Chapter

Application of Ketamine in Current Practice of Anesthesiology

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Abstract

Ketamine was discovered in 1964 by merging a ketone with an amine. Patients described feeling disconnected like they were floating in outer. Thus, it was characterized as a dissociative anesthetic. It is a unique drug that expresses hypnotic, analgesic, and amnesic effects. No other drug used in clinical practice produces these three important effects at the same time. Its newly found neuroprotective, anti-inflammatory, antitumor effects and low dose applications have helped to widen the clinical profile of ketamine. Ketamine as an analgesic adjunct in chronic pain patients is currently being researched. Combined use of ketamine and an opiate analgesic has been found to provide good perioperative pain control with reduction in symptoms such as nausea and vomiting, sedation, and respiratory insufficiency.

Keywords: ketamine, pain, dissociative anesthesia, NMDA receptors, ketamine physiology, ketamine side effects, ketamine as induction agent, ketamine for maintenance of anesthesia, ketamine contraindications, perioperative analgesia, anti-inflammation, sub anesthetic dose of ketamine

1. Introduction

The story of ketamine began in the 1950s in Park-Davis and Company's Laboratories as the search for a cyclohexylamine that would serve as an "ideal" anesthetic agent. This new agent would also have analgesic properties. In March 1956, Dr. Harold Maddox synthesized a compound [N-(1-phenyl-cyclohexyl)-piperidine] known as phencyclidine (PCP) using a new chemical organic Grignard reaction [1]. Several experiments were performed at Parke-Davis labs and Wayne State University; both on animals and in human trials. These experiments made it clear that phencyclidine was capable of producing a potent analgesic and cataleptic state defined as a "characteristic akinetic state with a loss of orthostatic reflexes, but without impairment of consciousness, in which the extremities appear to be paralyzed by motor and sensory failure" [2, 3]. After administering the drug, patients had an increase in blood pressure, respiratory rate, and minute volume while corneal and laryngeal reflexes were conserved. However, increased salivation and nystagmus were noted. With these findings, PCP was deemed to be a useful agent in the setting of anesthesia. However, with further studies, it became apparent that there was a profound and prolonged state of emergence delirium. This discovery would hinder the widespread use of PCP and begin the search for a new related compound [1, 3].

Finally, in 1962, Dr. Calvin Stevens was successfully synthesized a derivative of PCP – CI-581 or ketamine – which was selected to undergo human trials. On August 3 1964, the first human intravenous subanestheic dose of ketamine was successfully administered to volunteer prisoners at Jackson prison in Michigan [1]. About one-third of the patients had reported adverse effects of psychotic reactions which they described as a feeling of floating in outer space and having no feelings in their limbs. Due to this effect, Domino's wife Toni termed it "dissociative anesthesia" originating the concept of dissociative anesthesia [1, 4]. Dissociative anesthesia would later bed deifined as a state of electrophysiological and functional dissociation between thalamocortical and limbic systems. It was then concluded that ketamine is a potent analgesic and anesthetic with lower potency and shorter duration of action than PCP. Finally, in 1969, ketamine hydrochloride became available as a prescription drug under the name of Ketalar and a year later was approved by the US Food and Drug Administration [2, 3].

Unfortunately, the popularity of ketamine declined as it caused hallucinations and psychotic reactions that were an unpleasant experience for patients. However, in the early 1990s, ketamine made a come-back due to the peak of high-dose opioid anesthesia [3]. Ketamine is becoming widely used among anesthesiologists for both induction and maintenance in anesthetic and subanesthetic doses. Commonly it is used in combination with diazepam, midazolam, or propofol to help reduce hallucinations, psychotic reactions, and emergence delirium [1]. A recent interest has also sparked in opioid free anesthesia using ketamine. Contrary to yesteryears practice, today ketamine is widely used for a variety of different procedures for its valuable anesthetic, analgesic, and even amnestic properties, as we will discuss throughout this chapter.

2. Chemistry and pharmacology

Ketamine's chiral carbon center allows for the existence of two different steric configurations - S(+) and R(−) isomers. Each isomer has varying anesthetic, analgesic, dysphoric, and sympathomimetic properties. Several studies have shown that the S(+) isomer is more potent and has a higher NMDA affinity when used intraoperatively for anesthesia compared to the R(−) isomer. In addition, the S(+) isomer causes lower cardiac stimulation, less spontaneous motor activity, better analgesia, faster recovery, fewer psychotomimetic side effects, and decreased incidence of emergence delirium [1, 2].

