

A review on the recent application of ketamine in management of anesthesia, pain, and health care

Abolfazl Abdollahpour¹, Elham Saffarieh², Babak Hosseinzadeh Zoroufchi¹

¹Department of Anesthesiology, Kowsar Hospital, Semnan University of Medical Sciences, Semnan, ²Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran

ABSTRACT

Ketamine is considered as a promising drug for many clinical applications even after five decades since its discovery. Ketamine is a dissociative anesthetic agent with a variety of pharmacological effects from anesthetic induction and maintenance to analgesic and sedative depending on the consuming dose. It can be used solely or in combination with other co-adjutant drugs, increasing their efficacy. Many therapeutic properties of ketamine have been attributed to its antagonism mechanism to N-Methyl-D-aspartate receptor. Identifying new properties of ketamine such as neuroprotective, antiinflammatory, and antitumor effects, on one hand, and taking advantage of subanesthetic regimens of ketamine, on the other hand, have resulted in a widespread use of ketamine in various clinical applications. Ketamine is solvable in aqueous and lipid solutions, providing convenient administration via multiple routes, including oral, nasal, rectal, intravenous, intramuscular, subcutaneous, transdermal, sublingual, and intraosseous administration. Application of ketamine has some advantages over other sedative and anesthetic agents. It produces bronchodilation status, allowing for most secure induction of anesthesia in patients with life-threatening asthma and intense acute bronchial constriction. Ketamine has an excellent hemodynamic profile, makes it the agent of choice for patients with unstable hemodynamics, such as shocked or hypotensive patients. Ketamine usage has been associated with a lower risk of respiratory depression and relatively more conserved airway reflexes. Although being an anesthetic agent, ketamine has been increasingly used in subanesthetic doses for acute and chronic pain as well as depression. Using ketamine in pre and postoperative pain management is well established. However, the studies on ketamine performance in pain management demonstrated contradicting results. On the other hand, various side effects along with no confirmatory data on long-term treatment demand great caution when using ketamine for treating complex chronic pains. The present study aimed to provide a general review on the recent applications of ketamine in anesthesia, pain management, and critical care.

Keywords: Anesthetic agent, ketamine, NMDA receptor, pain management, subanesthetic dose

Introduction

Ketamine is a phencyclidine derivative which first synthesized in 1962, and two years later was tested on volunteers.^[1] The anesthetic features of ketamine were recognized in 1965, and its clinical use was approved by the US Food and Drug Administration (FDA) in 1970.^[2] A decade after its approval,

Address for correspondence: Dr. Babak Hosseinzadeh Zoroufchi, Department of Anesthesiology, Kowsar Hospital, Semnan University of Medical Sciences, Semnan, Iran.
E-mail: babakhz.anesthesia@gmail.com

Received: 10-10-2019

Revised: 03-02-2020

Accepted: 11-02-2020

Published: 26-03-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_875_19

researchers found the ability of ketamine in diminishing the stimulatory response to N-methyl-d-aspartic acid (NMDA) in central neurons, which reveals its NMDA receptor antagonism attributes.^[3] Since then, a variety of clinical applications have been discovered for ketamine, including anesthesia, pain management, and psychiatry.^[4] Ketamine can be considered as the most versatile drug used for anesthesia and many other medicine.^[5] It generates widespread pharmaceutical results including somatic analgesia, sedation, bronchodilation, catalepsy, and stimulation of the sympathetic nervous system.^[6]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Abdollahpour A, Saffarieh E, Zoroufchi BH. A review on the recent application of ketamine in management of anesthesia, pain, and health care. J Family Med Prim Care 2020;9:1317-24.

The unique properties of ketamine and its large versatility make it suitable to be used in prehospital medicine and emergency situations, and anesthetists and their assistants benefit its unique properties all over the world.^[7] Ketamine satisfies many requirements of an ideal opioid alternative, including strong analgesia,^[8-10] proper hemodynamic profile, very little inherent respiratory depression, and governable adverse effects.^[11,12] As a dissociative anesthetic, ketamine provides deep analgesia with amnesia.^[13] Compared to other anesthetic agents, ketamine usage results in lower risk of respiratory depression and relatively more conserved airway reflexes.^[14] Currently, using ketamine for anesthesia is limited due to the factors such as incidence of various side effects (e.g. excitation, illusion, and panic attacks), the availability of new alternatives, its disturbing emergence reactions, and the potential to be abused by individuals.^[15] For example, the application of ketamine in perioperative pain management is more common than using as an induction agent of general anesthesia.^[16,17] Using ketamine as an anesthetic has been reported to be beneficial in certain cases such as in the prehospital setting,^[2,7,13] in trauma patients with hemodynamic compromise,^[14,18] in military services for wounded troops, and for children requiring sedation for painful or frightening procedures in the Emergency Department.

