; however, buprenorphine maintenance therapy is fraught with problems and may need to be substituted with methadone.

Every possible component of the multimodal armamentarium should be introduced early during the patient's admission. However, success in preventing the escalation of opioid doses is not guaranteed, and the evidence for this approach is nascent.

Alpha$_2$-agonists offer added advantages in this special patient population because of their beneficial effects in preventing opioid withdrawal symptoms while doses are being adjusted or opioids are being rotated.

Case report

We present a case report of an opioid-tolerant patient who presented for sleeve gastrectomy. Her acute pain was managed with OFA as follows:

A 36-year-old woman with a body mass index of 40 kg/m^2 presented for elective sleeve gastrectomy *18 months after a sequential anterior and posterior lumbar intervertebral fusion. S*he was suffering from severe back pain and anxiety/depression.

Her maintenance drug regimen included long-term treatment with codeine 300 mg/day, citalopram and prednisolone. She was intolerant to

Table 4
Principles of acute pain management in opioid-tolerant patients.

Acute pain management in opioid-tolerant patients Table 4	
Preoperatively	
1. Preoperative planning	Assessment Patient education including management plan (admission to discharge) Ensure usual prescribed opioid (including buprenorphine) is taken on the day of surgery In MMT or BMT, consider arranging a 'take away' dose for self-administration on day of surgery Liaise with other healthcare professionals as indicated
Inpatient management	
2. Intraoperative analgesia	Replace usual opioid Titrate additional opioid to effect Consider risk of awareness Use non-opioid and adjuvant drugs
3. Postoperative analgesia	
a. Give adequate doses of opioid in addition to usual opioid	Incremental doses that are higher than the age-based doses usually prescribed for opioid-naive patients may be needed (including higher PCA bolus dose) Much higher than expected total daily opioid doses may be required Titration to effect for each patient remains important Monitor pain, functional activity scores and sedation Expect the need for more frequent review and adjustment of dosing
b. Strategies that may help to attenuate tolerance or OIH	Opioid rotation Ketamine
c. Use of non-opioid and adjuvant analgesic drugs	Limited or no evidence of benefit in opioid-tolerant patients but may be useful: Paracetamol and/or NSAIDs Gabanoids Lignocaine
d. Regional analgesia	Central neuraxial or other regional blockade (consider a catheter technique) Useful as part of a multimodal regimen Neuraxially administered opioids may not prevent opioid withdrawal
4. Prevention and treatment of withdrawal syndromes	Maintain usual opioid dose equivalent Give usual opioid (including buprenorphine) or give equivalent dose of another opioid or same opioid by a different route Monitor for drug withdrawal (opioids and other drugs) Drug replacement or symptom management (e.g. clonidine, benzodiazepines)
5. Close liaison with other treating clinicians and specialist teams	In-hospital and post-discharge pain management Related social, psychiatric and behavioural issues
Management after discharge	Liaison with community providers Discharge management plans Consider legislative restrictions for opioid prescribing Consider early follow-up or relevant new referral

(Reprinted from Anaesthesia and Intensive Care 2011; 39:804–23, 'Acute pain management in opioid-tolerant patients: a growing challenge' with permission from Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE.)

- NSAIDs
- Fentanyl
- Oxycodone
- Morphine
- Tramadol

However, she could tolerate pethidine, which unfortunately was no longer available at the hospital where she was treated.

Intraoperatively, she received an opioid-free anaesthetic using the modified Mulimix technique supplemented by desflurane and neuromuscular blockade. Sixteen milligrams of dexamethasone, paracetamol and intraperitoneal infiltration with ropivacaine 0.75% were also administered.

The surgical course was uneventful (Fig. 5, jpeg attached), and her immediate PACU stay was initially complicated by over sedation (chin lift needed) and nausea (droperidol 0.5 mg).

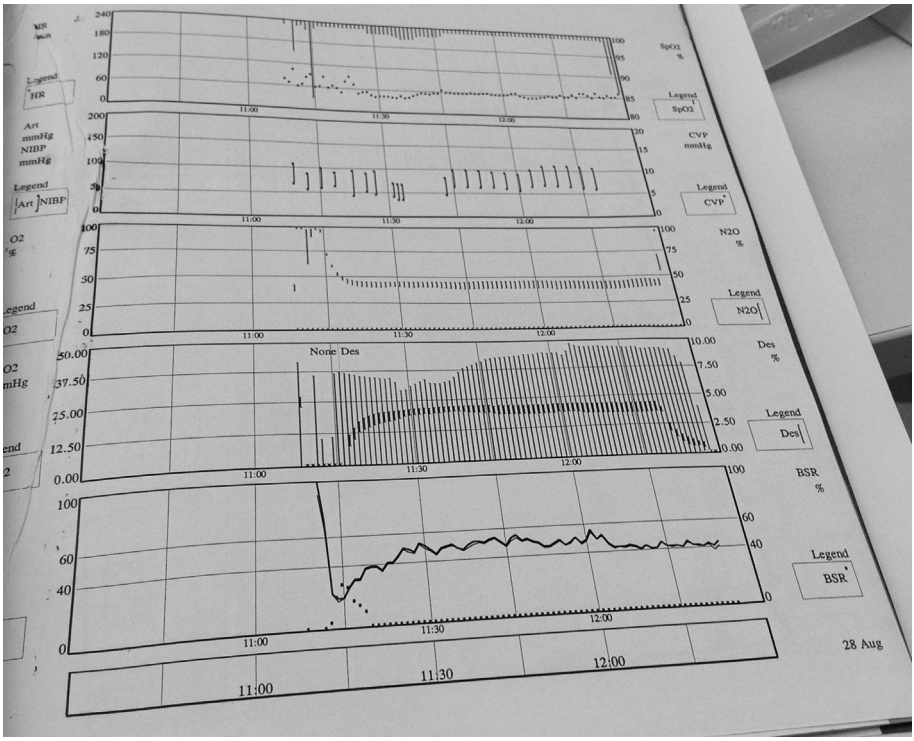

Fig. 5. Opioid tolerant Intraop data.

