REVIEW

OPEN

The nuts and bolts of multimodal anaesthesia in the 21st century: a primer for clinicians

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Purpose of review

This review article explores the application of multimodal anaesthesia in general anaesthesia, particularly in conjunction with locoregional anaesthesia, specifically focusing on the importance of EEG monitoring. We provide an evidence-based guide for implementing multimodal anaesthesia, encompassing drug combinations, dosages, and EEG monitoring techniques, to ensure reliable intraoperative anaesthesia while minimizing adverse effects and improving patient outcomes.

Recent findings

Opioid-free and multimodal general anaesthesia have significantly reduced opioid addiction and chronic postoperative pain. However, the evidence supporting the effectiveness of these approaches is limited. This review attempts to integrate research from broader neuroscientific fields to generate new clinical hypotheses. It discusses the correlation between high-dose intraoperative opioids and increased postoperative opioid consumption and their impact on pain indices and readmission rates. Additionally, it explores the relationship between multimodal anaesthesia and pain processing models and investigates the potential effects of nonpharmacological interventions on preoperative anxiety and postoperative pain.

Summary

The integration of EEG monitoring is crucial for guiding adequate multimodal anaesthesia and preventing excessive anaesthesia dosing. Furthermore, the review investigates the impact of combining regional and opioid-sparing general anaesthesia on perioperative EEG readings and anaesthetic depth. The findings have significant implications for clinical practice in optimizing multimodal anaesthesia techniques (Supplementary Digital Content 1: Video Abstract, http://links.lww.com/COAN/A96).

Keywords

chronic postoperative pain, EEG monitoring, general anaesthesia, locoregional anaesthesia, multimodal anaesthesia, opioid-free anaesthesia

INTRODUCTION

Anaesthesiologists are crucial in providing effective intraoperative anaesthesia and minimizing pain, delirium, and postoperative nausea and vomiting (PONV). With the opioid epidemic posing a significant threat, approaches like the opioid-free anaesthesia (OFA) [1] and multimodal general anaesthesia (MMA) [2] are gaining traction. These strategies aim to prevent opioid addiction and chronic postoperative pain, aligning with the goals of the Enhanced Recovery After Surgery (ERAS) protocols [3,4,5▪,6]. Thus, anaesthesiologists increasingly focus on preoperative, intraoperative, and postoperative analgesia to address factors contributing to chronic postoperative pain.

High-dose intraoperative opioid administration has been reported to possibly lead to increased postoperative opioid requirements, a phenomenon

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Curr Opin Anesthesiol 2023, 36:000–000

DOI:10.1097/ACO.0000000000001308

KEY POINTS

- Multimodal anaesthesia focuses on polypharmacological anaesthesia analgesia, aiming to provide a sedative effect and suppress nociception at multiple physiological levels.
- Combining regional and opioid-sparing general anaesthesia is recommended to achieve synergistic effects and reduce the need for systemic analgesia.
- Surgeons should actively be involved in sharing responsibility for intraoperative and postoperative analgesia.
- Postoperative analgesia should go beyond opioids, with options such as intravenous lidocaine or lidocaine-ketamine perfusion, aiming to minimize side effects and improve recovery.
- Sleep hygiene is a fundamental aspect of multimodal anaesthesia, involving opioid-sparing strategies, undisturbed sleep, and adequate analgesia to support pain management, cognitive function, and overall patient recovery.

known as ‘opioids engender opioids’ [7,8]. This review seeks to provide an evidence-based and practical guide to MMA. It will explore drug combinations and recommended dosages and illustrate the typical EEG changes associated with MMA. Additionally, the review will examine the relationship between MMA and current consciousness and pain processing models. Nonpharmacological interventions targeting preoperative anxiety and postoperative pain will be discussed. Deep states of general anaesthesia should be avoided to reduce overdose with possible hemodynamic and cognitive side effects such as postoperative delirium (POD), PONV, and delayed neurocognitive recovery (DNR).

