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Esketamine: Essential Differences Compared to Worldwide Used Racemic Ketamine and a Synopsis of its Peri-operative Benefits and Safety

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Abstract

Worldwide used ketamine is the racemic mixture of two enantiomers, with a mirror image relationship. S(+)-ketamine or esketamine, the dextrorotatory enantiomer, is 4 times more active as a non-competitive NMDA receptor (NMDAR) antagonist than levorotatory R(-) ketamine or arketamine. Esketamine is twice as potent as analgesic and anesthetic than racemic ketamine.

During emergence from anesthesia or drug exposure, esketamine improves awakening and neurocognitive impairment as compared to racemic or ar- ketamine at equipotent dose. Psychic adverse events are often less unpleasant or of positive quality with esketamine. One of the possible reasons for better preserved logical functions is less central cholinergic receptor antagonism.

There is emerging evidence from preclinical data that esketamine is preferable to racemic ketamine with regard to direct cardiac effects. Compared to arketamine, it showed less negative inotropic action and does not inhibit ATP-sensitive potassium channels that are activated by hypoxia or acidosis. Esketamine preserves experimental cardiac preconditioning-related protection which was inhibited by arketamine.

Neuroprotective properties of es- and racemic ketamine have been known for decades. In clinical study, both ketamines decrease the frequency of spreading depolarizations in head trauma patients and other acute intracranial pathologies. In animal models of acute and chronic disorders, both induce neuro- and astroglial plasticity and may activate adult born neurons with positive long-term outcomes. But only esketamine has so far demonstrated direct neuroregenerative effects when applied to neurons after injury in-vitro.

Especially perioperative regimen with adjunctive subanesthetic dose esketamine in adequate use schedules have been found to offer a multitude of beneficial effects: These include better hemodynamic stability and an improved quality of postoperative recovery with less pain,

less opioid consumption, less respiratory depression, less gastrointestinal dysfunction, less sleep disturbance, and less inflammation. In children, esketamine was associated with calmer awakening and less agitation after sevoflurane anesthesia. In patients of all age groups, racemic and es-ketamine may reduce postoperative neurocognitive disorder and / or delirium after major (non-cardiac) surgery. Esketamine was associated with earlier mobilization and better rehabilitation in the elderly. First studies show its particular value for prophylaxis and treatment of perioperative depression such as in cancer surgery and severe post-partum depression in Cesarean section.

Racemic and es- ketamine have been established as efficient antinociceptive components in opioid-sparing (OSA) and opioid-free anesthesia (OFA). Both techniques may be particularly advantageous in patients with obesity, respiratory handicap, and obstructive sleep apnea. OSA and OFA allow for a reduction of opioid-related adverse effects including less postoperative respiratory depression, less PONV, less impaired gastrointestinal transit time, less ileus, and less surgical complications. In these settings, especially esketamine was associated with better quality of recovery and patient satisfaction.

Major drawbacks in all of these positive trials include the lack of a more patient-centered approach including a differentiation with regard to patient's sex and relevant genetic predisposition. In the substantially heterogeneous trials, the drug doses used vary tremendously and it is hard to identify well replicated use schedules. To assess the "depth of anesthesia" when ketamine is added as adjunct to a multimodal general anesthesia regimen may be "complicated" with currently available commercial monitors. Often trials do not report whether they have reduced the dose of the other anesthetics applied after subanesthetic dose ketamine has been added. All of these factors may be confounders with regard to trial results and data interpretation.

In conclusion, the most important advantage with esketamine is the opportunity of providing comparable analgesia and anesthesia at half-dose racemic ketamine. This is additionally associated with quicker recovery and less neurocognitive dysfunction including less adverse psychic events.

Decisive for success and beneficial esketamine use is an individual, patient-centered and context-focused approach with appropriate drug dosing and scheduling.

Key words: Esketamine, potency, racemic ketamine, anesthesia emergence, hemodynamic and respiratory stability, multimodal analgesia, perioperative pain, postoperative recovery, neurocognition, perioperative depression, opioid-sparing, benefits, safety, pitfalls

1 Introduction: Main Differences in Comparisons Between Esketamine and Racemic Ketamine

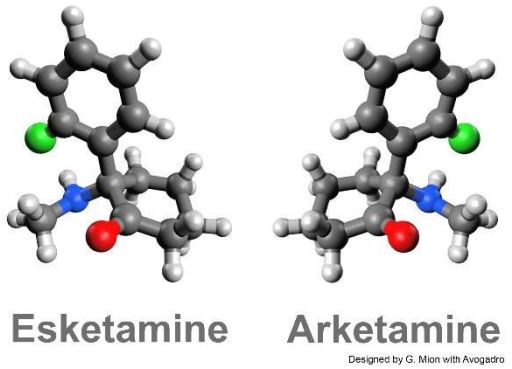

Fig. 1. The enantiomers show a mirror image relationship: Esketamine is the dextrorotatory enantiomer classified with the CIP nomenclature system as the "S" form. Grey atoms indicate: carbon, white: hydrogen, red: oxygen, blue: nitrogen, green: chloride

Worldwide used ketamine is an equimolar, racemic mixture of two isomers that deflect light in opposite directions. They are called enantiomers [1], showing a mirror image relationship (Fig. 1). The Cahn-Ingold-Prelog (CIP) nomenclature system generates an unequivocal name of R- (rectus or right) or S- (sinister or left) for the chiral center in a molecule on the basis of the sizes of its substituent groups [2]. S(+)-ketamine or esketamine is the dextrorotatory enantiomer [3], which has been available for clinical use as intravenous preparation since 1997 in some countries of the European Union. IV esketamine has also received marketing authorization in France in May 2019 and has recently been approved for medical use in China. A nasal spray esketamine formulation (Spravato®) has been released by the FDA in 2019 as fast-acting antidepressant for treatment of severe refractory depression [4]. It has also been approved in Canada, several European countries and other states.

1.1. Anesthetic and Analgesic Power

Ketamine produces narcosis and analgesia by interacting with numerous neurotransmitter systems, pathways, and networks, for example at monoaminergic, cholinergic, HCN1 receptors (Hyperpolarization-activated, Cyclic Nucleotide-gated channels), sodium and calcium channels, and through complex interactions with the gamma-amino butyric acid (GABAergic) system. Ketamine exerts only weak agonistic effects at opioid receptors in humans and naloxone does not antagonize the analgesic properties of ketamine in man [5,6]. The non-competitive antagonism at the NMDA receptor is still considered to be responsible as primary mechanism for many characteristic ketamine actions and downstream cascades, including hypnotic, psychosensory and analgesic effects [3].

In electroencephalography (EEG) studies, arketamine induced less EEG slowing than racemic or es- ketamine [2]. Esketamine is 4 times more active as a non-competitive NMDAR antagonist than the R(-) ketamine levorotatory enantiomer, arketamine [3]. This difference in affinity may explain at least in part why esketamine shows approximately twice the clinical analgesic and anesthetic potency of the racemate. In clinical study, this difference has been demonstrated in patients in which plasma concentrations of half-dose esketamine as compared to the racemic ketamine dose were measured at the same time as equi-analgesic effects [7]. Another human study similarly found the same level of analgesia at twice the dose of the racemate as compared to esketamine [8]. Most later trials in the anesthesia and analgesia literature therefore investigated esketamine at half dose racemic ketamine to allow for equipotent anesthetic and analgesic comparison [3].

1.2 Improved Anesthesia Quality and Emergence Characteristics

As early as 1980, it was recognized that esketamine produced a better quality of awakening than arketamine or the racemate. In mice, the therapeutic index (LD_{50}/ED_{50}) of esketamine is 10, only 6 for racemate, and 4 for arketamine [2].

Studies have also shown that racemate at equi-analgesic dose disturbed cognitive abilities during awakening to a greater extent than either of the two enantiomers taken in isolation [9]. In the 1980, White et al. observed that esketamine was more effective in terms of narcosis and analgesia than arketamine or the racemate: the measured potency was 3.4 times better for esketamine than for arketamine. Patients anesthetized with esketamine at half dose racemic ketamine were also calmer and more cooperative in the recovery room. The incidence of dreams was the same (84%), but they were often less unpleasant with esketamine and associated with more positive emotion. Patients who received arketamine were more agitated and combative in the recovery room, and more prone to dizziness, hallucinations (vivid illusions) and bizarre trips [10].