The opioid-free mixture of dexmedetomidine, lignocaine and ketamine was continued with a low-dose continuous infusion (equivalent to 0.5 μg/kg/h of dexmedetomidine, 0.125 mg/kg/h of ketamine and 1 mg/kg/h of lignocaine).

In the PACU, she was transitioned to a patient-controlled analgesia device programmed with the same mixture, whereby she would receive dexmedetomidine 10 μg, lignocaine 20 mg and ketamine 2.5 mg per bolus locked out for 5 min. Intravenous paracetamol at 1 g every 6 h for 24 h was part of the regimen.

The patient self-administered 7 doses of PCA overnight and was able to return to her routine oral medication the next day. No further opioid or non-opioid analgesia was required during her 2-day inpatient stay.

This case study suggests that multimodal OFA and analgesia play a role in the acute pain management of the opioid-tolerant patient presenting for incidental surgery. Further research is indicated.

Summary

Opioid-free anaesthesia has come of age as an alternative to standard opioid-based techniques in the management of morbidly obese patients for bariatric surgery.

Evidence-based techniques employing core analgesics and adjuvant drugs such as magnesium, ketamine, alpha$_2$-agonists and systemic lignocaine are effective in avoiding large doses of opioids and avoiding the use of remifentanil.

Hypnosis, analgesia, amnesia, sympatholysis and haemodynamic stability are achieved during pneumoperitoneum for upper gastrointestinal surgery, while immobile surgical conditions are maintained with accurate neuromuscular blockade.

Similar agents are used postoperatively to maintain opioid-free or opioid-sparing analgesia.

Opioid-induced hyperalgesia and the perioperative ill effects of opioids are thereby avoided. The technique may also be applied to

- Patients with respiratory compromise
- OSA without obesity
- Patients with opioid dependence and certain chronic pain syndromes and
- Oncology patients with clear benefits for ERAS protocols after colorectal and breast cancer surgery.

While groups of clinicians have embraced these concepts and techniques enthusiastically, large prospective studies from independent units worldwide are awaited. Such studies would cement the evidence base for obesity anaesthesia and the other special indications described in this study.

Conflict of interest

Dr. Adrian Sultana: None.
Dr. David Torres: None.
Professor Roman Schumann: None.

Practice points

- OFA techniques have been increasingly accepted, most frequently for morbidly obese patients undergoing bariatric surgery and especially in the context of sleep-disordered breathing.
- We have provided a specific example of a technique for a bariatric population that provides safe and effective OFA at SIOS.
- Multimodal techniques should include paracetamol and NSAIDs

Together with:

- Ketamine
- Dexmedetomidine
- Lignocaine
- Magnesium.

The level of evidence for magnesium is in support of its use in the context of OFA in clinical practice.

- Other sub-populations of patients may benefit from this technique including those with respiratory impairment, with chronic pain syndromes and opioid-tolerant patients.
- Basic science would suggest that patients having surgery for primary cancers may benefit from avoiding the immuno-depressant effects of opioids, and this technique has been clinically successful in breast and colorectal oncological surgery for reducing acute surgical pain.
- Avoiding opioids in high doses and remifentanil in particular would seem to be a clear method of avoiding opioid-induced hyperalgesia, and there is evidence for attenuation of hyperalgesic syndromes with the adjunctive use of ketamine and magnesium in adults.
- Opioid-tolerant patients presenting for acute painful interventions require expert care and planning. It is suggested that adding a multimodal opioid-free or opioid-sparing technique to their baseline opioid status may be of benefit for this challenging group of patients.

Research agenda

- Mulier's group has accumulated enormous data both prospectively and retrospectively with regard to OFA as applied to their practice for Roux-En = Y Laparoscopic Bypass [49].
- However, large outcome studies comparing standard opioid-based techniques with protocol-driven OFA are evolving from bariatric centres around the world.
- Patient population and procedure-specific regimen are awaiting clinical validation.
- The role of opioid-free adjuvants in preventing CRPS remains to be subjected to the same rigorous analysis for the management of this difficult condition.
- Despite difficulties, enrolment units with special experience in opioid-tolerant patients should investigate multimodal strategies in prospective clinical trials to assess the role of this pharmacological technique in the comprehensive management of their patients during acute pain episodes.
- The oncology community requires answers to the following questions: Are the immunogenic effects of opioids on cancer cells merely a study in cell biology or do they have relevance in the planning of anaesthetic techniques for cancer patients?"
- If avoiding opioids is ideal in surgical oncology, which cancers are most amenable to these techniques?

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