From a neurophysiological perspective, pain is no longer viewed solely as a bottom-up process. Emerging theories propose that consciousness actively generates hypotheses and predictions through predictive coding. These predictions interact with inputs related to maintaining internal balance, primarily controlled by the autonomic nervous system, brainstem, and subcortical affective circuits [9▪]. Disruptions to homeostasis trigger allostatic reactions to restore balance, leading to pain perception [10]. Preoperative anxiety and anticipation of pain can heighten postoperative pain levels and increase the need for opioids [11]. Recognizing the possibly predictive nature of consciousness underscores the importance of preemptive analgesia in MMA [12]. The interplay between the interoceptive system and nociceptive signals helps explain how inflammatory mediators and stress hormones influence the brain’s interpretation of pain. Additionally, understanding the placebo effect and its modulation of pain expectations through empathetic communication aligns with the principles of MMA [13,14] (Supplemental Digital Content 2, http://links.lww.com/COAN/A97).

WHY MULTIMODAL ANAESTHESIA?

The field of anaesthesia originates from using chemicals like ether and nitrous oxide to induce hypnosis, analgesia, and muscle relaxation [15]. Balanced anaesthesia, which combines hypnotic drugs and potent analgesics, was developed to optimize surgical outcomes. However, even classic balanced anaesthetic combinations, such as propofol + opioids or volatile anaesthetics + opioids, can sometimes lead to adverse effects such as PONV, worse pain control, impaired awakening, respiratory complications, and POD [15]. With the emergent opioid epidemic claiming numerous lives each year, there is a need for safer and more effective anaesthesia and analgesia approaches [16].

MMA, defined as combining anaesthetics and analgesics with different mechanisms of action [17], aims to provide additive or synergistic pain relief while minimizing side effects associated with higher opioid doses [18]. Surgeons also support using MMA, combining general anaesthesia with regional or local anaesthesia techniques, to improve outcomes [19–21]. They actively contribute to postoperative MMA by employing techniques such as local infiltration or inserting surgical site catheters [2,22–24]. The concept of ‘opioid stewardship’ is promoted by the ERAS Society, advocating for a critical evaluation of the opioid administration [25,26▪].

ARE OPIOIDS SAFE IN EVERY ANAESTHESIA?

The prevalence of opioid-based anaesthesia, its synergies with inhaled or propofol anaesthesia [27], and the lack of patient follow-up can contribute to uncertainty and resistance towards MMA. However, it has been observed that high doses of intraoperative opioids can result in increased postoperative opioid requirements and vice versa [28,29▪▪,30,31▪]. In a meta-analysis conducted in 2019, the level of postoperative pain 2 h after major abdominal and gynaecological surgery was found to be similar between opioid-free and opioid-inclusive anaesthesia, but the incidence of PONV was significantly higher in patients treated with opioids [32]. Despite a medical history of PONV, practitioners tend to administer propofol anaesthesia without restricting intraoperative opioids [33]. Hyperalgesia induced by opioids, even in healthy individuals without surgery, is still not widely recognized as a problem [34]. Short-acting opioids, such as remifentanil, can cause an increased incidence of postoperative hyperalgesia, while long-acting opioids can lead to long-lasting pain reduction [35]. N-methyl-D-aspartate (NMDA) receptors play a significant role in suppressing hyperalgesia [36], which highlights the importance of using NMDA antagonists like methadone, along with magnesium and ketamine, in modern analgesia. Recent studies have shed light on the neuroinflammatory pathophysiology of opioid-induced mast cell-mediated microglia activation and 'immunosenescence' [37], contributing to the chronification of pain, particularly in older patients [38,39▪▪].

Postoperatively, there is often a heavy reliance on opioid administration, which might exacerbate adverse events. For instance, the Prodigy study [39▪▪] revealed that opioid-induced respiratory depression is frequently underdiagnosed in hospital wards, leading to code-red calls. The association between opioids administered in oncologic surgery and poorer outcomes remains controversial and requires further clarification [40,41▪,42]. Figure 1 demonstrates how the abovementioned predisposing factors and intraoperative strategies might influence negative postoperative outcomes.

Intraoperative opioids can offer advantages beyond analgesia, particularly in brain and eye surgeries, effectively reducing brainstem reflexes such as coughing, gagging, and pressing. In cases where large wounds or bone trauma are not adequately covered by regional anaesthesia, administering opioids, along with ketamine, becomes imperative. Knowledge of the specific noxious surgical steps involved in a procedure enables the titration of analgesic boluses and the overall reduction of opioid infusion.