Most human studies compared esketamine at half the dose of the racemate [1,8,9,11,12,13,14,15,16,17,18]. They are summarized in Table 1.

Esketamine has been reported not to prolong recovery times after sevoflurane anesthesia [19]. This may be explained by several reasons:

First, esketamine is eliminated more rapidly than arketamine, with an average 30% higher clearance [11,20]. In the randomized Wang et al. study [16], 32 patients undergoing painless gastroscopy received a single dose of esketamine (0.5 mg/kg) or racemic ketamine (1 mg/kg). Esketamine was associated with a shorter time to recovery (9 mins vs. 13 mins) and orientation (11.5 mins vs. 17 mins). Second, when racemate is metabolized, arketamine competitively slows down esketamine metabolism [21]. Moreover, it was recently demonstrated in mice that esketamine accelerates emergence from isoflurane general anesthesia by activating paraventricular thalamus glutamatergic neurons [22], with a dose 5 times lower than the required dose of racemate in a previous study [23]. Further human trials confirmed that emergence from sedation or anesthesia is shorter with adjunctive esketamine [8,11,18]. Finally, cognitive functions are less impacted by esketamine than by the racemate which may in part be related to less antagonism at central cholinergic receptors [3].

In addition, the two isomers differ in their affinity for many other receptors and systems which is also demonstrated in their multiple interaction effects with the cardiocirculatory and cerebrovascular nervous system.

Table 1 Quality and speed of emergence after anesthetic or subanesthetic dose ketamine in human study comparing esketamine *vs* racemic ketamine and / or arketamine

Author, Year	Study Size, N	Drug, Dose	Ratio / setting / results
White et al 1980 [11]	60	EsKet, 1 mg/kg Rac, 2 mg/kg Arket, 3 mg/kg *then* *titrated as needed for surgery*	Dose Ratio 1:2:3 / Clinical potency ratio Esket : Arket 3.4 : 1 Ketamine anesthesia, elective outpatient surgery Esket: "More effective" anesthesia / less disorientation and less agitation; less fear, less pain Arket: More psychedelic symptoms (vivid illusions, delirium, weird trips, unpleasant dreams), combative behavior
White et al 1985 [1]	5 *cross-over*	EsKet, 140 mg Rac, 275 mg Arket, 429 mg	Dose Ratio 1:2:3 / Potency ratio Esket : Arket 3 - 5 : 1 Dose as used for anesthesia induction Both isomers: Shorter recovery *vs* Rac / healthy volunteers
Adams et al 1992 [12]	10 *cross-over*	Esket, 1 mg/kg Rac, 2 mg/kg	Dose Ratio 1:2 / Sedation Esket *vs* Rac: Shorter recovery of cognitive function, after (min) 7.9 *vs* 9.2 order follow, 9.0 *vs* 11.5 oriented to person, 10.1 *vs* 13.4 spatially oriented / healthy volunteers
Adams et al 1994 [13]	40	Esket, 1 mg/kg *then* 2 $mg.kg^{-1}.h^{-1}$ Rac, 2 mg/kg *then* 4 $mg.kg^{-1}.h^{-1}$	Dose Ratio 1:2 / Ketamine anesthesia, knee surgery patients > 60 yrs Esket *vs* Rac: Shorter recovery of cognitive function, after (min): 2.0 *vs* 4.9 order follow, 5.7 *vs* 14.6 oriented to person, 8.2 *vs* 17.4 spatially oriented
Arendt-Nielsen et al 1996 [8]	12	Esket, 180 ng/mL (~29 mg) Rac, 350 ng/mL (~ 60 mg)	Esket : Rac: titrated to plasma conc.1 : 2 / Analgesic potency ratio, Esket : Rac 2 : 1, objective pain quantification Esket *vs* Rac: Less prolonged reaction time to auditory and painful stimuli indicating less sedation and / or less motor impairment / healthy volunteers
Vollenweider et al 1997 [14]	10 *cross-over*	Esket and Arket *each* 15 mg *then* 1.2 $mg.kg^{-1}.h^{-1}$	Equimolar Dose / Short anesthesia Esket: Hallucinations, thought disorders, depersonalization, derealization; Arket: "State of relaxation" / healthy volunteers
Engelhardt et al 1998 [15]	12 *cross-over*	Esket, 0.65 mg/kg *for 15 min:* 2 $mg.kg^{-1}.h^{-1}$ Rac, 1.3 mg/kg *for 15 min:* 4 $mg.kg^{-1}.h^{-1}$	Dose Ratio: 1:2 / Short anesthesia Esket *vs* Rac: Shorter recovery of cognitive function; faster performance in neuropsychological tests / healthy volunteers
Wang et al 2019 [16]	32	Esket, 0.5 mg/kg Rac, 1 mg/kg	Dose Ratio: 1:2 / Sedation, Chinese gastroscopy patients Esket *vs* Rac: Shorter recovery time (9 *vs* 13 min) and shorter time to orientation (11.5 *vs* 17 min)
Pfenninger et al 2002 [9]	24 *cross-over*	Esket, 0.25 mg/kg Rac, 0.5 mg/kg Arket, 1 mg/kg	Equi-Analgesic Dose Ratio: 1:2:4, single injection Esket and Arket *vs* Rac: Early after injection, less tiredness and less cognitive impairment Esket *vs* Rac and Arket: Less decline in concentration capacity and memory / healthy volunteers
Pees et al 2003 [18]	100	Esket and Rac *each* 1 mg/kg *then* Esket, 2.28 $mg.kg^{-1}.h^{-1}$ Rac, 3.12 $mg.kg^{-1}.h^{-1}$	Analgesic potency ratio Esket:Rac: 1.4 : 1 when titrated with midazolam as needed / sedation, spontaneous ventilation in Cardiac catheterization / Newborns and children, 0-11 yrs / Esket *vs* Rac: More efficient analgesia and sedation / average "awakening" period (min): 98 vs 127 (*ns)*
Passie et al 2021 [17]	30	Esket, 0.1 mg/kg, *for 60 min* 0.36 $mg.kg^{-1}.h^{-1}$ Rac, 0.2 mg/kg, *for 60 min* 0.72 $mg.kg^{-1}.h^{-1}$	Dose Ratio: 1:2, Plasma conc. Esket : Rac 159 : 300 ng/mL Esket and Rac *vs* Placebo: Psychopathological symptoms and cognitive impairment, no difference between Esket and Rac /healthy volunteers

Synopsis summarizes randomized, controlled trials in healthy volunteers and surgical patients except for the prospective randomized observation by Pees et al. *Esket* esketamine, *Rac* racemic ketamine, *Arket* arketamine, *vs* versus, *conc* concentration, *ns,* not significant.

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1.3 Cardiocirculatory Effects

Anesthetic doses of racemic ketamine produce an increase in heart rate (HR) and blood pressure (BP) which appear to be essentially associated with a stimulation of the sympathetic centers and the increase of circulating catecholamines by inhibiting their reuptake. A study in healthy subjects compared increasing doses of es- and racemic ketamine and concluded that an increase in cardiac output was dependent on esketamine [24]. However, there were no major hemodynamic differences between esketamine and the racemate during coronary artery bypass graft surgery [25].

Racemic ketamine exerts a moderate negative inotropic effect on the human cardiomyocyte [26]. An in vitro study on human myocardium showed that in contrast to arketamine, esketamine had a positive inotropic effect. It was not before supra-therapeutic concentrations that both isomers had a negative inotropic effect [27]. Similarly, in an isolated guinea pig heart model, esketamine exerted no negative inotropic action at 25 µM/L, and showed less negative inotropic effects than arketamine at 50 µM/L [28].

Esketamine and racemate differ with regard to their microvascular effects. The circulatory effect in vivo is an increase in BP, but the direct vascular impact of ketamine is vasodilatory because of calcium entry blocking properties. Specific receptors are involved in another type of vasodilation, namely the ATP-sensitive potassium channels, that are activated by hypoxia or acidosis. In rat aortic rings, the racemate, but not esketamine, inhibited agonist-induced relaxation through the channels in a dose-dependent manner [29]. Moreover, in a porcine coronary artery model, esketamine exerted greater vasodilatory effect than arketamine [30].