Ketamine primarily works by inhibition of NMDA receptors and has two different mechanisms through which it exerts its function. NMDA receptors are excitatory amino acid receptors that have been implicated in pain [5]. The first mechanism of NMDA antagonism is as a channel blocker. The second mechanism is through an allosteric mechanism that decreases the opening frequency of the NMDA channel. It can also exert its effect through a variety of other mechanisms such as inhibition of L-type calcium channels, BK channels, HCN channels, and voltage-gated sodium channels. Other mechanisms of actions include monoamine blockade and inhibition of serotonin reuptake [2].

Ketamine has a slow off-rate compared to other anesthetic agents. This means that it continues to exert its effect even after glutamate; the substrate for NMDA receptors, has dissociated. This allows for a better anesthetic effect.

Ketamine has a high lipid solubility allowing it be rapidly taken up by the brain and redistributed to highly perfused tissue with a distribution half-life between 10 and 15 minutes [2]. Its metabolism is highly dependent on the liver using the cytochrome P450 system. Ketamine can be converted into active or inactive metabolites,

Intravenous	
Induction	1–4.5 mg/kg (60s)
Maintenance (general)	1–6 mg/kg/hr
Maintenance (sedation)	0.4–1 mg/kg/hr
Subanesthetic	0.2–0.8 mg/kg
Intramuscular	
Anesthetic	6.5–13 mg/kg
Subanesthetic	2–4 mg/kg

Table 1.
Doses of ketamine.

which are then further hydroxylated to increase water solubility through various CYP450 enzymes. The metabolites are then renally eliminated [1, 6].

Research has shown that ketamine has a dose dependent effect. In this chapter, we will focus on anesthesia and analgesia. Analgesic effects are seen at levels of 100–160 ng/ml. Induction of anesthesia is usually achieved at 9000–25000 ng/ml and can be maintained with 2000–3000 ng/ml. Ketamine's half-life at anesthetic doses is approximately 79 minutes, and its actions decrease when the drug redistributes from the brain into other tissue. The threshold between consciousness and emergence from anesthesia is 1000 ng/ml. The psychic state is usually seen with doses between 50 and 200 ng/ml. The onset and duration of these psychedelic effects varies based on the route of administration [1, 6].

Because ketamine is both water and lipid soluble, it can be administered intravenously, intramuscularly, orally, and sublingually. However, due to its significant first pass metabolism oral administration yields very little bioavailability. Intravenous administration is the preferred route of administration as it allows for 100% bioavailability. Recommended doses, shown in **Table 1**, are between 1 and 4.5 mg/kg over the course of 60 seconds for induction. For general maintenance 1–6 mg/kg/hr. and 0.4–1 mg/kg/hr. for continuous sedation is recommended [6]. Ketamine can be given intramuscularly that has a 93% bioavailability and is useful in emergencies, uncooperative patients and burn patients. When administered intramuscularly higher doses, between 6.5–13 mg/kg, are needed. For subanesthetic doses the intravenous dose is between 0.2–0.8 mg/kg and 2–4 mg/kg if given intramuscularly [2].

Table 1 summarizes the various suggested doses of ketamine administration depending on route, phase and administration method of anesthesia.

For review, Induction is the transition from an awake state to an anesthetized state with a sole agent such as ketamine or propofol or a combination of drugs [2]. Maintenance involved sustaining this anesthetic [7]. The role of ketamine in induction and maintenance in the practice of anesthesia will be discussed later in this chapter.

3. Use of ketamine in anesthesia

In the first ever human trial done with ketamine, a 1–2 mg/kg dose was given to patients, which resulted in analgesia and anesthesia with an onset time of one minute and lasted for about five to ten minutes. Within one to two hours the patients were back to their initial state. An increase in blood pressure and heart rate, hyperactive reflexes, and increase in lacrimation was noticed. A transient respiratory

depression was also seen but returned to baseline within seven minutes. Even so, reflexes were preserved throughout. No labs were significantly affected. However, during the recovery period, as with PCP, psychic reactions, mood and affect alterations were observed but laster for a shorter duration and were less severe than the reaction with PCP that subsided within 30 mins after awakening. Many of the effects that were seen with ketamine were not seen with the anesthetics used commonly during that time period [4]. This led to the conclusion that ketamine results in a short-acting and effective induction of anesthesia and analgesia.