Over the past decade, several new clinical applications of ketamine have been explored by researchers. Some of the newer uses of ketamine include: using low-dose analgesic protocols to treat moderate to severe acute and chronic pain,^[2,7,19] using for reactive airways disease, applications as a strong and rapid antidepressant in patients with high depression while therapy,^[20] using as adjuvant therapy in local anesthetic nerve blocks, and applications as procedural sedation in normal and complex procedures among others.^[7] Although being an anesthetic agent, using ketamine at low or subanesthetic doses is a very effective pain reliever for many painful conditions. It can also be applied as a potent adjunct in perioperative duration.^[11] Anesthesiologists and other clinicians from various disciplines have used subanesthetic or low doses of ketamine to treat chronic pain syndromes which are resistant to therapy.^[2] The analgesic^[21] and antidepressant^[22] characteristics of ketamine in subanesthetic doses have been explored by researchers of many countries. Although there is no decisive clinical proof supporting its use, a large number of clinicians, based on their observations of its positive effects during treatment, are using low-dose ketamine as an auxiliary analgesic for acute and chronic pain management.^[23-25]

Despite the great potential of ketamine in pain management, its various treatment regimens lead to concerns regarding adverse effects.^[26] The adverse effects of ketamine vary based on the administered dose, and a range of the side effects has been related to using high doses of ketamine.^[13,27,28] Despite the importance of prescription dose levels of ketamine in the occurrence of the side effects, there is no general consensus on dose or administration regimen.^[5] The aim of the present study is to provide an overview of recent literature on the various applications of ketamine and its benefits and risks for patients

in various clinical settings. It also summarizes the proposal doses of ketamine for many clinical settings.

Methods

In order to find relevant articles with the subject of this study, extensive research was performed on PubMed, Embase, and Google Scholar electronic databases as well as some other clinical websites and journals. The text words used in the search included “ketamine,” “anesthesia,” “ketamine side effects,” “sub-anesthetic dose,” “analgesia,” “acute pain,” “chronic pain,” and “cancer pain.” After finding the relevant articles, the information and data was extracted according to the objectives of the study. The bibliographies of obtained articles were investigated for new relevant publications that were missed in the initial search. Then, articles were reviewed and our criteria for selecting articles were applied. Only those articles were selected that were written in English and published after 2010.

Search Results

Totally, 784 records were obtained through searching databases and other sources, of which 195 duplicate records were removed. Of the remaining 589 records, 403 unrelated articles were excluded. The remaining 186 relevant articles were screened by their year of publication, and 98 records were excluded. After removing some other records, finally 84 related articles were selected in this review. The collected articles were categorized within four main groups including “pharmacology of ketamine,” “ketamine as anesthetic drug,” “ketamine for pain management,” and “ketamine as an antidepressant.” Figure 1 shows the flowchart of the selection steps of related articles for this study.

Structure of ketamine

Ketamine belongs to a group of compounds called arylcyclohexylamines. They consist of several substances with psychoactive impacts, which can be used either as medicals or drugs of abuse. The chemical structure of ketamine is (+/-) 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone with the chemical formula of C₁₃H₁₆ClNO and a molecular weight of 274.4 g/mol.^[15] It is a chiral compound, containing an asymmetric carbon atom and two optical isomers: R-(-)-isomer and S-(+) isomer [Figure 2].^[29] The S-(+)-isomer is pharmacologically more active^[30] and has more potent anesthetic and analgesic properties than the R-(-) isomer.^[13,31]

Pharmacology of ketamine

Pharmacokinetics (PK)

Ketamine has low protein-binding ability and is quickly solved in lipid and aqueous solutions.^[13,30,32] This allows the ketamine to quickly transfer across the blood-brain barrier and increase the concentration there to 4-5 times of the concentration in the plasma.^[7] This results in the rapid commencement of acute analgesic effect.^[2] Ketamine is metabolized in the liver by cytochromes of CYP2B6, CYP3A4, and CYP2C9 to norketamine

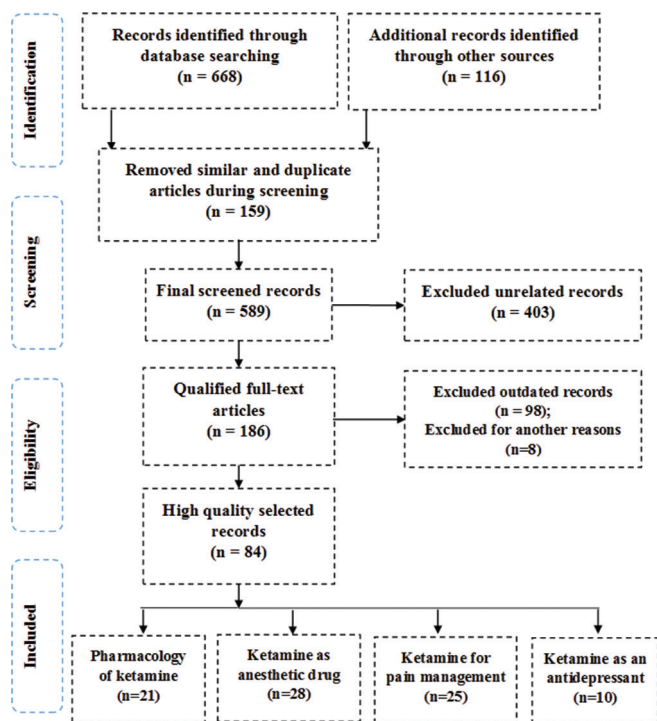


Figure 1: Flowchart illustrating the article selection steps in this study according to PRISMA technique

via ring hydroxylation and N-demethylation pathways,^[33] and further metabolized into 4-, 5-, and 6-hydroxynorketamine by CYP2B6 and CYP2A6. As the main metabolite of ketamine, norketamine has less anesthetic potency than ketamine.^[7,30] It is generated a few minutes after intravenous ketamine and reaches its peak levels within 30 min after administration. The norketamine is excreted through urine and bile after glucuronidation in the liver.^[2,7]