When looking at the ischemic myocardium, esketamine preserved experimental cardiac preconditioning, indicating that prior ischemia protected the cardiomyocyte from further, later occurring ischemia. In contrast, arketamine inhibited this mechanism [31].

At the cardiocirculatory level, esketamine therefore seems to be preferable to the racemate, particularly in situations of cellular hypoxia as described in preclinical study.

1.4 Cerebrovascular Effects

Like the racemate, esketamine enhances cerebral blood flow (CBF) and increases the intracranial pressure (ICP) only in case of concomitant hypercapnia or hypertension. Esketamine and the racemate have demonstrated neuroprotective properties in preclinical and clinical study, but there are still no long-term clinical outcome data after ketamine treatment of acute intracranial pathologies such as head trauma, subarachnoid hemorrhage or stroke. Ketamine decreases the frequency of spreading depolarizations in head trauma [32] and other cerebral vascular attacks [33], and high dose esketamine (100 µM) protected the rat cortex from global ischemia [34]. Esketamine was more effective than the racemate in preventing glutamate-induced neuronal damage in rat hippocampal neurons, whereas arketamine had no effect. In addition, only esketamine induced neuro-regeneration in injured neuronal cells in-vitro [35].

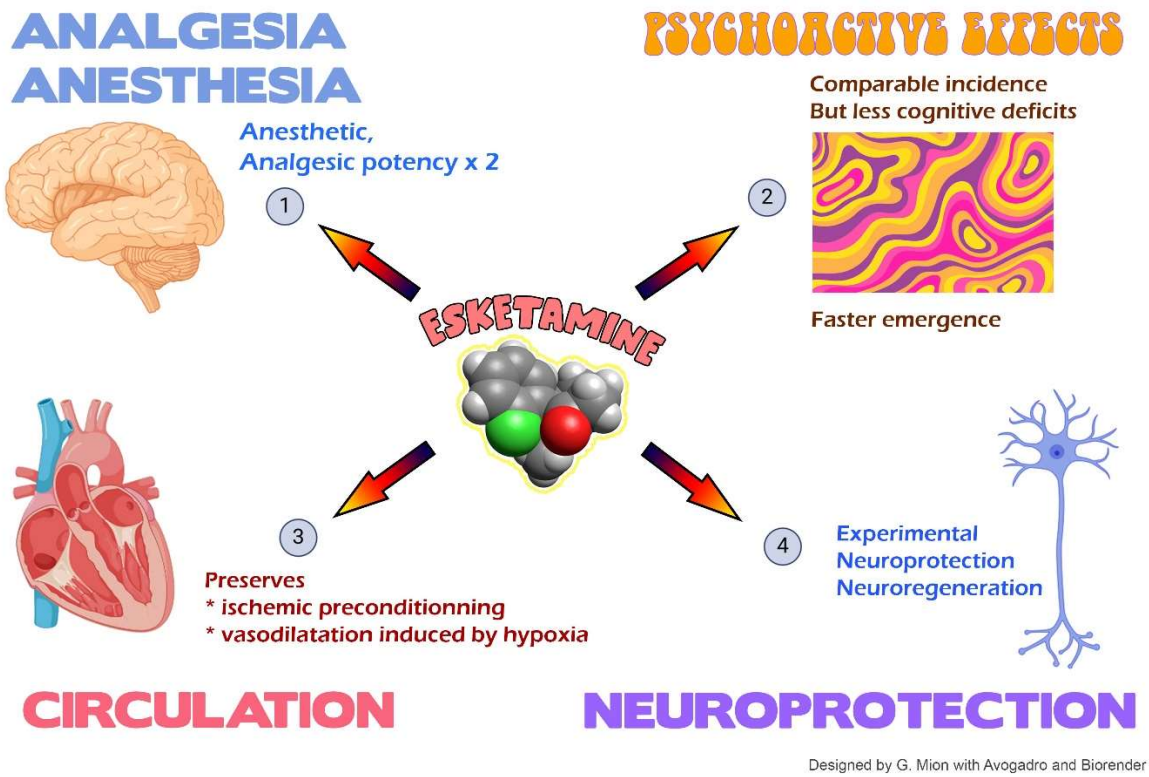

Fig. 2. Different advantageous effects of esketamine compared to ketamine racemate

2 The Evidence in Favor of Esketamine in Clinical Trials

Recent clinical evidence reporting beneficial action of esketamine in perioperative care will first be described, and study pitfalls and limitations will be presented in a summarizing discussion in the appropriate sections at the end of the narrative review.

2.1 Intra- and Post-Operative Benefits of Esketamine Mostly Compared to Placebo

In multimodal perioperative regimen which included subanesthetic dose esketamine, the primary postoperative benefit is improved analgesia [3], which has often been associated with a reduction in opioid consumption of approximately 30%. Some studies and recent meta-analysis could even show a reduction in the development of chronic post-surgical pain at 3 or 6 months after the procedure. In addition to this analgesic efficacy, esketamine's impact is complex and depends on numerous molecular targets [36] resulting in a host of postoperative benefits: This includes greater hemodynamic stability and less respiratory depression, calmer awakening without agitation which is particularly valid in children after sevoflurane anesthesia and appropriate ketamine use, potentially improved postoperative neurocognitive function especially in the elderly, better quality of recovery, less digestive dysfunction, and a reduction in postoperative depressive symptoms.

2.2 Improved Intraoperative Hemodynamic and Respiratory Stability

Generally, most patients receiving esketamine needed less hypnotics and morphinics [37,38], with the result of more stable hemodynamics, less hypotension and adverse HR variation. This was observed in various procedures, like sedation for endoscopy, in adults [38,39,40,41], obese [42] or elderly patients [43], endoscopic variceal ligation [44], suspension laryngoscopy [45], transbronchial needle aspiration [46], lung tumor percutaneous radiofrequency ablation [47], hysteroscopy [48], anesthesia for abortion [49], induction of bariatric surgery [50] and postoperative analgesia in children [51] .

Subanesthetic doses of esketamine within the range of at least 0.2 mg/kg [52] to 0.4 mg/kg [44] appear to be effective. Larger doses of approximately 0.5 mg/kg may cause more delirium on awakening in short procedures [53]. On the other hand, esketamine may reduce hypertensive peaks during intubation with a double-lumen tracheal tube [54].

In procedural sedation with spontaneous ventilation, opioid replacement or dose reduction with adjunctive use of esketamine [55] or propofol reduction in propofol-esketamine combinations leads to a decrease in episodes of dreaded respiratory depression and hypoxemia [44,48,51,56,57,58,59].

A recent meta-analysis including 14 studies confirmed that combining esketamine with propofol in procedures with maintained spontaneous breathing reduced both circulatory and respiratory depression. Furthermore, in this meta-analysis, esketamine reduced pain on propofol injection without increasing the incidence of adverse psychic events [60].

Another recent meta-analysis of 18 studies showed that the addition of esketamine to propofol reduced not only the amount of propofol required for sedation, but also decreased the time to recovery and overall complications (RR = 0.65). This included pain on propofol injection, hypotension and respiratory complications. There was no effect on PONV (which may have been prevented by propofol), or on the incidence of hypertension or tachycardia. Interestingly, this reduction of complications was only observed in patients who received the largest esketamine doses from 0.2 to 0.5 mg/kg [61].

The most recent meta-analysis confirmed that esketamine reduces respiratory complications during gastrointestinal endoscopy (RR 0.37) [62].

Furthermore, concomitant use of esketamine and the short-acting benzodiazepine remimazolam produced less respiratory depression, hypotension, and bradycardia than a combination of esketamine and propofol [63,64,65,66].

2.3 Calmer Awakening in Children

In young children, separation from parents causes anxiety. This may add to promote restless awakening from sedation and anesthesia, which has been associated with long-term negative mental health consequences [67]. Agitation itself may negatively impact on the results of the surgical procedure, and / or children may injure themselves [68].

In 3 – 6-year-old children who had to undergo strabismus surgery, a nasal spray of esketamine (0.5-1 mg/kg) was administered randomly 10 minutes before induction of anesthesia while children were still accompanied by their parents. This practice halved kids' separation anxiety and facilitated their acceptance of the mask for inhalational anesthesia induction. Agitation on awakening after sevoflurane was considerably reduced by esketamine spraying at a rate of 2.5 times less agitated children without prolongation of recovery room stay [67].