EFFECTS OF OPIOIDS ON THE EEG

Opioids can induce changes in the perioperative EEG [43▪,44], often having a synergistic effect to increase or stabilize hypnotic effect. These changes can include the loss or retention [44,45] of alpha waves (8–12 Hz) or an increase in delta power (0.5–4 Hz). These alterations can be observed in the raw EEG [46]. The spectrogram can sometimes show an increase in theta power. When analgesia is provided by a combination of ketamine and magnesium with propofol, opioid partial NMDA receptor agonists such as remifentanil and methadone can increase beta power in the EEG [47], and commercial indices can falsely indicate a lighter level of hypnotic depth.

PRACTICAL THOUGHTS ON MULTIMODAL GENERAL ANAESTHESIA FOR CLINICIANS

Premedication: anxiolysis and preemptive analgesia

One of the ERAS aims is to improve analgesia and minimize preoperative anxiety. Nonpharmacological methods, such as establishing a positive patient–clinician relationship, can release endogenous opioids and mitigate stress reactions. Mind–body therapies like hypnosis, meditation, cognitive–behavioural therapy, and guided imagery positively impact pain perception and reduce opiate consumption [48–50]. Music, computer games, or films can replace pharmacological premedication [51–53]. Music-induced analgesia reduces medication use

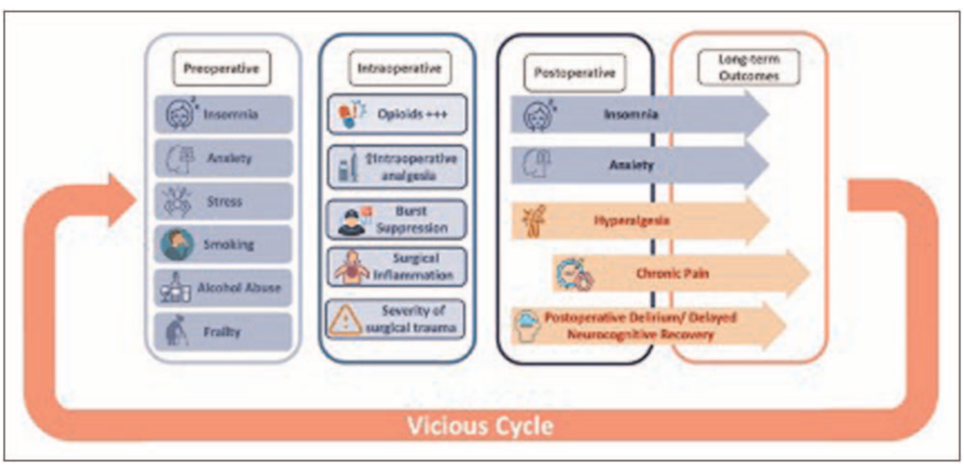

FIGURE 1. The interplay of preoperative risk factors and postoperative pain. A simplified chart illustrating the connection between postoperative pain, preoperative anxiety, and other risk factors like sleep disorders or smoking. Risk factors influence and intensify each other, are potentiated by certain intraoperative actions, influencing pain and its chronification, sleep patterns, and cognitive recovery, in a vicious cycle.