Ketamine and other related arylcyclohexylamines operate as noncompetitive antagonists at N-methyl-D-aspartate (NMDA) receptors.^[2,28,30,34] Many therapeutic properties of ketamine such as anesthetic and analgesic as well as antidepressant properties have been attributed to this mechanism in the brain and dorsal horn neurons.^[35] Ketamine interactions with other receptors^[28,36] and cholinergic, monoamine, purinergic, and adrenoceptor systems have also been reported.^[30,37]

Ketamine provokes the sympathetic nervous system, leading to increased cardiac output, blood pressure, and heart rate.^[11] As a result, using ketamine for patients with ischemic heart disease requires major caution.^[7] On the other hand, ketamine due to its effect of increasing blood pressure is often used in trauma patients with hemodynamic compromise.^[14] Ketamine has negligible effects on central respiratory system, providing airway relaxation by targeting various receptors.^[29,30] However, airway reflexes in children less than 12 months are unpredictable and uncertain. Moreover, a slight respiratory depressive effect during ketamine administration has been reported. Due to producing bronchodilation status, ketamine is preferred for patients with

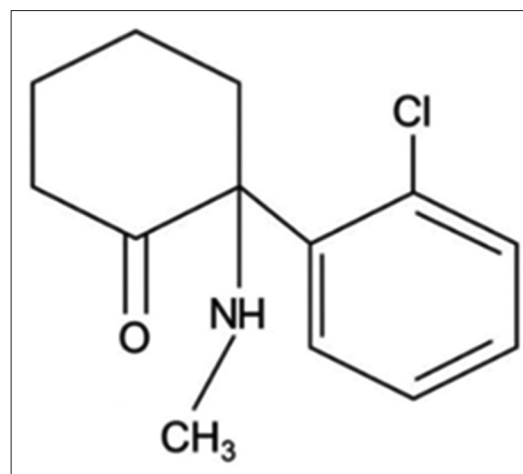


Figure 2: Structure of ketamine. The chiral center of the cyclohexanone ring results in S-(+) and R-(-) isomers

intensive asthma who require mechanical ventilation. Ketamine affects the central nervous system, producing a cataleptic state with strong analgesia and sedation.^[7] It produces a unique dissociative state where the patient eyes are open but detached from the surroundings.^[30]

Route of administration

Due to the solvability of ketamine in aqueous and lipid solutions, it could be conveniently administered via multiple routes. Clinical considerations are vital in selecting the route of administration to prevent suboptimal concentrations of the drug in the plasma.^[38] The traditional routes for ketamine administration are intravenous or intramuscular,^[5,39] which provides the highest percentages of bioavailability at 100% and 93%, respectively.^[40] However, these routes are not always achievable in some circumstances (e.g. in some emergencies or in children and obese patients). There are a number of alternative routes for administering ketamine with acceptable outcomes including oral, nasal, rectal, transdermal, sublingual, subcutaneous, and intraosseous administration.^[2,7,40,41] Intraosseous route has recently been shown to provide a rapid and safe method for ketamine administration.^[42,43] This method is especially useful for geriatrics, remote administration, and preclinical emergency.

Therapeutic applications of ketamine

Ketamine as general anesthesia in the operating room

The application of ketamine in the operating room dated back to nearly 50 years. Ketamine as an intravenous anesthetic agent produces a “dissociative anesthesia” and commonly used in hospital and prehospital environments for emergency situations. In the case of general anesthesia, a dose of 1–2 mg/kg intravenously is typically administered with a duration of action about 5–10 min of administration.^[13] However, the same dose can be applied via rapid sequence induction, producing dissociative anesthesia about 1–2 min after administration.^[7]

Ketamine produces bronchodilation status, allowing for most secure induction of anesthesia in patients with life-threatening

asthma and intense acute bronchial constriction.^[28] The role of ketamine in diminishing bronchospasm in the patients who suffer from respiratory distress has been well documented. It is reported that ketamine doses of 0.1–0.2 mg/kg pursued by an infusion of 0.15–2.5 mg/kg/h can be used in patients with refractory bronchospasm and intensive status of asthma.^[29,30]

Ketamine has many hemodynamic advantages over more traditional intravenous induction agents such as propofol or thiopentone, makes it the agent of choice for patients with unstable hemodynamics, such as shocked or hypotensive patients.^[7,28] The application of ketamine for general anesthesia induction in caesarean operation has also been confirmed. It is reported that using ketamine 1.5 mg/kg in hypotensive and hypovolemic parturient such as uterine rupture or placental abruption prevents the increase of uterine tone and maternal awareness. No respiratory depression of neonates has been reported by this dose.^[1]