Similarly, a randomized IV injection of low-dose esketamine (0.2 mg/kg) at the end of tonsillectomy or adenoidectomy decreased pain scores, and incidence and severity of agitation in awakening of preschool children. After anesthesia with propofol and sevoflurane, esketamine did not lengthen extubation time or the incidence of PONV [68].

Finally, a randomized study applying sketofol (esketamine 0.5 mg/kg + propofol) for sedation of children with spontaneous breathing to insert an implantable venous access port showed less kids' agitation on awakening than if general anesthesia with intubation and morphine was used [69].

However, the opposite occurred in a non-randomized cohort of preschool children who received around 0.5 mg/kg IV esketamine during intravenous induction for a short procedure after separation from their parents. Surgery lasted less than 40 minutes and esketamine caused a

dose-dependent increase in agitation during awakening [70]. In a multicenter, randomized study of slightly older children who had upper GI endoscopy, 0.5 mg/kg IV esketamine facilitated endoscope insertion compared with nalbuphine, but increased agitation on awakening [71].

In contrast, 0.3 mg/kg IV esketamine administered postoperatively with an infusion of 0.15 mg/kg/h did not increase agitation in preschool children after hypospadias surgery as compared to kids receiving hydromorphone [51].

The data of these studies from relatively short procedures suggest that esketamine may be beneficial in premedication in the lower dose range (< 0.3 mg/kg) especially in young children when still being together with their parents. Injection of a low dose at the end of a painful procedure such as tonsillectomy may be an alternative, but doses > 0.5 mg/kg should better be avoided.

A recent network meta-analysis of prophylaxis for pediatric emergence delirium in desflurane-based anesthesia included seven randomized controlled studies, including 573 children aged 3 to 5, operated for infraumbilical surgery, strabismus or adenotonsillectomy. Ketamine-propofol was most effective in preventing postanesthetic delirium. Dexmedetomidine was better than fentanyl / midazolam, midazolam or propofol alone or than gabapentin [72]. A previous meta-analysis showed the benefit of ketamine in reducing awakening agitation in children sedated with sevoflurane [73].

2.4 Improved Neurocognitive Recovery after General Anesthesia

A reduction in post-operative neurocognitive decline after intraoperative ketamine has been reported especially in some recent study with esketamine. An initial trial from 2009 with two groups of 29 patients undergoing extracorporeal circulation showed that those receiving 0.5 mg/kg intraoperative ketamine experienced ten times less confusional episodes after surgery than those with placebo (3% vs. 31% incidence). Studying the same dose regimen and 1 mg/kg racemic ketamine, the subsequent PODCAST study randomizing over 200 patients failed to confirm this result [74]. Nevertheless, a meta-analysis of 6 randomized studies suggested to look at more subtle protective effects of ketamine against post-operative cognitive dysfunction (POCD), potentially attributable to reduced neuroinflammation [75].

Perioperative neurocognitive disorders (PND) have been defined to include postoperative delirium (POD) usually occurring within the first 3 days after surgery, delayed neurocognitive recovery (DNR) occurring within 30 days after surgery, and postoperative neurocognitive disorder (POND) developing weeks to months after surgery [76]. Major surgery, whether cardio-thoracic, abdominal, particularly carcinologic, or joint replacing causes significant perioperative stress, including hemodynamic disturbances and finally the induction of severe inflammatory cascades. In elderly patients, who may already be cognitively impaired prior to surgery, circulating inflammatory mediators may further deteriorate brain function via neuroinflammation. PND manifest as decline in memory, information processing, self-expression, and anxiety, and have been correlated with hypotensive episodes and cerebral hypoperfusion [77]. Neuroinflammation may disrupt cerebral calcium homeostasis which may manifest as excitotoxicity, i.e. excessive glutamatergic stimulation of NMDAR with the potential result of neuronal dell death. As described above, esketamine has a relatively high affinity in blocking NMDAR being twice as potent as the racemate. Because es- and racemic ketamine also possess anti-inflammatory pharmacologic properties, both have been assumed to be able to reduce PND.

A recent meta-analysis from 2023 including 9 studies with 2 esketamine trials failed to demonstrate an overall protective effect of racemic and es- ketamine on PND [78]. Similar to the previous PODCAST study, a single bolus dose of racemic ketamine administered at anesthesia induction [74] was found not to reduce PND. Nevertheless, several trials reported benefits with

esketamine: In a randomized study of elderly patients undergoing gastrointestinal tumor surgery, patients receiving esketamine (0.25 mg/kg bolus then 0.125 mg/kg/h infusion) benefited from better hemodynamics (less hypotension, tachycardia, and vasoconstrictor requirements) and needed less remifentanil during the procedure as compared to placebo. Although the difference in overall POD between the groups was not significant, esketamine patients had a lower incidence of DNR at day 3 compared with the controls (16% versus 39%). Esketamine was also associated with better analgesia which is one essential factor in the prevention of POD [77]. In another study of gastrointestinal surgery in elderly patients, a single bolus low dose of 0.15 mg/kg esketamine decreased DNR at 7 days but did not alter POCD at 3 months. Surgery-induced increases in pro-inflammatory factors IL-6 and the glial cell injury indicating biomarker S-100 ß proteins were attenuated after esketamine [76]. In another randomized study in thoracic surgery in elderly patients receiving either 0.5 mg/kg esketamine or dexmedetomidine (0.7 µg/kg then 0.2 to 0.5 µg/kg/h), the incidence of POD was 4% with esketamine versus 19% with dexmedetomidine. Again, esketamine improved analgesia and decreased depression and anxiety at postoperative day 5 [79]. In a randomized study in video-assisted thoracic surgery in adult patients, the esketamine group received an 0.3 mg/kg bolus and then an 0.2 mg/kg/h infusion in addition to a paravertebral regional anesthesia block. In comparison, postoperative analgesia was better after esketamine than placebo and the paravertebral block only. There was less hemodynamic instability, less remifentanil need, less nausea, and fewer pulmonary complications with esketamine. The incidence of PND was lower after esketamine and the paravertebral block, but there was no difference between the two treatments [80]. A recent randomized study showed that a single dose of esketamine (0.25 mg/kg) injected immediately before induction reduced the incidence of delirium in patients who underwent on-pump cardiac surgery. POD occurred in 23% of patients in the esketamine group versus 45% in the placebo group [81].

However, a randomized study in 106 open heart surgery patients from 2004 comparing a propofol - high-dose esketamine (2.5 mg/kg bolus then 125 µg/kg/min) with a propofol-remifentanil regimen could only find a non-significant improvement in overall summarizing cognitive test performance at 10 weeks after surgery. Obviously, this study was disappointing because at that time, rather high-dose esketamine was considered to be neuroprotective and very high intraoperative plasma concentration (4-8 µg/mL) had been achieved. Nowadays, we are aware of the fact that ketamine’s neuroprotective effects are regulated in a tight dose range with too low and too high doses being rather counterproductive and without neuroprotective efficacy. In addition, harmful mechanism during extracorporeal circulation and aortic clamp include adverse microemboli “showering” events which may not directly be counteracted by racemic or es- ketamine administration [82].

2.5 Less Postoperative Depression

Depression and anxiety are recognized as high risk factors for increased acute postoperative pain and its progression to persistent chronic pain and opioid dependence after surgery [83]. More than 300 million people worldwide suffer from depression, and 800,000 humans commit suicide every year. This is a major global health problem. Unfortunately, conventional antidepressants need several weeks to take effect while increasing patient drive, and even a third of patients with Major Depressive Disorder (MDD) are resistant to treatment with these drugs. Ketamine's powerful and rapid antidepressant effect in good responders occurs within less than one hour and this phenomenon is considered as the major discovery of the last 60 years in psychiatry [84]. It can be dated back to Berman's et al study in 2000 [85], and finally resulted in the US-FDA approval of (S)-ketamine as nasal spray for treatment-resistant patients with MDD in 2019 [86].

In 2002, Kudoh et al. showed that intraoperative ketamine improved the depressive state of patients after surgery [87]. Meanwhile, several studies have reported that especially intraoperative administration of esketamine may reduce symptoms of postoperative depression. This is an important issue especially in the context of cancer treatment. This anxiety-provoking disease generates depressive states with increased mortality [88].