Ketamine has been shown to be safe and effective for maintenance sedation in several studies. It decreases airway resistance, improves dynamic compliance, preserves functional residual capacity, tidal volume, and minute ventilation [7]. Another advantage observed was that with ketamine, pharyngeal and laryngeal reflexes were conserved. In addition, ketamine provides an additional benefit in patients with refractory bronchospasms as it decreases audible wheezes, bronchodilator requirements, and hypercarbia making it the drug of choice in patients with bronchospasms [7]. Furthermore, in patients with refractory status asthmasticus, it helps reduce the need for initiation of mechanical ventilation [8]. Ketamine is also a popular induction agent [2]. For induction, ketamine is usually used in combination with other agents such as propofol or diazepam for reduction in emergence excitement, or dissociative effects that often result when ketamine is used [8].

Since ketamine is known for its ability to cause dissociative anesthesia, it has been hypothesized to be particularly beneficial for painful or distressing procedures. For example, endotracheal intubation using ketamine has been successful in some cases with the added advantage of maintaining or even increasing cardiorespiratory tone. We will discuss four methods for endotracheal intubation that have been evaluated. In delayed sequence intubation, dissociative doses of ketamine are given to allow the patient to enter an unconscious state so that proper preparation and pre-oxygenation can be taken before a paralytic is given. With this method, there were reduced adverse events and improved oxygen saturation. In ketamine-only breathing intubation, a dissociative dose of ketamine monotherapy is used in spontaneously breathing patients. This strategy seems to be useful in patients with anatomically difficult airways, physiologic limitations and profound acidosis. With traditional rapid sequence intubation, ketamine was given with the traditional rapid sequence intubation protocol. In review, rapid sequence intubation is when an induction agent and a paralytic are administered simultaneously during endotracheal intubation without the need for bag mask ventilation. This method has an advantage when apnea caused by the paralytic agent is not a concern. Finally, in ketamine for post-intubation analgesia and sedation, ketamine given after intubation provides two benefits - stimulating heart rate and blood pressure and analgesic and sedative properties. This allows for the reduction of conventional sedative use which has been linked to prolonged ICU stay and delirium. Although advantages have been noted, using ketamine for airway management using these strategies should be done with careful planning and caution, as there still is limited evidence [9].

4. Effects of ketamine use

A major advantage of ketamine, unlike many other anesthetic agents, is hemodynamic stability. It is also generally well tolerated in both pediatric and geriatric patients. As mentioned previously, ketamine when given in a combination with propofol for induction significantly improves hemodynamic stability within the first ten minutes [10]. This advantage makes ketamine extremely beneficial in managing

hemodynamically unstable patients such as those who have suffered severe trauma. For example, in which ketamine has been useful is in the management of burn patients especially during the acute phase of injury. During the acute phase, the burn victims are undergoing significant fluid shifts leading to cardiovascular and respiratory insufficiency [11].

4.1 Anti-inflammatory effect

Inflammation is a normal mechanism that the body uses to fight infection caused by viruses and bacteria. This mechanism is initiated by pro-inflammatory cytokines that are released by the immune cells. These pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, IFN-γ, IL-18, and Tumor Necrosis Factor (TNF) [12]. However, inflammation can also be disadvantageous in that it can lead to pain and swelling in the acute setting. Concentrations of proinflammatory cytokines during the perioperative period may significantly impact surgical outcome. Ketamine has been shown to modulate the perioperative cytokine response and plays a significant anti-inflammatory role. It inhibits the systemic response without affecting the healing process that is necessary during the postoperative state [12]. One such mechanism is the reduction of leukocyte migration through endothelial monolayers. It is well studied that neutrophils play a key role in defense against foreign pathogens. Upon activation, neutrophils need to cross endothelial cell layers. Researchers investigated the effects of ketamine on leukocytes and endothelial cells independently and together. In a dose-dependent fashion, ketamine suppressed migration when leukocytes alone were treated. Interestingly, when the endothelial cells were treated with ketamine, there was no significant reduction in migration. However, when both leukocytes and endothelial cells were treated, the suppression in migration was much higher than when only leukocytes were treated [13]. One possible mechanism that may achieve this is is the inhibition of the up-regulation of CD18 and CD26L on neutrophils. CD18 and CD26L are stimulated during inflammation and are important cell surface markers for adhesion of neutrophils to endothelial cells promoting neutrophil migration [14].