The successful application of ketamine as an alternative to etomidate in endotracheal intubation of patients with severe sepsis,^[30] patients with traumatic brain injury,^[44] and those with cardiac tamponade and restrictive pericarditis^[33] has been documented. Moreover, it is reported that using ketamine as an alternative to sevoflurane in patients with congenital heart disease leads to better hemodynamic stability while and after the operation.^[45] Administration of ketamine increases vascular resistance and therefore decreases the blood flow from the right heart to the left heart. As a result, it is considered as a preferable agent for inducing anesthesia in patients with congenital heart disease with right to left shunt, especially in children.^[46] Moreover, ketamine improves oxygenation by increasing pulmonary blood flow.^[26] It is shown that giving reduced doses of ketamine intravenously (0.25–0.5 mg/kg) before full induction of anesthesia results better preoxygenation in agitated patients.^[47]

Ketamine can be used solely or in combination with some hypnotics like benzodiazepines and propofol. It can be combined in low doses (0.5 mg/kg) with intravenous diazepam or midazolam, producing local and regional anesthesia in adults and children.^[33] To maintain anesthesia, intravenous doses of 0.5 mg/kg, or 10 to 30 µg/kg/min continuous infusion can be applied. It is suggested that infusion to be discontinued 20 to 30 min before the completion of surgery.^[7]

Ketamine for pain management

After five decades of its discovery, ketamine is considered as a promising drug for many clinical setting. Although being an anesthetic agent in doses between 1 and 4.5 mg/kg, ketamine has been increasingly used in subanesthetic doses for acute and chronic pain as well as depression.

Use in acute pains

Managing acute pain in patients is of great importance since insufficient management can increase the risk of chronic

pain, reducing the quality of life among these patients.^[9,48] In recent years, opioids have always been a part of acute pain management. However, using opioids increases the hyperalgesia possibility, resulting more analgesic requirements. Administration of low-dose ketamine can prevent sensitivity to opioids.^[28] It is reported that ketamine can reduce the need for opioid consumption and the risk of post-surgical pain.^[49,50] Moreover, it has been applied successfully to patients with weak response to traditional opioids.

The analgesic characteristics of ketamine are primarily established via the NMDA receptors located at the central nervous system,^[51] and to some extent through opioid receptors.^[52] Ketamine is especially preferred for patients with high pain scores, such as surgery patients who experience high levels of postoperative pain.^[26] Clinical studies have examined the role of ketamine in multiple clinical scenarios.

Using ketamine has been reported to provide the same analgesia with opioids in war and accident injuries.^[53] There are a large number of studies on using ketamine to provide analgesia in patients with burns and severe pain.^[28,54] The application of ketamine in burn dressings, dressing changes or excisions, and grafting is very common and is shown to be practical and tolerable for pediatric patients with burns.^[55] Despite all of these, the main advantage of using ketamine for patients with burns is that it maintains the normal function of the respiratory system and provides a good sedoanalgesia.^[56]

There is a large body of studies examined the effects of ketamine on peri and postoperative pain management. Many researchers have reported that perioperative ketamine alleviates pain severity after operation.^[57-60] It has been shown that ketamine reduces the need for opioid consumption and results in less postoperative nausea.^[57,60,61] Recently, a Cochrane review has also shown that prescribing subanesthetic ketamine can reduce postoperative morphine necessity and provide better outcomes for nausea and vomiting.^[62] According to this review study, perioperative ketamine was well-tolerated by patients and no significant side effects were identified. A recent meta-analysis is reported that patients receiving continuous subanesthetic ketamine experienced considerably less pain than those treated by traditional opioid therapies.^[63]

There are a variety of dosing regimens for ketamine administration in various clinical scenarios. Higher doses are prescribed for induction of anesthesia with 1–4.5 mg/kg intravenously, rapid-sequence intubation with 1–2 mg/kg intravenously, and for procedural sedation with 0.5–1 mg/kg intravenously.^[31] Lower doses of ketamine can be administered for pain management. Low-dose ketamine has various definitions based on the route of administration. In the case of intramuscular administration, a bolus dose of less than 2 mg/kg considered as low-dose, while for intravenous or epidural route, it is less than 1 mg/kg. Moreover, an intravenous infusion rate of ≤20 µg/kg/min is considered as low-dose or subanesthetic ketamine.^[64] Ketamine

has dose-dependent side effects. Severe adverse effects have mostly occurred in high doses. However, occurring side effects in low doses, albeit at a lower incidence, is possible; thus, caution is advised when administering any doses of ketamine, especially in patients with cardiovascular disease.

Use in noncancer chronic pains

Central sensitization or neuropathic processes induced by prolonged nociceptive stimulation can result in chronic pains. The inhibition effect of ketamine on NMDA receptors can play a role in chronic pain management.^[28] The reports on the clinical use of ketamine for chronic pain states dated back to late 1990s, where ketamine used to treat chronic neuropathic pain.^[53] Since then, ketamine has been used in various chronic conditions, especially those with a neuropathic origin, and cancer pain.^[65,66] Using ketamine in low doses results in robust analgesia for patients with neuropathic pain. This effect thought to be primarily as a result of blocking the NMDA receptor by ketamine.^[67] The NMDAR, which is existing at spinal and supraspinal sites, is an excitatory glutamatergic receptor, participating in nociceptive signal transmissions.