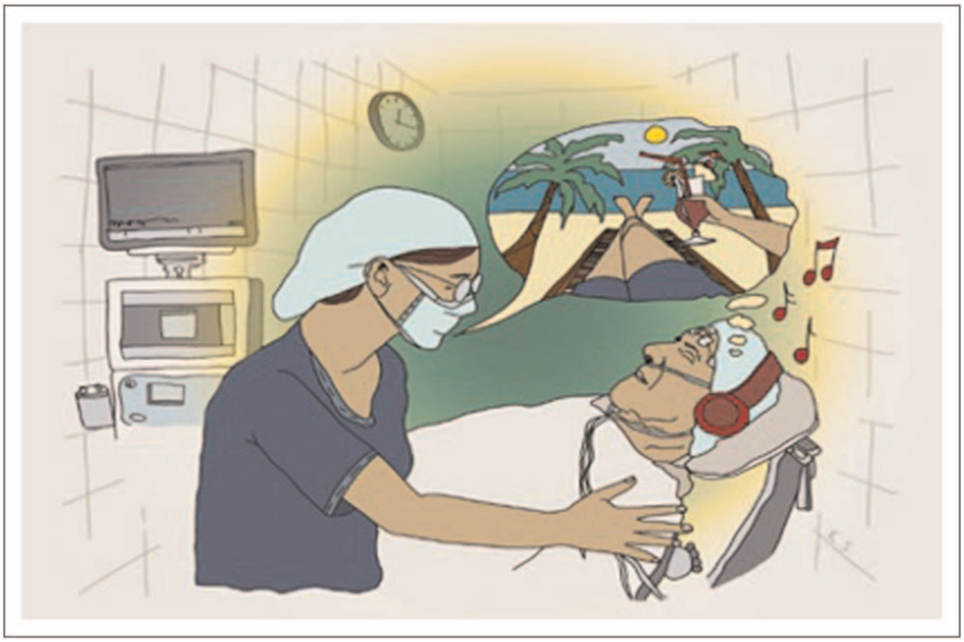

FIGURE 2. Nonpharmacological interventions in analgesia and anxiolysis: clinicians are increasingly employing nonpharmacological therapies for preoperative anxiety. A caring relationship releases endogenous opiates in patients as outlined in Jaak Panksepps's 'brain opioid hypothesis of social relations' [57]. This moderates adrenergic stress reactions, engaging mu-receptors for further pain reduction [58▪]. 'Mind–body therapies' (hypnosis, meditation, cognitive–behavioural therapy, guided imagery, etc.) can positively influence anxiety, nociception, and opiate consumption [48]. Music [52,54], a computer game, or a film can be added to pharmacological premedication as distractive elements, especially with children. 'Music-induced analgesia' [59] can be explicitly used as premedication, as confirmed in a meta-analysis including 4968 patients from 55 studies, where the use of midazolam, opiates, and propofol was significantly reduced.

without affecting the length of hospital stay [54] (see Fig. 2). Additionally, preemptive analgesia with NSAIDs and acetaminophen help reduce postoperative pain and the need for additional analgesics [55,56▪].

PHARMACOLOGICAL INTERVENTIONS IN MULTIMODAL GENERAL ANAESTHESIA

Alpha 2-receptor agonists

Alpha 2-receptor agonists like clonidine and dexmedetomidine are commonly used for co-analgesia, sedation, and delirium prevention. However, they can cause rebound hypertension and bradycardia. Dexmedetomidine, in particular, has significant sedative effects and induces 'biomimetic sleep' [60]. It can be used postoperatively in older patients to prevent or treat delirium [61,62▪▪]. Intranasal, oral, and intravenous administration routes are available, with intranasal use common in children [63]. Dexmedetomidine has shown efficacy in preventing POD [62▪▪,64▪]. Still, its antidelirium effect may be less evident in patients after cardiac or major surgeries because of its multifactorial cause in these populations [65]. When alpha agonists are given as premedication, they can reduce the induction dose of propofol required [66]. Therefore, EEG monitoring should ideally start while the patient is awake to minimize burst suppression during induction, especially in older patients [67▪]. It is worth noting that dexmedetomidine use can be expensive.

NSAIDs and acetaminophen

The preemptive administration of NSAIDs and acetaminophen is essential to ERAS protocols [68▪,69▪▪]. These medications provide preemptive analgesia by reducing inflammation and offering analgesic and anti-inflammatory effects. Studies have shown that preoperative use of NSAIDs and acetaminophen can reduce postoperative opioid consumption in various surgical procedures such as gynaecological [70], orthopaedic [71,72], and colorectal surgeries [73]. NSAIDs and acetaminophen can be safely used as postoperative analgesics in healthy patients and those with liver function impairment [74]. Oral administration of acetaminophen is cost-effective and comparable to intravenous administration [75]. To ensure safety, it is recommended to administer acetaminophen preoperatively in the hospital setting. Nonsteroidal analgesics play a significant role in MMA as they help decrease the reliance on opioids [76,77]. The guidelines provided by the ERAS Society support the use of acetaminophen and NSAIDs for visceral surgery, with higher evidence supporting their use in general gastrointestinal, gynaecological, and bariatric surgeries [78].