It has also been suggested that this effect might be mediated by the suppression of microglial activation in the CNS or the inhibition of large conductance calcium activated potassium channels in the microglia. Specifically, there is a reduction in postoperative pro-inflammatory cytokines such as serum IL-6, TNF-a, nuclear factor kb, CRP and nitric oxidase synthase [15]. In addition, an increase in post-operative serum IL-10 levels, an anti-inflammatory cytokine. Ketamine was also shown to impair neutrophil chemotaxis, inhibit superoxide radical production, inhibit differentiation of immature dendritic cells, and increase Treg cell concentration [16]. Ketamine may also alter the oxidative stress response in patients. When ketamine was administered, patients had lower total thiol molecules and a lower total antioxidant capacity. They also had higher lipid peroxidation, and higher superoxide dismutase and glutathione peroxidase activity [17].

4.2 Psycho modulator effects

Ketamine has several effects on brain activity that can be monitored by EEG. When subanesthetic doses are given, the complexity of EEG changes is elevated relative to the baseline. At anesthetic doses the pattern alternates between a high and low complexity. Eventually the pattern stabilizes at a high complexity that is similar to baseline. This shows that ketamine can induce a fragmented state that shows alternating patterns of conscious and anesthetic states. A bolus of ketamine induces unconsciousness causing a change from slow waves to a gamma-burst

wave pattern on the EEG, which later evolved into a stable gamma pattern most likely due to decreasing plasma ketamine levels [18]. In addition, in hippocampal and cortical neurons, ketamine can increase activity of extrasynaptic GABA-a receptors which generate tonic inhibitory currents. Ketamine has been shown to increase potency of low concentration of GABA at these receptors as well [19]. Secondary effects on the dopamine system due to ketamine alters the firing rate of mesocortical and mesolimbic dopamine neurons causing an increase in extracellular dopamine in the striatum and prefrontal cortex which has been hypothesized to be a contributing factor the psychotic-like behaviors observed with ketamine [20].

Another interesting aspect of ketamine is that its effect varies depending on other anesthetic agents used with it or if it is used as a sole agent. For example, in a study done with rats it was found that when ketamine was added to ongoing sevoflurane or propofol, on EEG there was either no change or a shift to higher frequencies. However, when ketamine was given alone there was a simultaneous increase in both lower and higher frequencies. Also, when ketamine is used as a sole anesthetic agent patients can experience dissociative effects. However, at the same time ketamine is also found to be neuroprotective in preventing or mitigating postoperative delirium. This might explain why ketamine is being used both as an experimental model of psychiatric diseases as well as a proposed treatment for psychiatric diseases [21].

Ketamine's unusual cataplectic properties make it a dissociative anesthetic. At low doses, it causes alteration in visual and auditory stimuli and feelings of detachment from one's surroundings that manifest themselves as delirium, hallucinations, delusions, and confusion [20]. This leads to a potential for abuse and explains why ketamine is a class III-controlled substance and often referred to as "Special K". Long term effects of repeated ketamine use may lead to flashbacks, attentional and other cognitive dysfunctions, and decreased sociability. On the other hand, its continued use is reinforced by the other psychotropic effects. Therefore, some anesthesiologist may choose to avoid ketamine especially when it comes to patients with Post Traumatic Stress Disorder (PTSD) [15]. However, a recent study presented a trial of repeated intravenous ketamine administration for patients with PTSD. Infusion of ketamine demonstrated a clear superiority in reduction of symptoms compared to midazolam. More research on this aspect of ketamine is needed to help guide its use in anesthesia in patients with PTSD [10]. Caution should also be used when using ketamine for anesthesia in schizophrenic patients. This is because ketamine has been found to induce hallucinations, delusions and thought disorders, resembling an active schizophrenic episode of their illness. These episodes are also resistant to haloperidol, the drug traditionally used to treat active episodes [22].