The direct analgesic characteristic of ketamine along with its efficacy in hyperalgesia and opiate tolerance has accelerated its use in chronic pain conditions. However, clear evidence for ketamine efficiency in the management of chronic pains is scarce. The studies on ketamine performance in chronic pain treatment show contradicting results. On the other hand, various side effects along with no confirmatory data on long-term treatment demand great caution when using ketamine for treating complex chronic pains.

According to some studies, using ketamine have some short-term benefits for pain therapy in patients with chronic peripheral and central neuropathic pain, chronic regional pain syndrome, phantom and ischemic limb pain, chronic migraine, fibromyalgia, and visceral pain.^[33] Moreover, ketamine has been used in patients with chronic pain, who poorly responded to standard analgesics and other treatments.^[68] Intravenous infusions of ketamine have been increasingly used for refractory chronic pain. In these situations, patients may be received infusion treatment over several days. The used doses should be kept as low as possible.^[26] It is reported that intravenous infusion of ketamine in the rate of 300 µg/kg over 3 h resulted in complete sedation of phantom limb pain.^[69] Moreover, using low-dose intranasal ketamine has been reported to be beneficial in patients with neuropathic pain.^[49] Using ketamine in patients with therapy-resistant severe neuropathic pain should be restricted due to the side effects like cardiovascular stimulation, psychedelic symptoms, and hepatotoxicity.^[19]

Use in cancer pains

Ketamine is often administered together with other co-adjuvant drugs in palliative care practice, when the pain cannot be relieved by the use of opioids and other traditional drugs such as

amitriptyline, gabapentinoids, and nonsteroidal antiinflammatory drugs. The use of ketamine together with opioids can improve the efficacy of cancer pain therapy.^[26] Nowadays, ketamine is regarded as an essential adjuvant drug in palliative care in many countries. It could be administered in various regimens through oral, intravenous, intrathecal, subcutaneous, and topical routes of administration. Low-doses are preferable since ketamine has dose-dependent side effects. As a result, ketamine is always administered with low doses and increased to higher doses if required.

The oral doses can begin with 2–25 mg/3-4 times per day and increased up to 40–60 mg/4 times per day to produce sufficient analgesia. The intravenous and subcutaneous doses for analgesia are usually varied between 2.5–5 mg and 2.5–25 mg, respectively.^[15,70] It is reported that oral ketamine may result in fewer side effects and provide stronger analgesia compared to subcutaneous ketamine.^[71] The same study has argued that an intrathecal dose of 22.5 mg per day in combination to morphine resulted in pain relief of metastasis and urethral carcinoma patients who suffered from leg pain.

It is suggested that ketamine can produce antitumor effects by blocking the NMDA receptor.^[72] Moreover, using ketamine as an adjunct to morphine has been reported to enhance the morphine efficacy in cancer pain therapy.^[73] Ketamine is effective for the cases that cancer pain is refractory to opioids and adjuvant drugs. Conducting trials in cancer patients is undoubtedly challenging. This limited the sufficient evidence on the efficacy of ketamine in this group of patients. Although there are a variety of causes for pain among cancer patients, it could be articulated that ketamine is a drug of choice for the cases where opioid tolerance, inflammatory pain, neuropathic pain component, and depression or a combination of these factors are problematic.^[26] It is favorable to evaluate the benefits against its risks and costs before using ketamine for treating cancer patients. Moreover, it is recommended that ketamine administration to be restricted until there are sufficient evidence on its safety.

Ketamine as an antidepressant

The antidepressant effect of ketamine has been recognized since its application in a clinical setting.^[67] Ketamine has both antidepressant and analgesic effects. According to a recent study, the underlying mechanism for the antidepressant effect of ketamine may be attributed to hydroxynorketamine, which is a metabolite of ketamine.^[74] The results of one meta-analysis showed that ketamine produced a high response rate and rapid effect in depressed patients.^[75] Ketamine quickly effects, reducing depression within 2 h, while other conventional antidepressants require weeks to effect.^[76,77] Several case studies also found similar results, stating that the intravenous administration of subanesthetic ketamine resulted in antidepressant effects about a few hours, and remained for 4 to 7 days after administration.^[78,79] Ketamine has a great potential to be used for treatment-resistant depression; however, additional studies are needed on its

mechanism of action, of action, long-term and the adverse effects.

Ketamine use limitations

Using ketamine has been associated with a high occurrence of nightmares, hallucinations, and other transient psychotic effects. The use of ketamine is not indicated in conditions such as hypertension, stroke, severe cardiac disease, preeclampsia or eclampsia, raised intracranial pressure, and acute porphyria.^[80] Ketamine is also not recommended in newborns and patients with schizophrenia and raised intraocular pressure.^[7,30] Oral administration of ketamine with high doses may lead to hepatic failures, ulcerative cystitis, and secondary renal damage. Moreover, epidural and spinal administration can increase the risk of toxicity and is not recommended.^[30] Ketamine is a drug of abuse which can result in long-term memory disorders if frequently abused.^[81]

Conclusion

Ketamine is a versatile drug, which through its complex mechanisms of action have been successfully used in a variety of clinical applications all over the world. Nowadays, the use of ketamine is not limited to anesthesia, but it is increasingly used for pain management and palliative care. It can be used solely or as an adjunct to other drugs. When used in low doses, ketamine produces a potent analgesic effect, making it a suitable alternative drug for the cases that pains are refractory to opioid and other adjuvant drugs.