SYSTEMIC LIDOCAINE INFUSION

Based on the available evidence, perioperative lidocaine infusion can benefit patients undergoing open and laparoscopic abdominal procedures. These benefits include a small but significant reduction in opioid consumption, duration of ileus, and PONV [79]. This can enhance recovery and lead to a shorter hospital stay, particularly after colorectal surgery. In cardiac surgical patients, it has also been reported to be advantageous for respiratory outcome and confusion [80]. It is important to note that the initial bolus of lidocaine infusion should not exceed 1.5 mg/kg, and the maintenance [81▪] dose should not exceed 1.5 mg/kg/h to avoid the risk of fatal overdosing. Lidocaine infusion can be an alternative for patients who cannot undergo neuraxial analgesia because of contraindications [26▪,79,82].

Lidocaine's potential pro-epileptic effects are dose-dependent and rare [83]. In addition to its opioid-sparing effects [84], lidocaine has been shown to synergistically contribute to the sedative efficacy of propofol when administered systemically or epidurally, as suggested by a study using BIS measurements [13]. Furthermore, in awake patients, intravenous administration of a 1 mg/kg bolus of lidocaine has been observed to increase power in the delta, alpha, and beta frequency bands in the EEG [85].

KETAMINE

In MMA, ketamine is primarily used for its analgesic properties and ability to reduce the need for opioids [86▪,87]. However, it also has an antidepressant effect that can be beneficial during surgery [88▪]. The anti-inflammatory and neuroprotective effects of ketamine are discussed in the medical field [89]. A combination of ketamine and lidocaine infusion seems to be a reasonable approach to reduce the administered opioid dose further, but at least in colorectal surgery did not prove to be more efficient than given individually [90▪].

A recommended intraoperative dose of ketamine for MMA is typically between 0.2 and 0.5 mg/kg as an intravenous bolus, followed by a maintenance dose of 0.1–0.5 mg/kg/h [91]. When ketamine is administered, processed EEG readings can often be erroneously confusing as the indices may falsely indicate awake values. Alternatively, burst suppression, characterized by periods of bursting high-amplitude EEG activity followed by periods of low-amplitude inactivity, can occur when ketamine is added to propofol anaesthesia, especially in elderly patients. Monitoring the EEG response can provide valuable information about the resilience of the elderly patient's brains [92▪▪].

It is worth noting that ketamine alone can lead to gamma-burst suppression in the EEG, a specific pattern of brain activity [93▪]. Additionally, ketamine boluses are known to increase the risk of postoperative nightmares [94].

REGIONAL ANAESTHESIA IN COMBINATION WITH OPIOID-SPARING ANAESTHESIA

In various surgical procedures, the use of local anaesthetics can be beneficial. Local anaesthetics provide effective pain relief by blocking the amplification of nociceptive (pain) signals in the spinal cord's dorsal horn. This technique is particularly useful in eye surgery [95]. Additionally, anaesthesiologists may perform additional regional blocks such as PECS (pectoral nerves), TAP (transversus abdominis plane), axillary, femoral, and popliteal blocks to complement the analgesic requirements of specific surgeries. These combinations of local anaesthesia and regional blocks contribute to reducing the need for opioids and narcotics [19,20].

It is recommended to consult specific guidelines and recommendations for different types of surgeries to determine the most appropriate anaesthesia approach [78]. Generally, in surgeries involving larger surgical fields, such as abdominal, thoracic, and cardiac procedures, epidural, spinal, or fascial sheath regional anaesthesia is strongly recommended [96–101,100▪]. Co-administration of dexamethasone [101,102] with regional anaesthesia has been shown to enhance its effect. Another strategy to minimize systemic opioid doses is intrathecal morphine, which can provide targeted pain relief [103].

MELATONIN

Melatonin is increasingly recognized for its potential as a perioperative anxiolytic and co-analgesic. A Cochrane analysis [104] comparing melatonin to benzodiazepines found that melatonin has similar effects in reducing preoperative and postoperative anxiety. In addition to its anxiolytic properties, melatonin has been shown to have analgesic effects and can help reduce opioid consumption in the postoperative period [105,106]. It has also been found to reduce the induction doses of propofol and alleviate postoperative cognitive disadvantages [107].