Interestingly, ketamine and its metabolites modulate distinct neural circuits to produce dissociation and analgesia. The channel blocking effect of ketamine at the NMDA receptors may partially explain its dissociative properties. This is because ketamine blocks excitatory NMDA receptors on fast-spiking cortical interneurons more effectively than those on pyramidal neurons. This results in markedly dysregulated pyramidal neuronal activity. The relative inactivity of cortical interneurons leads to glutamate-mediated pyramidal–pyramidal neuronal facilitation. Consistent with this notion, lamotrigine, an antiepileptic medication that reduces cortical glutamate release and pyramidal neuron facilitation, suppresses the dissociative properties of ketamine. In the same fashion, midazolam reduces pyramidal neuron facilitation by downstream activity resulting from binding at gamma amino-butyric acid receptors on pyramidal neurons [23]. This could explain why ketamine causes a feeling of dissociation when it is used as an anesthetic agent.

4.3 Neuroprotective effects

There is also evidence that ketamine has neuroprotective effects. It is thought that this occurs due to the inhibition of calcium influx that occurs with ketamine administration. This calcium influx inhibition helps prevent ischemia and apoptosis providing a protective benefit to neurons. When ketamine was compared with other anesthetic agents such as midazolam, fentanyl, and propofol there was a reduction of spreading depolarizations with ketamine administration. Spreading depolarizations can cause neurovascular decoupling and potentiate the secondary phase of brain damage. Therefore, it is hypothesized that when ketamine is used, the suppression of these spreading depolarization allows for the maintenance of the electrochemical gradient and prevents neurovascular decoupling. This works together to have neuroprotective effects. However, the opposite effects could occur if repeated high doses are given as ketamine has the potential to cause neurotoxicity particularly in the developing brain. When ketamine is given in repeated high doses, there is an increase in a subunit of NMDA receptors, NR1. This allows the opposite effect, increasing the influx of calcium leading to apoptosis [8].

Traditionally, it was thought that ketamine increased intracranial pressure. In recent years, this theory has been rejected. Ketamine has successfully been used to reduce intracranial pressure. One study examined the effects of ketamine on intubated and sedated pediatric population at a regional trauma center with elevated ICP >18 mmHg resistant to first tier therapies. The results of 82 ketamine administrations in 30 patients were analyzed. Overall, following ketamine administration, ICP decreased by 30% (from 25.8 ± 8.4 to 18.0 ± 8.5 mm Hg) ($p < 0.001$) and Cerebral Perfusion Pressure (CPP) increased from 54.4 ± 11.7 to 58.3 ± 13.4 mm Hg ($p < 0.005$). In Group 1, ICP decreased significantly following ketamine administration and increased by >2 mm Hg during the distressing intervention in only 1 of 17 events. In Group 2, when ketamine was administered to lower persistent intracranial hypertension, ICP decreased by 33% (from 26.0 ± 9.1 to 17.5 ± 9.1 mm Hg) ($p < 0.0001$) following ketamine administration. They concluded that in ventilator-treated patients with intracranial hypertension, ketamine effectively decreased ICP and prevented untoward ICP elevations during potentially distressing interventions, without lowering blood pressure and CPP. In addition, these results refute the notion that ketamine increases ICP. Ketamine is a safe and effective drug for patients with traumatic brain injury and intracranial hypertension, and it can be used safely in trauma emergency situations [24].

4.4 Hemodynamic and respiratory effects

Ketamine's ability to promote central sympathetic stimulation and inhibition of neuronal catecholamine reuptake has brought upon its resurgence as an excellent sedation maintenance drug [7]. These effects favor hemodynamic stability. A prospective double-blind controlled study compared the use of ketamine vs. fentanyl for sedation in the ICU. It was observed that patients on ketamine had an increased MAP and a decreased incidence of shock. This characteristic is what makes it an excellent choice for induction of anesthesia for potentially unstable cardiac patients, especially when combined with midazolam. This benefit was observed in patients with septic cardiomyopathy [8].

In addition, clinicians have adapted 'ketofol,' a combination of ketamine and propofol especially for sedation cases. Propofol when used alone can cause myocardial depression and systemic vasodilation that both lead to hypotension, especially in a fasting patient. When propofol was used alone, it causesd a 20% reduction in systolic blood pressure in the first 5 and 10 minutes compare to 'ketofol' [10].