Most of the main therapeutic properties of ketamine have been attributed to its antagonism mechanism to NMDA receptor; however, its interaction with other receptors has been explained. Ketamine is soluble in water and lipid solutions, allows it to be conveniently administered via multiple routes, including oral, nasal, rectal, intravenous, intramuscular, subcutaneous, transdermal, sublingual, and intraosseous administration. However, ketamine administers in a variety of regimens and there are serious concerns regarding adverse effects. High doses of ketamine have been associated with a range of adverse effects and are not recommended.

Using ketamine as an anesthetic has been reported to be beneficial in prehospital setting, in trauma patients with hemodynamic compromise, in military services for wounded troops, and for children requiring sedation for painful or frightening procedures in the Emergency Department.

The applications of ketamine in the perioperative setting have been associated with reduced pain scores, opioid requirements, and postoperative nausea and vomiting, without any considerable side effects. Moreover, good results have been established on using ketamine for surgery patients with high levels of postoperative pain.

The evidence regarding ketamine efficacy for chronic pain management is limited, and the studies demonstrated

contradicting results. Generally, it could be concluded that although using ketamine may provide short-term benefits in chronic pain patients, there is not enough proof on its long-term benefits. However, the use of ketamine together with opioids can improve the efficacy of cancer pain therapy. Ketamine is a drug of choice for the cases where opioid tolerance, inflammatory pain, neuropathic pain component, and depression or a combination of these factors are problematic.

Acknowledgment

We would like to thank the Clinical Research Development Unit of Amir al-Momenin Educational and Research and Therapeutic Center of Semnan University of Medical Science for providing facilities for this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tang Y, Liu R, Zhao P. Ketamine: An update for obstetric anesthesia. *Transl Perioper Pain Med* 2017;4:1-12.
2. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: Risks and benefits. *Br J Clin Pharmacol* 2013;72:357-67.
3. Sheehy KA, Lippold C, Rice AL, Nobrega R, Finkel JC, Quezado ZM. Subanesthetic ketamine for pain management in hospitalized children, adolescents, and young adults: A single-center cohort study. *J Pain Res* 2017;10:787-95.
4. Li L, Vlisides PE. Ketamine: 50 years of modulating the mind. *Front Hum Neurosci* 2016;10:612.
5. Jonkman K, Dahan A, van de Donk T, *et al.* 2017. Ketamine for pain. *F1000Res*. 6. pii: F1000 Faculty Rev-1711. doi: 10.12688/f1000research.11372.1. eCollection 2017.
6. White PF, Elig MR. Intravenous anaesthetics. In: Barash PG, editor. *Clinical Anaesthesia*. 6th ed. China: Lippincott Williams and Wilkins; 2013. p. 478-500.
7. Gales A, Maxwell S. Ketamine: Recent evidence and current uses. *WFSA, Tutorial 381*. 2018. Available from: www.wfsahq.org/resources/anaesthesia-tutorial-of-the-week.
8. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, Hurley RW, *et al.* Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018;43:521-46.
9. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, *et al.* Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018;43:456-66.
10. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011;58:911-23.
11. Cohen SP, Bhatia A, Buvanendran A, *et al.* Consensus

- guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018. doi: 10.1097/AAP.0000000000000808
12. Schwenk ES, Goldberg SF, Patel RD, Zhou J, Adams DR, Baratta JL, *et al.* Adverse drug effects and preoperative medication factors related to perioperative low-dose ketamine infusions. *Reg Anesth Pain Med* 2016;41:482-7.
 13. Sean S. H, Dave B, Grace J, *et al.* A review of ketamine abuse and diversion. *Depression and anxiety* 2016;33:718-27.
 14. Jensen AG, Callesen T, Hagemo JS, Hreinsson K, Lund V, Nordmark J; Clinical Practice Committee of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Scandinavian clinical practice guidelines on general anaesthesia for emergency situations. *Acta Anaesthesiol Scand* 2010;54:922-50.
 15. Advisory Council on the Misuse of Drugs. Ketamine: A review of use and harm, 2013. Report. Available from: http://www.gov.uk/government/ACMD_ketamine_report_dec13.pdf. [Last accessed on 2014 Jul 08].
 16. Assouline B, Tramer M. R, Kreienbuhl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: Systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *Pain* 2016;157:2854-64.
 17. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: A systematic review and meta-analysis of randomized trials. *Can J Anaesthesia* 2016;63:311-25.
 18. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: A systematic review. *Acta Anaesthesiol Scand* 2011;55:638-43.
 19. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: Risks and benefits. *Br J Clin Pharmacol* 2014;77:357-67.
 20. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, *et al.* Intravenous esketamine in adult treatment-resistant depression: A double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry* 2016;80:424-31.
 21. Sheehy KA, Muller EA, Lippold C, Nouraie M, Finkel JC, Quezado ZM. Subanesthetic ketamine infusions for the treatment of children and adolescents with chronic pain: A longitudinal study. *BMC Pediatr* 2015;15:198.
 22. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, *et al.* A randomized add-on trial of an N-Methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010;67:793-802.
 23. Butler FK, Kotwal RS, Buckenmaier CC 3rd, Edgar EP, O'Connor KC, Montgomery HR, *et al.* A triple-option analgesia plan for tactical combat casualty care: TCCC guidelines change 13-04. *J Spec Oper Med* 2014;14:13-25.
 24. Martinez V, Derivaux B, Beloeil H; Regional Anaesthesia and the Pain Committee of the French Society of Anaesthesiology and Intensive Care. Ketamine for pain management in France, an observational survey. *Anaesth Crit Care Pain Med* 2015;34:357-61.
 25. Lo TC, Yeung ST, Lee S, Skavinski K, Liao S. Reduction of central neuropathic pain with ketamine infusion in a patient with Ehlers-Danlos syndrome: A case report. *J Pain Res* 2016;9:683-7.
 26. Bell RF, Kalso EA. Ketamine for pain management. *Pain Rep* 2018;3:e674.
 27. Shahzad K, Svec A. Analgesic ketamine use leading to cystectomy: A case report. *Br J Med Surg Urol* 2012;5:188-91.
 28. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. *Acta Pharmacol Sin* 2016;37:865-72.
 29. Goel S, Agrawal A. Ketamine in status asthmaticus: A review. *Indian J Crit Care* 2013;1793:154-61.
 30. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain and critical care. *Anesth Essays Res* 2014;8:283-90.
 31. World Health Organization (WHO). Ketamine, Update Review Report. Expert Committee on Drug Dependence Thirty-sixth Meeting Geneva; 2014. p. 16-20.
 32. Saad A. Ketamine for post-operative analgesia in paediatrics. *Health Sci J* 2017;11:538.
 33. Reves JG, Glass PS, Lubarsky DA, McEvoy MD. Intravenous nonopioid anesthetics. In: Miller RD, Fleisher LA, Johns RA, *et al.*, editors. *Miller's anesthesia*. 6th ed. Philadelphia: Elsevier; 2005. p. 317-78.
 34. Roth B, Gibbons S, Arunotayanun W, Huang XP, Setola V, Treble R, *et al.* The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. *PLoS One* 2013;8:e59334.
 35. Quibell R, Prummer EC, Mihalyo M, Twycross R, Wilcock A. Ketamine. *J Pain Symptom Manage* 2011;41:640-9.
 36. Stahl SM. Mechanism of action of ketamine. *CNS Spectrums* 2013;18:171-4.
 37. Persson J. Wherefore ketamine? *Curr Opin Anaesthesiol* 2010;23:455-60.
 38. Andrade C. Ketamine for Depression, 4: In What Dose, at What Rate, by What Route, for How Long, and at What Frequency? *J Clin Psychiatry* 2017;78:e852-7.
 39. Jones GM, Wiss AL, Goyal N, Chang JJ. Successful use of ketamine for central neurogenic hyperventilation: A case report. *Neurohospitalist* 2017;7:192-5.
 40. Hana Z, Abdulla S, Alam A, Ma D. Ketamine: Old drug but new use for neuropathic pain. *Transl Perioper Pain Med* 2018;5:1-13.
 41. Cevik E, Bilgic S, Kilic E, Cinar O, Hasman H, Acar AY, *et al.* Comparison of ketamine-low-dose midazolam with midazolam-fentanyl for orthopedic emergencies: A double-blind randomized trial. *Am J Emerg Med* 2013;31:108-13.
 42. Jonkman K, Duma A, Velzen M, Dahan A. Ketamine inhalation. *Br J Anaesth* 2017;118:268-9.
 43. Jonkman K, Duma A, Olofsen E, Henthorn T, van Velzen M, Mooren R, *et al.* Pharmacokinetics and bioavailability of inhaled esketamine in healthy volunteers. *Anesthesiology* 2017;127:675-83.
 44. Sih K, Campbell SG, Tallon JM, Magee K, Zed PJ. Ketamine in adult emergency medicine: Controversies and recent advances. *Ann Pharmacother* 2011;45:1525-34.
 45. Goyal R, Singh S, Bangi A, Singh SK. Case series: Dexmedetomidine and ketamine for anesthesia in patients with uncorrected congenital cyanotic heart disease presenting for non-cardiac surgery. *J Anaesthesiol Clin Pharmacol* 2013;29:543-6.
 46. Tavakolian AR, Allahyary E. The comparison of the effect of three anesthetic induction regimens on the arterial oxygen