Studies have reported that melatonin administration reduces the incidence of POD, although the optimal dosage for this purpose is still undetermined [108]. Melatonin may also improve perioperative sleep [105] and reduce the risk of DNR [109]. It is worth noting that intranasal dexmedetomidine has shown better efficacy than melatonin [110■] in protecting children against emergence delirium. Although melatonin has demonstrated sedative, anxiolytic, and co-analgesic effects in adults and children [111], there is considerable heterogeneity in the literature [104], particularly regarding its impact on POD in older patients with melatonin deficiencies [112].

GABAPENTINOIDS

Pregabalin and gabapentin have been frequently mentioned as part of MMA approaches to reduce acute and long-term postoperative pain. However, the recommendations regarding their use in this context are contradictory [113].

A meta-analysis conducted in 2020, which included over 26 000 patients, found no significant improvement in acute, sub-acute, or chronic postoperative pain with pregabalin or gabapentin [34]. Although there was a slight improvement in PONV with gabapentinoids, patients reported side effects such as ataxia, dizziness, and visual disturbances. Importantly, the meta-analysis did not find evidence that gabapentinoids increased the side effects of opioids [27].

Based on the available evidence, pregabalin and gabapentin are not included in the proposed 'MMA Bundle' for perioperative pain management (Fig. 3). Although they have been widely used in the past, their effectiveness and safety profile in this context are still under debate. It is important for healthcare professionals to carefully weigh the potential benefits and risks before considering the use of pregabalin or gabapentin in MMA approaches. Supplemental Digital Content 3, http://links.lww.com/COAN/A98 shows an example of an MMA prescription for an elderly polymorbid patient in ophthalmic/plastic surgery.

POSTOPERATIVE ANALGESIA AND SLEEP HYGIENE

Postoperative sleep disorders significantly impact pain processing and cognitive function, highlighting the importance of hospital sleep hygiene for patient recovery. The first night after surgery is often characterized by poor sleep quality, frequent arousals, and insufficient deep sleep stages (N3 and rapid eye movement (REM) sleep) crucial for cognitive and emotional well being [114■]. Sleep deprivation in the hospital can also contribute to increased levels of inflammatory mediators after surgery [115].

General anaesthesia disrupts the natural surges of endogenous melatonin, leading to symptoms similar to jet lag [116]. The intraoperative administration of opioids can further exacerbate sleep disturbances. Therefore, it is recommended to