In a large randomized study of 151 patients with lung cancer operations, patients receiving esketamine during surgery (0.1 mg/kg bolus + 0.1 mg/kg/h intraoperative infusion) and in the postoperative PCA (0.015 mg/kg/h + 0.015 mg/kg boluses) for 48h presented with significantly less depressive symptoms at one-month post-surgery versus the controls (1.3% versus 11.8% incidence). Esketamine doses were rather low, and there was no inter-group difference in postoperative analgesia [88]. Another randomized study examined breast cancer patients. Postoperative depression (POD) can affect 20 to 40% of women with this disease. 300 patients undergoing radical mastectomy were randomized in a double-blind fashion to placebo, racemic ketamine or esketamine, both used at the same dose of 0.25 mg/kg. As compared to placebo, postoperative pain scores were reduced with both ketamines but to a greater extent with esketamine. Above all, depression scores were lower at 3 days, one week and one month after surgery with esketamine being more effective than the racemate. No difference was detected at three months after surgery [89].

In a series of over 400 patients with total hysterectomy because of cervical cancer, patients were randomized in a double-blind fashion into 4 groups receiving either 0.5 mg racemic ketamine, 0.5 mg/kg or 0.25 mg/kg esketamine or placebo one hour after anesthesia induction. With regard to improving postoperative analgesia, depressive symptoms, peripheral levels of brain-derived neurotrophic factor and serotonin, the higher subanesthetic dose of esketamine was the most effective. Not surprisingly, half-dose esketamine was effective as racemic ketamine, confirming esketamine's double therapeutic potency. There was no difference between the 4 groups by postoperative day 5 with these dosing regimen [90].

Similarly, intraoperative esketamine administration (0.25 mg/kg then 0.12 mg/kg/h) during intestinal resection in Crohn's disease patients improved postoperative analgesia and reduced depressive symptoms during the first postoperative week. Patient reported improved quality of recovery although there was no difference in CRP or IL-6 [91].

A meta-analysis of 17 studies involving 2462 patients confirmed the reduction in the prevalence of perioperative depression (Relative Risk, RR: 0.50, 95% CI (0.36, 0.70) and the intensity of symptoms both for the first week and longer term [92].

Finally, a number of studies examined the problem of postpartum depression (PPD) especially in the context of Cesarean section. Meanwhile this procedure is performed in over 20% of births. However, 10-20% or even more of mothers suffer from PPD [93] with very serious consequences, ranging from breast-feeding problems, poor care of the newborn, less bonding between mother and child to maternal suicide or even infanticide [94].

Retrospective and prospective, randomized trials in this setting have reported that the addition of esketamine to PCA (for example as 0.01 mg/kg bolus and same hourly dose as continuous infusion) after Cesarean section improved postoperative analgesia and reduced opioid consumption. Far beyond, esketamine significantly reduced the incidence of PPD until the 6th postoperative week, reduced postoperative anxiety and improved sleep quality [93,94,95,96]. A recent randomized study in which 0.25 mg/kg esketamine was injected during Caesarean section and then administered within a PCA regimen, showed that PPD decreased until the 7th postoperative day [97].

Other studies have shown that a simple injection of 0.2 mg/kg esketamine after vaginal [98] or caesarean [99,100] delivery as compared to placebo is sufficient to decrease the incidence of PPD (3.4% vs. 15.3% incidence) up to 6 weeks after birth. In one study, the reduction in PPD

was accompanied by a decrease in stress and inflammatory markers such as circulating catecholamines, CRP and IL-6 [98]. One Chinese study reported that esketamine added to ropivacaine in epidural labor analgesia reduced PPD for up to six weeks after delivery [101]. In some of these studies [100], the incidence of maternal adverse effects such as dizziness, blurred vision, drowsiness and hallucination was increased.

2.6 Improved Quality of Recovery and Patient Satisfaction after Anesthesia

Several studies have looked at the quality of postoperative recovery after adjunctive perioperative esketamine. As a metric, the QoR-40 score questionnaire which evaluates five components of patient recovery has been used. It consists of questions about physical comfort (12 items), physical independence (5 items), emotional state (9 items), psychological support (7 items), and pain (7 items). Similarly, the QoR-15 explores physical comfort, emotional state, psychological support, physical independence and pain.

The quality of recovery was significantly improved in several randomized studies, for example after radical mastectomy for breast cancer with varying regimen: Esketamine was administered either at anesthesia induction as 0.25 mg/kg [102] or 0.5 mg/kg [103] bolus, or as 0.1 - 0.2 mg/kg bolus followed by 0.1 - 0.2 mg/kg/h infusion [104] or 0.5 mg/kg bolus and 2 - 4 µg/kg/h [105,106] infusion. Drug schedules and doses depended on heterogenous study designs, such as whether esketamine replaced morphine or was combined with dexmedetomidine. Improved recovery was often accompanied by lower depression and anxiety, greater patient satisfaction [103], better sleep quality [105], and sometimes improved cognitive performance [107]. Taken together, outcomes were mostly better with subanesthetic dose esketamine in the higher dose range, which was sometimes associated with prolonged awakening, extubation time, and PACU stay.

Similarly, in patients undergoing colorectal cancer surgery, intraoperative esketamine (0.1 mg/kg then 0.1 mg/kg/h) reduced fatigue in the first postoperative week [108], and at higher dose (0.25 mg/kg then 0.12 mg/kg/h) improved QoR-15 scores and bowel recovery [109]. Less impaired gastrointestinal functions were confirmed in several other studies if esketamine was added to a multimodal regimen [110,111]. Elderly patients with femoral neck fractures treated with total hip replacement demonstrated comparable improvements in global recovery scores. When esketamine PCA was compared to opioid PCA, better postoperative ambulation with reduction of PONV and depressive symptoms was observed [112]. Finally, in a randomized study of laparoscopic bariatric surgery, intraoperative esketamine (0.5 mg/kg/h) improved analgesia and the quality of recovery score 40 (QoR-40) at postoperative day 1 [113].

3 Esketamine in Opioid-Sparing and Opioid-Free Anesthesia

3.1 Background, Rationale and Concepts for Opioid-Reduced Anesthesia

Especially the opioid crisis, unwanted opioid adverse effects, ketamine's analgesic properties allowing for a considerable reduction of morphine and opioid analgesic requirements, and enhanced recovery after surgery concepts (ERAS) have provided an impetus for the development of techniques that minimize opioid use such as Opioid Sparing Anesthesia (OSA) or Opioid Free Anesthesia (OFA). It appears that these techniques are not only feasible, but actually reduce severe adverse opioid effects [83]. However, if less opioids are administered during surgery, it is not only an ethical precept to replace their analgesic action with other drugs but also a pathophysiological necessity to prevent the unwished, opposite effect of more

postoperative pain [114]. Along with alpha-2 agonists and various local anesthesia and analgesia applications, esketamine has become a pillar of intraoperative analgesia during OFA.

After the Second World War, the introduction of opioids into anesthesia was a major step forward. They made it possible to limit activation of the sympathetic system while reducing hypnotic agent concentrations, thereby improving the hemodynamic impact of general anesthesia [115]. The synthesis of fentanyl in 1960 led to the concept of "high-dose fentanyl anesthesia", which enabled doses of 25 to 75 µg/kg to preserve cardiac output in highly unstable patients undergoing mitral replacement or coronary artery surgery [116]. The synthesis of remifentanil in the early 90s, an opioid with a very short contextual half-life (4 min), seemed to promise a bright future for opioid-based anesthesia (OBA). However, its use soon revealed that patients receiving remifentanil suffered from increased postoperative pain, which lead to the recognition of opioid-induced hyperalgesia (OIH) [117] in the early 2000s.

First endeavors to completely replace morphinics with ketamine date from this period: The NMDAR antagonist is the only IV anesthetic agent with powerful analgesic effects, and OIH is based upon several pathophysiological mechanisms such as involving cholecystokinin receptors [118] which are largely triggered by NMDAR activation [119]. Moreover, pain induced by surgical lesions recognizes the same mechanisms as OIH and ensuing metabolic cascades. As expected, ketamine blocks the surgery-related prolonged depolarization, windup and nociceptive sensitization in neurons of the posterior horn of the medulla, and thus prevents or reduces morphine tolerance and OIH [119].