In addition, Ketamine tends to relax bronchiole smooth muscles. Thus, it can protect asymptomatic patients with asthma from developing bronchospasm and it can also effectively relieve bronchospasm in patients who already have respiratory problems before anesthesia. In addition, it has been used as an analgo-sedative in patients with status asthmaticus, not responding to the usual therapeutic options; as this can reduce the need for mechanical ventilation [8]. A review of prospective and observational studies showed a noticeable increase in chest wall dynamics in patients with status asthmaticus. They noticed that patients receiving ketamine continuous infusion also had reducible wheezing and even reduced bronchodilator requirement [7]. It should also be noted that unlike opioids, it does not increase histamine release; further reducing the possibility of bronchospasm [8].

These benefits extend to the pediatric population. Research has shown ketofol use as an induction agent as an alternative to propofol led to better laryngeal mask airway (LMA) insertion in children. In addition, during the LMA the use of ketofol showed faster induction time, lower injection pain, better jaw relaxation, better full mouth opening, and less incidence and duration of apnea when compared to using propofol alone [25]. Another study showed that induction with adjunctive use of ketamine and propofol, 1 mg/kg ketamine at induction and 5 mg/kg/h propofol infusion for maintenance for MRI sedation in children resulted in better induction quality, lower propofol infusion rate for maintenance, and faster time to full recovery [26]. Ketofol seems to have an effect that is dependent on the ratio of propofol to ketamine. In a clinical trial performed, it was determined that a 10:1 propofol ketamine ratio seems to have the greatest benefit during surgery due to better hemodynamic stability maintenance and faster recovery time [27].

5. Ketamine and opioid free anesthesia

With the opioid epidemic in recent years, clinicians are exploring options to provide pain relief with reduced or no opioid administration. Although opioids provide excellent analgesia, they can also produce unpleasant adverse effects such as nausea, vomiting, tolerance, pruritis, hyperalgesia, urinary retention, constipation, respiratory depression and have an extremely high potential for abuse. Approximately 2 million Americans use opioids for recreational purposes. According to the United State National Institute of Drug Abuse, overdose deaths involving prescription opioids rose from 3442 in 1999 to 17029 in 2017. Studies have shown that patients who consume high doses of opioids in the inpatient setting have a higher probability of report of increase opioid use after discharge. This is especially true for patients who leave the hospital with a prescription for opioids [28].

With regards to cancer pain control, the role of opioids has come into question in recent years as new data emerges about opioids, such as Morphine having pro tumor effects. Morphine may stimulate proliferation, facilitate metastasis, and promote angiogenesis leading to increased tumor burden. However, generalizations about these effects should not be extended to all opioids as research is still ongoing on this topic [29].

In recent years, clinicians are fast adopting Early Recovery After Surgery (ERAS) protocols that have an increased focus on a multimodal approach to pain control to reduce the consumption or even exposure to opioids. In the preoperative setting drugs such as celecoxib, acetaminophen and gabapentin are being utilized to begin pain control even before surgical incision is made. In the operating room Ketamine, among others such as Dexmedetomidine, Intravenous Lidocaine, Intravenous Magnesium, are some of the drugs on the forefront to achieve opioid free or opioid reduced pain relief.

In 2019 a study to evaluate the effect of Opioid Free Anesthesia (OFA) on post-operative morphine consumption and the post-operative course was initiated. Ketamine was used in both arms of OFA and Opioid Anesthesia (OA) for induction. A statistically significant result of reduced supplemental opioid consumption in the OFA group was observed (0.001). It should be noted, however, that ketamine was used in conjunction with lidocaine and dextromethorphan in the OFA group. In addition, the reduction in opioids used may also be due to reduced opioid tolerance. It was noted that postoperative pain scores did not differ between groups, indicating that OA and OFA provided comparable analgesia [30].

Multiple studies on the role of NMDA receptor antagonists in preventive analgesia have been reviewed. Preventive analgesia a concept in which the administration of a drug at any point in the perioperative period and the presumed associated reduction in central sensitization may reduce pain, analgesic consumption, or both beyond the clinical activity of the target drug. Their systemic review showed that ketamine and dextromethorphan produced significant preventive analgesic benefit in 58% and 67% of studies, respectively. In addition, a direct analgesic benefit of the drug occurred in the early postoperative period [5]. It can then be inferred that if pain is controlled early in surgery, then there may be reduced need for additional analgesic medications, including opioids.