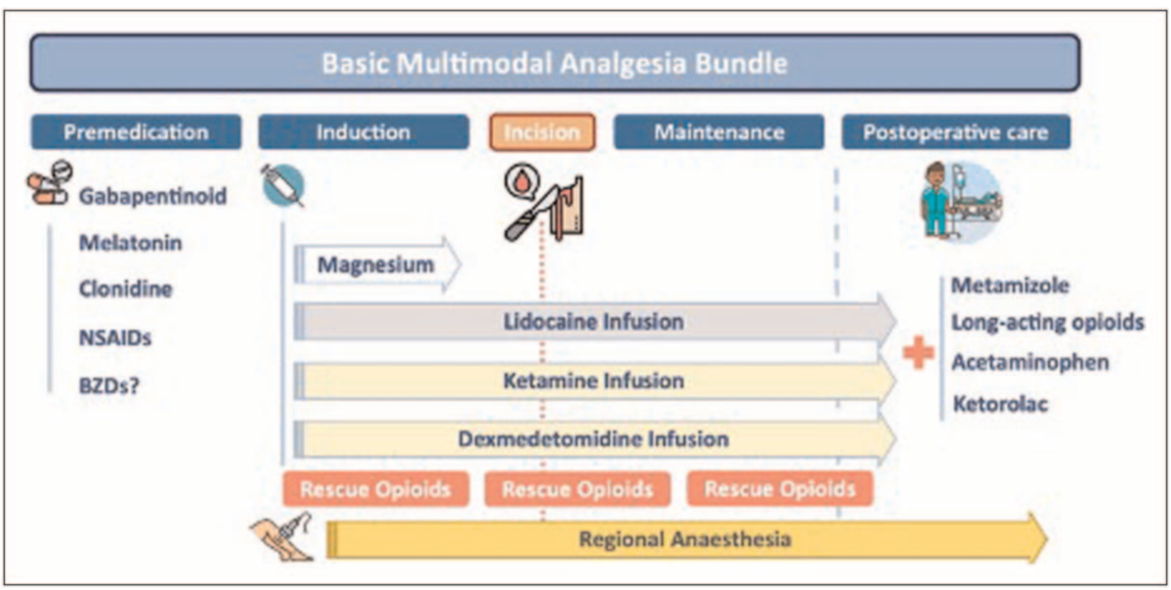

FIGURE 3. Multimodal analgesia bundle. Schematic representation of multimodal anaesthesia divided according to premedication, induction, maintenance, and postoperative analgesia in chronological sequence. This bundle can also be used with sevoflurane as the primary anaesthetic. MMA's main principle states that pharmacological analgesia synergistically inhibits nociception and arousal. For this reason, the primary anaesthetic must be reduced during maintenance based on the EEG signal.

incorporate a sleep-promoting approach as part of an MMA strategy, especially in the recovery room and in the hospital ward.

Several measures can be implemented to promote sleep in the postoperative period. Minimizing nursing checks, creating a quiet and familiar environment, and considering using medications like dexmedetomidine [117] can help establish a conducive sleep environment. Recognizing the importance of family members as anxiolytic factors, particularly for children and elderly patients, and allowing their presence in the postanaesthesia care unit can positively impact sleep quality and overall patient well being.

EEG AND MULTIMODAL GENERAL ANAESTHESIA

MMA involves using various drugs with different EEG signatures, which can lead to inaccuracies in processed EEG indices values. Therefore, clinicians must develop proficiency in visually interpreting EEG signals, such as the power spectrum, spectrogram, and raw EEG, as they provide a clearer understanding of the underlying neurophysiology. In clinical practice, the EEG signature during multimodal drug combinations is primarily influenced by the dominant GABAergic anaesthetic drug's EEG signature [118].

The synergistic hypnotic and analgesic effect of combining multiple drugs in MMA must be clearly understood. Without proper dose adaptation guided by EEG monitoring, there is a risk of oversedation and serious side effects [119▪]. This emphasizes the fundamental importance of EEG monitoring during anaesthesia. Using EEG signals as a guide, clinicians can accurately adjust the dosage of primary anaesthetic agents, typically propofol or sevoflurane, and titrate them appropriately to avoid burst suppression.

For instance, an example spectrogram (Fig. 4) demonstrates the EEG signatures associated with dexmedetomidine premedication, propofol anaesthesia, and a bolus of ketamine in a 35-year-