These early attempts demonstrated that anesthesia for sometimes complex surgical procedures could be achieved by combining ketamine infusion with midazolam (such as in the Restall protocol for war surgery) [120] or with propofol [121] without recourse to opiates [122,123]. After awakening, it was observed that intraoperative hemodynamics were more stable, and that patients did not require more analgesics than patients who had received intraoperative opiates.

As written above, techniques which completely ban the intraoperative use of opioids have been coined OFA [124], which gained momentum in use because of the realization that hundreds of thousands of US-American deaths during the opioid epidemic resulted from over-prescription of perioperative morphinics [125]. Increasing knowledge of OIH, the uncertainty about the possibility of a favoring role of opioids on metastatic cancer cell migration [126], and improved ERAS concepts which demonstrated a harmful potential of morphinics in postoperative recovery contributed to increasing OSA and OFA. Unwanted opioid effects include a prolongation of gastrointestinal transit time, postoperative ileus, and an increase in PONV. Respiratory complications may be particularly dangerous during anesthesia emergence in obese patients, patients with respiratory handicap, and / or obstructive sleep apnea [127, 128]. Obese patients are more often exposed to hypoxemia after opioids because of tongue drop, upper airway collapse, obstructive sleep apnea etc. They also suffer from less parietal compliance and functional respiratory capacity (FRC), with higher pulmonary resistance and closure volume. Opioids impair post-operative cognitive performance [125].

Adjunctive esketamine increases the depth of anesthesia, while preserving circulatory and respiratory functions. It offers the opportunity of avoiding the above-named opioid-related complications and may be associated with a better carcinologic prognosis [129,130,131]. Several key considerations are necessary in such a pharmacological strategy: Multimodal analgesia including paracetamol, steroidal and non-steroidal anti-inflammatory drugs, tramadol, nefopam and others are used together with clonidine, dexmedetomidine or recently remimazolam to achieve a reduction in intraoperative opioid needs by approximately 40%. The main disadvantage of alpha-2 agonists is the generation of unstable hemodynamics with arterial hypotension, whose prognosis is known to be poor, and bradycardia, which can be catastrophic when alpha-2 agonists are administered in excessive doses [132]. They are also associated with

unwanted postoperative sedation [133]. Sometimes they are replaced by beta-blockers. The second milestone in OSA and OFA are regional and local anesthesia and analgesia (RA) whenever possible including all kinds of application (such as plexus and nerve blocks, epidural, caudal or spinal anesthesia) in combinations with general anesthesia. If RA is not possible, intravenous lidocaine may be administered throughout the surgical procedure. This technique has been dubbed as "poor man's epidural". Nevertheless, adjunctive intraoperative ketamine and a fortiori esketamine may reduce postoperative opioid needs by at least 20% [134], and offers the potential of preventing central sensitization and the development of chronic postoperative pain [135]. In addition, combining an alpha-2 agonist with esketamine is not only synergistic in terms of sedation and narcosis, but reduces possible hemodynamic overstimulation and psychic side effects of esketamine.

3.2 Opioid-Sparing and Opioid-Free Trials with Esketamine

Various randomized trials report esketamine-related advantages if used as adjunctive agent in OSA or as analgesic replacing an opioid in OFA (Table 2). Intraoperative esketamine improved hemodynamic stability (less hypotension and bradycardia) through sympathomimetic stimulation, reduced parasympathetic activation [41,136,137,138,139], and caused less postoperative respiratory depression [138].

In thoracic surgery [140] or in sedation with maintained spontaneous breathing, respiratory parameters were improved with esketamine. In Fan and co-workers' study of 60 patients undergoing video-assisted thoracic surgery without intubation for tumor removal by "wedge" resection, the quality of lung collapse was better in the OFA group [137]. The authors attributed this result to the bronchodilatory properties of esketamine. Respiratory parameters were also more favorable and included a better respiratory rate (15 OFA vs. 8 / min with opioids), oxygenation index, and normalization of spontaneous ventilation. In Jia and co-workers' study of 80 elderly patients with pertrochanteric fractures, respiratory stability was better in OFA, especially at the beginning of surgery [138].

Esketamine improved postoperative analgesia in OSA and OFA [141,142,143,144], which was associated with a reduction in chronic post-surgical pain development in some studies [145]. Esketamine lowered opioids consumption [141,143] and reduced the occurrence of PONV [103,133,136,139,145,146,147]. In several studies, esketamine improved recovery scores [103,138] including getting out of bed and time to first eating [142]. Esketamine-based OFA improved patient satisfaction [103] which is very important in ambulatory surgery and in ERAS concepts [139]. It reduced anxiety and depression scores [100], improved sleep quality [143], and may reduce inflammatory parameters (CRP, IL-6, IL-8 and TNF-α) in OFA [103,144].

In some studies, OFA with esketamine improved digestion with earlier recovery of transit time and eating [141,142,143]. Esketamine sometimes reduced surgical complications such as fistula development [141], and decreased hospitalization length [138,141]. A reduction of adverse digestive effects of opioids may translate into directly improved prognosis in OFA [141].

In comparisons of several doses of esketamine mostly those in the higher subanesthetic dose range appeared to be the most effective for postoperative analgesia, such as 0.25 mg/kg/h in the randomized study by Yuan et al [142]. In epidurals, esketamine was less effective than morphine [145].

Esketamine is often combined with dexmedetomidine, which may slightly increase the time to awakening:15 vs. 13 min in Chen et al.'s study [146]. 7 vs. 5 min in Qian et al.'s study [139]. It is also combined with local anesthetics, either in regional or local anesthesia and analgesia or IV lidocaine. It is well combined with propofol, reducing its dose and the respiratory and hemodynamic depressant effect. It can also be combined with remimazolam. Recovery time

may then be shorter than with propofol, and fewer hypoxic episodes with such a regimen were observed in sedation of obese patients.