- saturation in children with tetralogy of fallot undergoing cardiac surgery. *Iran Red Crescent Med J* 2011;13:702-6.
47. Mosier JM, Joshi R, Hypes C, Pacheco G, Valenzuela T, Sakles JC. The physiologically difficult airway. *West J Emerg Med* 2015;16:1109-17.
 48. Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketamine-a narrative review of its uses in medicine. *Am J Ther* 2016;23:e1414-26.
 49. Hüge V, Lauchart M, Magerl W, Schelling G, Beyer A, Thieme D, *et al.* Effects of lowdose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain* 2010;14:387-94.
 50. Reid C, Hatton R, Middleton P. Case report: Prehospital use of intranasal ketamine for paediatric burn injury. *Emerg Med J* 2011;28:328-9.
 51. Cohen SP, Liao W, Gupta A, Plunkett A. Ketamine in pain management. *Adv Psychosom Med* 2011;30:139-61.
 52. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: A randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth* 2013;110:1010-6.
 53. Persson J. Ketamine in pain management. *CNS Neurosci Ther* 2013;19:396-402.
 54. McGuinness SK, Wasiak J, Cleland H, Symons J, Hogan L, Hucker T, *et al.* A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* 2011;12:1551-8.
 55. O'Hara D, Ganeshalingam K, Gerrish H, Richardson P. A 2 year experience of nurse led conscious sedation in paediatric burns. *Burns* 2014;40:48-53.
 56. Gündüz M, Sakalli S, Güneş Y, Kesiktaş E, Ozcengiz D, Işık G. Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients. *J Anaesthesiol Clin Pharmacol* 2011;27:220-4.
 57. Assouline B, Tramer MR, Kreienbuhl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: Systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *Pain* 2016;157:2854-64.
 58. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014;58:1199-213.
 59. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative ketamine for analgesia in spine surgery: A meta-analysis of randomized controlled trials. *Spine (Phila Pa 1976)* 2018;43:E299-307.
 60. Ye F, Wu Y, Zhou C. Effect of intravenous ketamine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: A metaanalysis. *Medicine (Baltimore)* 2017;96:e9147.
 61. Zhu J, Xie H, Zhang L, Chang L, Chen P. Efficiency and safety of ketamine for pain relief after laparoscopic cholecystectomy: A meta-analysis from randomized controlled trials. *Int J Surg* 2018;49:1-9.
 62. Brinck ECV, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, *et al.* Perioperative intravenous ketamine for acute postoperative pain. *Cochrane Database Syst Rev* 2018;12:CD012033. doi: 10.1002/14651858.CD012033.pub4.
 63. Kator S, Correll DJ, Ou JY, Levinson R, Noronha GN, Adams CD. Assessment of low-dose i.v. ketamine infusions for adjunctive analgesia. *Am J Health Syst Pharm* 2016;73:S22-9.
 64. Lee SK. The use of ketamine for perioperative pain management. *Korean J Anesthesiol* 2012;63:1-2.
 65. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: A systematic review and synthesis of the literature. *Pain Med* 2013;14:1505-17.
 66. Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. *Eur J Pain* 2014;19:984-93.
 67. Domino EF. Taming the ketamine tiger. *Anesthesiology* 2010;113:876-86.
 68. Schug SA, Goddard C. Recent advances in the pharmacological management of acute and chronic pain. *Ann Palliat Med* 2014;3:263-75.
 69. Shanthanna H, Huilgol M, Manivackam VK. Early and effective use of ketamine for treatment of phantom limb pain. *Indian J Anaesth* 2010;54:157-9.
 70. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: A double-blind, randomized, placebo-controlled trial. *J Anesth* 2014;28:12-8.
 71. Chaudhary WA, Kennet J. Ketamine as an adjuvant to opioids for cancer pain management. *Anaesth Pain Intensive Care* 2012;16:174-8.
 72. Hirota K, Lambert DG. Ketamine: New uses for an old drug? *Br J Anaesth* 2011;107:123-6.
 73. Bell RF, Eccleston C, Kalso E. A. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2012;11:CD003351.
 74. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, *et al.* NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 2016;533:481-6.
 75. Lee EE, Della SMP, Liu A, Himelhoch S. Ketamine as a novel treatment formajor depressive disorder and bipolar depression: A systematic review and quantitative meta-analysis. *Gen Hosp Psychiatry* 2015;37:178-84.
 76. Reardon S. Rave drug tested against depression: Companies and clinicians turn to ketamine to treat mental-health disorder as pipeline of new drugs dries up. *Nature* 2015;517:130-1.
 77. Salvatore G, Singh JB. Ketamine as a fast acting antidepressant: Current knowledge and open questions. *CNS Neurosci Ther* 2013;19:428-36.
 78. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, *et al.* Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: Results from a 4-week, double-blind, placebocontrolled study. *Neuropsychopharmacology* 2012;37:1526-33.
 79. Mathew SJ, Murrrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol* 2010;13:71-82.
 80. Sosipatros B, Sohag NS. Clinical Efficacy of Ketamine for Treatment-resistant Depression. *Cureus* 2019;11:e5189. Published online 2019 Jul 22.
 81. Hosseini JSA, Hosseini VSM, Hatamian S. Comparison between effect of lidocaine, morphine and ketamine spray on post-tonsillectomy pain in children. *Anesth Pain Med* 2012;2:17-21.