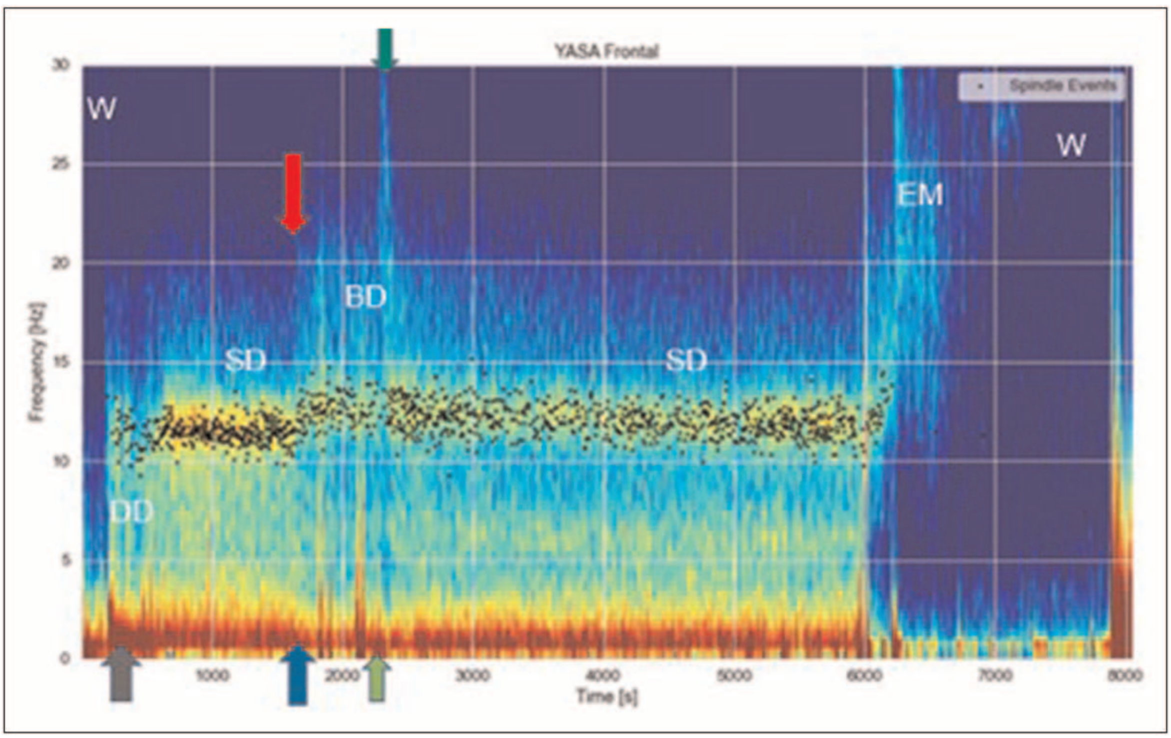

FIGURE 4. Case vignette of a frontal EEG during multimodal anaesthesia: representation of frontal EEG in a multitaper spectrogram. The black dots reflect spindle density and were detected by an automatic spindle detection program (YASA, Yet Another Spindle Algorithm) [120]. After a dexmedetomidine bolus, induction was undertaken with propofol and alfentanil, resulting in delta-dominant anaesthesia with few spindles (grey arrow). After emerging from burst suppression, spindle-rich anaesthesia (8–12 Hz) with high delta (0–4 Hz) power ensues. Administering a ketamine bolus (red arrow) adds power in the beta frequency range and elevates the spindles' frequency to 13–15 Hz for about 15 min. At the same time, a decrease in delta power (blue arrow) can also be observed. A lidocaine bolus of 0.5 mg/kg was administered during the application of the sub-Tenon block (lower green arrow): the EEG shows a short-term synchronous increase in delta waves, a temporary reduction in spindle density and an eye-muscle artefact because of the application of the eye block (upper green arrow). BD, beta-dominant GA; DD, delta-dominant GA; EM, emergence period; SD, spindle-dominant GA; W, wakefulness.

old man who underwent vitreoretinal surgery with a sub-tenon's block.

CONCLUSION

MMA focuses on polypharmacological anaesthesia and analgesia and aims to suppress nociception at multiple physiological levels. Synergistic effects of combined drugs in MMA contribute to anaesthetic unconsciousness, and can be guided by EEG monitoring. Combining regional and opioid-sparing general anaesthesia with preemptive analgesia and alternative methods like surgical site catheters is recommended. Surgeons should share responsibility for analgesia, and opioid stewardship is important. Postoperative analgesia should go beyond opioids; intravenous or ketamine infusion can be beneficial. Opioid analgesia poses risks, especially in certain patient populations. Sleep hygiene involves opioid-sparing strategies, rapid mobilization, undisturbed sleep, and adequate analgesia. Sleep hygiene should be integral to comprehensive pain therapy and delirium prophylaxis.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

J.B.E. is an ESAIC eLearning, Scientific and Examinations Committee member. She also has received support from Medtronic for implementing the Safe Brain Initiative. The remaining authors declare no conflicts of interest.

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▪ of special interest
▪▪ of outstanding interest

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Compares two very interesting adjunctive drugs that have proved useful each and of its own in paediatric sedation in the past. Hopefully paving the way to studies where both drugs are administered in a bundle to provide more biomimetic sleep and sedation in a circadian context.

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Hospital sleep is too shallow, lacking in great proportions of non-rapid eye movement (NREM) 3 and REM-sleep, the deep sleep stages so desperately needed in recovery situations after surgery. Elegant study speaking to a whole gap of ignorance about anaesthesia's consequences on postoperative sleep

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