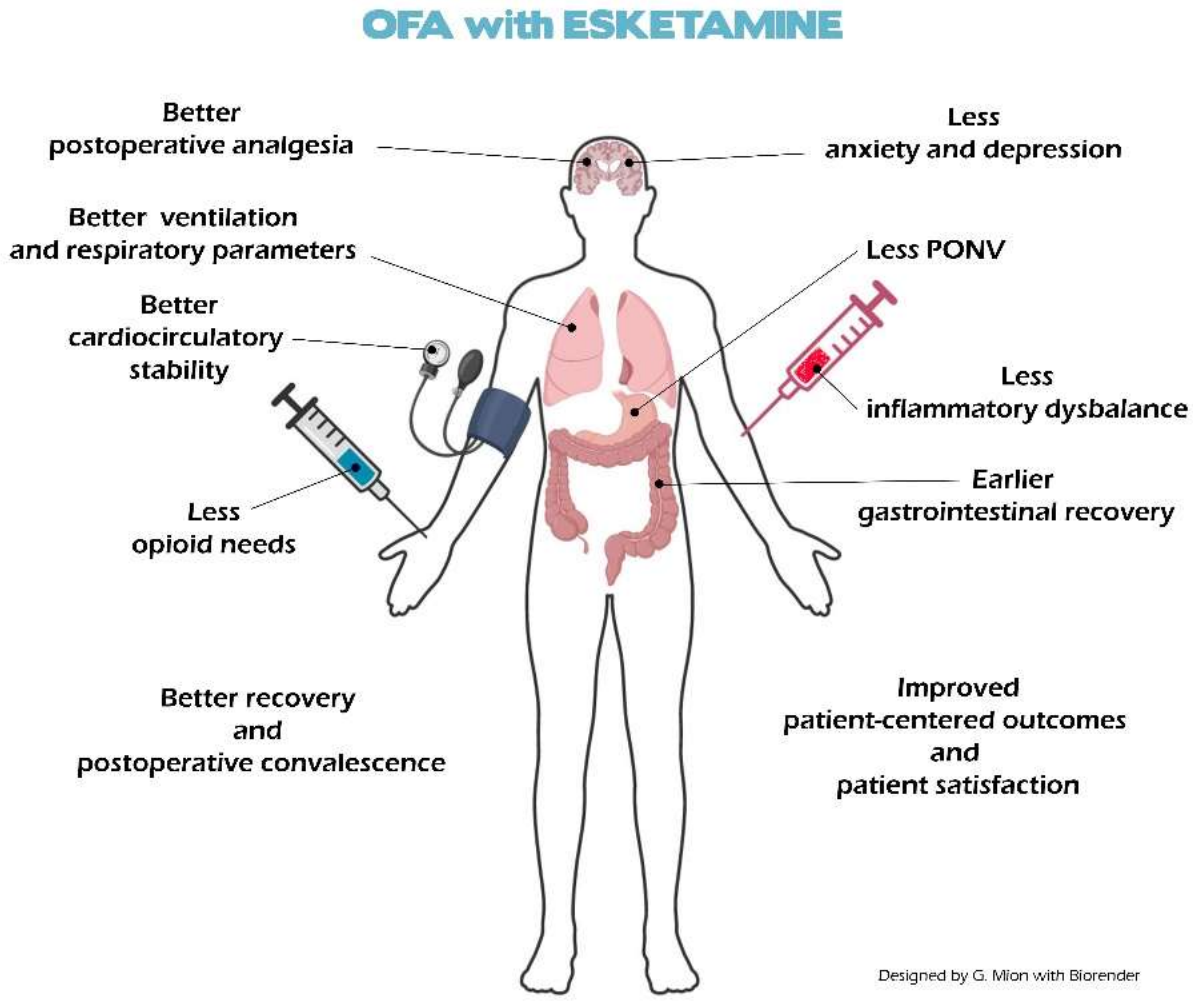

Fig. 3. Beneficial effects of esketamine in OFA

Table 2: Randomized controlled trials reporting esketamine-related benefit when used as analgesic adjunct in opioid-sparing anesthesia (OSA) or as sole analgesic in opioid-free anesthesia (OFA)

First author, year	Study design	Surgery	N	Opioid-free / opioid-sparing anesthesia (OFA / OSA)	Opioid-based anesthesia (OBA)	Main differences
Massoth et al 2021 [133]	RCT	Laparoscopic gynecological surgery	152	Dexmed + esketamine (0.15 mg/kg then 0.15 mg/kg/h, median dose 0.5 mg/kg)	Sufentanil (0.3 mg/kg + Re-injections 0.15 mg/kg)	OFA: Less PONV and less antiemetic need
Chen et al 2022 [49]	RCT	Abortion	178	3 Esketamine groups 0.2, 0.25 and 0.3 mg/kg	Fentanyl (1 µg/kg)	OFA: Less or no hypotension (0 vs. 20%) and less hypoxic episodes (0 - 2 vs 11%) in all esketamine groups With 0.3 mg/kg esketamine: more PONV and adverse psychic phenomenon, a 1 min prolonged recovery time, and 3 min longer ICU stay than with fentanyl Authors recommendation: Use mean dose of 0.25 mg/kg esketamine
Yu et al 2022 [103]	RCT	Mastectomy	136	RA: Pecs II block + esketamine (0.5 mg/kg then 0.25 mg/kg boluses) Dexmed + remifentanil Dexmed + esketamine PCA (bolus 0.02 mg/kg)	RA: Pecs II block + Sufentanil (0.3-0.4 mg/kg) Remifentanil Sufentanil boluses Dexmed + sufentanil PCA	OSA: Higher BP and HR after induction Postoperative: No difference in analgesia Less PONV (12 vs. 28%), Higher recovery and satisfaction score (QoR-40) Less anxiety and depression (HADS) Lower IL-6
Zhu et al 2022 [136]	RCT	Minor gynecological surgery	141	Esketamine 0.2 mg/kg with Low Alf + 0.5mg/kg/h with Low and Moderate Alf	3 Alfentanil groups, Ctrl: 20 µg/kg then 40µg/kg/h Moderate Alf: 20 µg/kg Low Alf: 10 µg/kg	OSA: Less PONV after Moderate Alf Fewer hemodynamic disturbances with Low Alf Comparable postoperative analgesia
Hublet et al 2022 [141]	Retro	Pancreatic resection surgery	77	Dexmed 0.5 µg/kg/h, Lidocaine, esketamine (0.25 mg/kg then 0.125 mg/kg/h)	Remifentanil + Intrathecal morphine	OFA: Better postoperative analgesia Reduced morphine consumption (60%) Reduced hospital stay (10 vs 14 days) Less surgical complications

Zhang et al 2023 [45]	RCT	Suspension laryngoscopy	111	Esketamine (0.5 mg/kg)	Sufentanil (0.125 µg/kg)	OFA: More stable hemodynamics Less bradycardia (39 vs 60%) and hypotension (34 vs 56%) No difference in hypertensive episodes Less hemodynamic disturbances (area under the curve)
Fan et al 2023 [137]	RCT	Intubation-free video-assisted thoracic surgery for tumor removal by wedge resection	60	RA: intercostal block Propofol-TCI Dexmed (0.5 mg/kg then 0.5 – 1 µg/kg/h) Esketamine (0.5 mg/kg then 0.2 – 0.5 mg/kg/h, mean dose 58 mg)	RA: intercostal block Propofol-TCI Dexmed (0.5 mg/kg then 0.5 – 1 µg/kg/h) Remifentanil	OFA: Better pulmonary collapse Fewer hypotensive episodes requiring phenylephrine Higher RR (15 vs 8), better oxygenation index Faster recovery of spontaneous ventilation Identical analgesia (NRS < 3) OFA: Delayed awakening (32 vs 24 min), But no increase in time spent in ICU
Jia et al 2023 [138]		Intertrochanteric fractures of the femur	80	RA: iliofascial block (Ropivacaine + Dexmed 0.5 µg/kg) Esketamine (0.3-0.5 mg/kg then 0.3 mg/kg/h ± one single 0,25 mg/kg bolus)	RA: iliofascial block (Ropivacaine + Dexmed 0.5 µg/kg) Remifentanil and LMA-assisted ventilation	OFA: Better circulatory and respiratory stability at the start of surgery Identical postoperative analgesia Better quality of recovery at 24 hours after surgery (QoR-15 score) Shorter hospitalization (10 vs 15 days)
Qian et al 2023 [139]	RCT	Outpatient breast lumpectomy	74	Dexmed (0.5 µg/kg, then 0.1 - 0.2 µg/kg/h), Esketamine (0.1 mg/kg, then 0.1 - 0.2 mg/kg/h), Lidocaine (1.5 mg/kg then 1 - 1.5 mg/kg/h)	Sufentanil then Remifentanil	OFA: Less hypotension and bradycardia Slightly longer time for first analgesic request (7.4 vs 6.2 min) Pain according to VAS comparable (< 3) Slightly longer awakening (7 vs 5 min) and time to orientation (12 vs 7 min) Less PONV (11 vs 51%) Better patient satisfaction
Yu et al 2023 [143]	RCT	Laparoscopic cholecystectomy	150	Esketamine 0.3 mg/kg, Dexmed 0.6 µg/kg, IV Lidocaine 1.5 mg/kg then 2 mg/kg/h + Local anesthetic incision infiltration	Remifentanil 1 µg/kg then 0.1–0.3 µg/kg/min + Local anesthetic incision infiltration	OFA: Better analgesia Lower morphine consumption Less rescue analgesics Earlier time to first flatus Longer time to LMA removal and to recovery of orientation

Dai et al 2023 [144]	RCT	Pelvic or abdominal surgery	122	RA: lumbar block Propofol and dexmed Esketamine 1 mg/kg Esketamine PCA (0.015 mg/kg/h)	RA: lumbar block Propofol and dexmed Sufentanil	OFA: Better postoperative analgesia Less increase in CRP, IL-6, IL-8 and TNF-α No difference in PONV
Yan et al 2023 [145]	RCT	Tumor removal by video-assisted thoracoscopy	159	RA: epidural anesthesia Dexmed (0.5-1 µg/kg) + Propofol-TCI Esketamine (0.125 mg/kg) Epidural esketamine (0.25 mg/kg) Esketamine PCEA	RA: epidural anesthesia Dexmed (0.5-1 µg/kg) + Propofol-TCI Fentanyl 2 mg Epidural morphine Morphine PCEA	OFA: more esmolol (during surgery), OBA: more ephedrine OFA: Less PONV (5 vs 39%) and pruritus (2.5 vs 81%) H24: Pain (VAS > 4) more frequent in OFA (17.5 vs 0%) H48: same level of pain OFA: Less chronic pain at 3 months (17.5 vs 34.2%) and at 6 months (11.3 vs 29.1%) after surgery
Chen et al 2023 [146]	RCT	Laparoscopic gynecological surgery	77	Dexmed (0.1 -0.3 µg/kg/min) Esketamine (0.3 -0.5 mg/kg then 0.3 mg/kg/h) Esketamine PCA	Sufentanil then remifentanil Sufentanil PCA	No difference in hemodynamics during surgery and in postoperative analgesia OFA: Lower incidence of PONV (10 vs 29%) and Slightly delayed awakening (15 vs 13 min)