A randomized, prospective, double blinded placebo- controlled study investigating the efficacy of preemptive ketamine infusions in patients with chronic pain undergoing elective back surgery was conducted. These patients had a history of at least 6 weeks (about 1 and a half months) of opiate use. They demonstrated that intraoperative preventative ketamine reduced opiate consumption in the acute postoperative period by 37% in these patients. In addition, it seemed that these patients who received ketamine infusions had a reduced pain sensation in the PACU (post anesthesia care unit) and even 6 weeks in the post operative period, leading to a reduction in morphine consumption [31]. As previously discussed, this reduction in pain sensation is due to reduction central sensitization *via* NMDA receptor antagonism, reduction in opiate tolerance, and some impact on the balance of neurotransmitters. This concept of preemptive analgesia was further explored by studying the effects of preemptive doses of ketamine before laparoscopic cholecystectomies at three doses; 1 mg.kg, 0.5 mg/kg and 0.25 mg/kg. In addition, researchers evaluated their effects on cardiovascular hemodynamics and hallucinations. There was a definitive role in reducing postoperative pain and analgesic requirement in patients. A low dose of 0.5 mg/kg was devoid of hemodynamic changes and hallucinations, making it the optimal dose for patients undergoing laparoscopic cholecystectomy [32].

Ketamine is being favored in bariatric surgery as obese patients tend to have obstructive sleep apnea and obesity hypoventilation syndrome that can be difficult to manage during induction and emergence of anesthesia. Due to its favorable stability on the cardiovascular system, respiratory system and gastrointestinal systems as detailed above. While only in a single case study, an opioid free anesthetic delivered to an obese lady with BMI of 50.1. She received an initial bolus of ketamine 5 $mg{\cdot}kg^{-1}$ was followed by a continuous infusion at 5 $\mu g{\cdot}kg^{-1}$ $min^{-1.}$ She underwent surgery without complication, rapidly met all extubation criteria, was never hypoxic, and was ambulating unassisted after 90 minutes in the recovery room without pain. She received ketorolac and IV Acetaminophen as the multimodal regimen. No opioids were used [33]. This case study lays the foundation for an excellent randomized double blinded study to improve outcomes in bariatric surgery. Furthermore TIVA with propofol, ketamine and dexmedetomidine (59 patients) vs. opioids and volatile anesthetics (60 patients) and their effects on postoperative nausea and vomiting (PONV) has been studied. Patients in both groups

had similar clinical characteristics, surgical procedure, and PONV risk scores and required similar amounts of postoperative opioid. 37.3% in the Opioid group compared to only 20% group reported PONV with a statistically difference (0.02). It was concluded that opioid-free TIVA is associated with a significant reduction in relative risk of PONV compared with balanced anesthesia [34].

Overall, OFA has gained in popularity to enhance early recovery and so spare opioids for the postoperative period. Pain is an extremely complex interaction of biological, cognitive, behavioral, cultural and environmental factors. Whether it is possible to deliver a safe and stable anesthesia without intraoperative opioids to many patients undergoing various surgical procedures. OFA still raises questions. Accurate monitoring to measure intraoperative nociception and guide the use of adjuvants is not available. Also, there is a need for procedure specific strategies as well as indications and contraindications to the technique. OFA does not seem to reduce the amounts of opioids prescribed at discharge which needs to be addressed and thought about by health care professionals.

6. Conclusion

Ketamine has made a strong resurgence as a versatile drug in the field of anesthesia. We reviewed the history of anesthesia from its discovery to its application as an anesthetic. In addition, we aimed to demonstrate how ketamine has favorable properties with regards to hemodynamics, its neuroprotective properties, psychomodulator effects, and anti-inflammatory effects. These favorable properties have made it one of the drugs on the forefront of the opioid free anesthesia concept discussed in this chapter. We remain excited about the ongoing research on Ketamine's role in treatment of patient with Post Traumatic Stress Disorder and various other applications in the field of Anesthesia.

Acknowledgements

We want to acknowledge Dr. Alex Bekker, MD, PhD, Chairman of Department of Anesthesiology for the encouragement and support.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.100461

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