Alf alfentanil*, BP* blood pressure, *Ctrl* control, *Dexmed* dexmedetomidine*, HADS* hospital anxiety and depression scale*, H24* 24 h after surgery*, H48* 48 h after surgery, *HR* heart rate*, IV* intravenous, *LMA* laryngeal mask airway*, NRS* numeric rating scale*, PCA* patient-controlled analgesia, *PCEA* patient-controlled epidural analgesia, *Pecs II block* (ultrasound-guided) pectoral nerve block type II*, PONV* postoperative nausea and vomiting, *RA* regional anesthesia, *RCT* randomized controlled trial*, RR* respiratory rate*, TCI* target-controlled infusion, *VAS* visual analogue scale, *vs* versus

4. Safety, Contraindications, Pitfalls

4.1 Safety

Little formal research on specific safety issues with esketamine has been performed in anesthesia and analgesia in recent years; many items are therefore derived from key considerations with racemic ketamine (for questions regarding safety with intranasal esketamine, the reader is kindly referred to the psychiatry chapters).
Because esketamine preserves respiratory activity, a lethal overdose in an otherwise relatively healthy patient is rather unlikely. In comparison to other analgesics, opioids, and hypnotics, esketamine has a wide range of safety. Nevertheless, as a general precaution, a mechanical ventilation apparatus and somebody experienced with artificial ventilation and intubation should be available for safety reasons as soon as IV ketamine is used above low-dose of the subanesthetic dose range.
Psychedelic adverse effects are one of the most common unwanted side effects associated with esketamine: They are strictly dose-dependent and cognitive disturbances may manifest in self-perception, color recognition, memory, attention, reaction, and sense of place and time.

Two examples of typical (es-)ketamine-associated adverse effects shall briefly be described:

If esketamine is used as mono-anesthesia with the goal of increasing the efficacy of electroconvulsive therapy (ECT), expected cardiovascular effects (tachycardia and hypertension) have to be managed properly. If necessary, esmolol and urapidil have been advocated to control an excessive increase of cardiac frequency or arterial pressure in an at-risk patient [148].

In a recent meta-analysis of seven studies (808 patients) [149], typical positive effects and the result of unwanted esketamine action have been described: Combining esketamine with propofol reduced the risk of hypotension (RR: 0.37) and bradycardia (RR: 0.34) when compared to propofol alone. The reduction of respiratory depression (RR: 0.73) was not significant. However, the meta-analysis also showed an increased risk of agitation on awakening (RR: 1.15) with esketamine. One explanation could be that more than half the studies used a dose of 0.5 mg/kg esketamine, which is too high for short procedures. In addition, the psychic disorders were short-lived and self-terminating.

4.2 Contraindications and precautions

Allergy: Allergy to ketamine is particularly rare.
Cardiovascular Contraindications: In situations where tachycardia or hypertensive episodes such as with intracranial, thoracic or abdominal aneurysm are very dangerous, ketamine is rather contraindicated. Especially a bolus injection can be hazardous in case of unstable angina, uncontrolled hypertension, severe heart decompensation, high-risk coronary vascular disease, recent myocardial infarction, or pulmonary hypertension.
Children Below 3 Years of Age: Very young children have a higher risk of laryngospasm.
Endocrinological Contraindications: Hyperthyroidism, particularly thyrotoxicosis, and pheochromocytoma are contraindications for ketamine administration.
Epidural or Intrathecal Application: Although most ampoules of esketamine are marketed without preservative, the drug itself carries a risk for spinal neurotoxicity. Epidural or intrathecal administration can therefore not be recommended. It may be used on a compassionate basis in patients with limited life expectancy and pain refractory to other treatments.

ICU: With prolonged ketamine sedation and analgesia (at higher dose), hepatobiliary functions must be carefully monitored because of potential ketamine toxicity.

Liver Disease: In case of severe hepatic dysfunction, esketamine should be avoided because of its risk of hepatotoxicity and the fact that esketamine metabolism is hepatic.

Neurological Contraindications: Elevated intracranial pressure (ICP), intracranial mass bleeding or subarachnoid hemorrhage were classical contraindications for the use of ketamine until two decades ago [150]. However, esketamine does not increase the ICP with controlled ventilation and concomitant use of a GABA agonist.

Elevated Intraocular Pressure, Acute Globe and / or Penetrating Eye Injury, Glaucoma: The literature is contradictory; only very cautious low-dose use may be considered.

Pre-Eclampsia and Eclampsia: Both disorders are meanwhile considered as relative contraindications for ketamine use, mainly because of fear of uncontrollable hypertension.

Schizophrenia: Because ketamine may reactivate delirious episodes in schizophrenic patients, it is nowadays regarded as relatively contraindicated.

4.3 Pitfalls

Unfortunately, almost all studies lack a more individual, patient-centered approach. For example, although it has been shown that ketamine exerts effects of differing intensity depending on patient's sex, this parameter is virtually never taken into account in therapeutic use programs. Different genetic predispositions that influence pharmacokinetics and plasma concentrations are as yet rarely considered in routine care. In addition, the large safety margin of esketamine may explain why the doses used are highly variable. It is complicated to assess the "depth of anesthesia" in order to adapt the ketamine dose, because monitoring devices were designed for GABAergic agonists. When esketamine is used as an adjunct to balanced general anesthesia or as part of OFA techniques, it is possible to reduce the dose of other anesthetics and analgesics. However, it is often difficult to know if and how this has been done. Eventually, studies are only just beginning to incorporate patients' subjective experiences as parameters for assessing the quality of anesthetic management. All these points contribute to the enormous heterogeneity of reported trials, and may be confounding factors in trial results and data interpretation.

Last but not least, it may take some practice to beneficially "handle" the prodigious, multi-faceted anesthetic that is esketamine. It sometimes seems as if we're wavering between low-dose use, without knowing whether or not this quantity will bring about the desired effect, and higher dose administration with undesirable and unpleasant psychedelic and behavioral action.

5. Limitations

This review has some limitations. Recent controlled studies are mostly monocenter trials and come from China where esketamine was recently authorized for clinical use. Anesthetic techniques may somewhat differ from those in western countries and genetic variations may explain some metabolic differences.

Another limitation is the lack of direct comparisons between racemic ketamine and esketamine. Most of this work has been conducted years or decades ago.

OFA techniques cannot be applied to all patients. They may be dangerous in those with compromised hemodynamic equilibrium who need strict control of tachycardia and hypertension.

Finally, despite several pharmacokinetic studies, too little work links clinical effect to measured plasma concentrations of ketamine and its metabolites.

6. Conclusion

Esketamine has only recently been commercialized in France. Its main advantage is its affinity for the NMDA receptor, which is 4 times greater than that of levorotatory arketamine: This results in twice the analgesic potency of esketamine compared to racemic ketamine.

When used at equianalgesic dose, esketamine has proven more acceptable in terms of adverse action. While it produces as many psychomimetic effects as the racemate, their quality is more favorable with less anxiety or bad trips. It also provides a quicker awakening with less impairment of cognitive and logical functions.

Like the racemate, it offers the benefit of improving circulatory and respiratory stability during anesthesia and in almost all other settings: It exerts desirable effects in the general context of post-operative recovery, improving respiratory, digestive and cognitive functions. It may reduce post-operative depression, which affects many patients suffering from anxiety-inducing illnesses. As such, it has become an indispensable component of the so-called OFA or OSA techniques, which seem to be gaining a foothold in modern anesthesia. Excessively low dose esketamine appears to be of little value, but higher than subanesthetic dose esketamine should mostly be avoided in perioperative adjunctive use as well.

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