Chapter 8
Sedation and Analgesia for the Critically Ill Child: Ketamine

Judith J. M. Wong, Angela S. H. Yeo, Siti N. H. Buang, and Yoke Hwee Chan

Introduction

Ketamine has been used as an anesthetic for decades, but its use has diversified and gained in popularity for indications in the pediatric intensive care unit (PICU) such as intensive care sedation, procedural sedation, acute and chronic pain, prevention and management of opioid withdrawal, bronchoconstriction, and seizure disorders [1]. The popularity of ketamine is due to its ability to provide analgesia, but with less respiratory depression, making it ideal for non-intubated patients undergoing painful procedures or as an analgesic to reduce postoperative pain. It is considered a dissociative agent and is closely related to phencyclidine (PCP).

Pharmacokinetics and Pharmacodynamics

Ketamine is a racemic mixture consisting of two optical enantiomers, R(−) and S(+). It is frequently administered via the intravenous (IV) or intramuscular (IM) route, which has the highest bioavailability (93%) as compared to other routes of administration such as oral (16–29%), sublingual (29%), intranasal (45–50%), rectal (25%), and epidural [2–5]. The highly lipid-soluble ketamine has a

J. J. M. Wong · S. N. H. Buang · Y. H. Chan (✉)
Department of Paediatric Subspecialties, Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore
e-mail: Judith.Wong.JM@singhealth.com.sg; Siti.Nur.Hanim@singhealth.com.sg; Chan.Yoke.Hwee@singhealth.com.sg

A. S. H. Yeo
Department of Pediatric Anaesthesia, KK Women's and Children's Hospital, Singapore, Singapore
e-mail: Angela.Yeo.S.H@singhealth.com.sg

P. P. Kamat, J. W. Berkenbosch (eds.), *Sedation and Analgesia for the Pediatric Intensivist*, https://doi.org/10.1007/978-3-030-52555-2_8

two-compartment pharmacokinetic profile with an alpha half-life of approximately 10–16 mins and a beta half-life of 2.5–4.9 hours [2, 5–7]. Ketamine is rapidly distributed into highly perfused tissues, including the brain, and has plasma protein binding of 10–50% [7, 8]. Metabolism of ketamine occurs via demethylation by the cytochrome P450 liver enzymes – CYP2B6, CYP2C9, and CYP3A4 to predominantly biologically active norketamine and further metabolized to biologically inactive dehydronorketamine (DHNK) and hydroxynorketamine (HNK) [1, 9]. Elimination of ketamine is primarily performed by the kidneys, with low levels excreted as ketamine (2%), norketamine (2%), and DHNK (16%). Clearance is highly dependent on the liver blood flow and occurs in 2–5 hours in adults and half that time in children [1, 6, 7].

Mechanism of Action

There is a myriad of pathways by which ketamine exerts its anesthetic and analgesic effects. N-Methyl-d-aspartate receptor (NMDAR) antagonism is the predominant mechanism of action. Ketamine acts in a dose-dependent manner on the NMDAR channel, a tetrameric protein complex that forms a ligand-gated calcium ion channel. It blocks the closed NMDA channel at lower concentrations, giving rise to its analgesic properties. At higher concentrations, both open and closed channels are blocked, resulting in its dissociative, anesthetic, and amnesic properties becoming more evident [10]. Its two different mechanisms at the same receptor are the blocking of the open channels, resulting in reduction of mean open time, and the blocking of the closed channels through binding to the allosteric PCP site located within the pore, resulting in a decrease in the frequency of channel opening [11]. These receptors are highly permeable to calcium ions, which trigger the activation of intracellular pathways in neurons and glial cells. At resting state, NMDAR channels are tonically blocked by magnesium (Mg2+) and membrane depolarization is required to displace Mg2+. NMDAR binding is dependent on the differential capacity for Mg2+ binding and interactions between the drug and Mg2+ within the channel.

While NMDAR antagonism is the main mechanism for ketamine's analgesic property, other putative mechanisms through cholinergic, opioid, and serotoninergic receptors may also play a role and could explain its effect in nonneuropathic pain [12]. Binding to dopaminergic and serotoninergic receptors has also been described. Ketamine at clinically relevant doses acts as a noncompetitive antagonist of the nicotinic acetylcholine receptors [1]. Administration of ketamine also induces an increase in extracellular serotonin (5-HT) levels in the prefrontal cortex and dorsal raphe nucleus of mice and is thought to mediate its analgesic effect. Possibly contributing also to its analgesic effects is ketamine's ability to bind opioid receptors. It is likely that ketamine is an agonist to the κ opioid receptors and antagonist to the μ receptors as naloxone does not reverse its analgesic effect [13]. Interactions between ketamine and the opioid system may be more relevant in prolonged opioid use, in which ketamine reduces opioid tolerance. Ketamine's actions on δ receptors could

be involved in the neuroplasticity-related effects of the drug [14, 15]. Lastly, ketamine also interacts with the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [1]. These voltage-gated cation channels are activated by membrane hyperpolarization facilitated by cyclic nucleotides, including cyclic adenosine monophosphate (cAMP), and binding mediates ketamine's anesthetic effects.

Animal studies indicate that at supratherapeutic doses, ketamine may potentiate inhibitory GABAergic postsynaptic signals in neurons [16]. This was not shown to occur at clinically relevant doses. Instead, clinically relevant concentrations of ketamine increased the activity of high-affinity extrasynaptic $GABA_A$ receptors in the hippocampus and cortex, an effect that likely contributes to ketamine's neurodepressive properties [16].

Dosing

Ketamine has a wide therapeutic index and the optimal dosage depends on the intended therapeutic effect. Ketamine has been reported to effect analgesia at plasma concentrations of 100–200 ng/ml, arousal from anesthesia at 750 ng/ml, arousal from tactile or loud verbal stimulus at 1000 ng/ml, and arousal from painful stimulus at 1500 ng/ml [2, 17]. In a population pharmacokinetics study of IM and IV ketamine in children, the recommended procedural sedation dose for IV ketamine was 2 mg/kg, and IM ketamine was 8 mg/kg (for children between 6 and 11 kg) and 6 mg/kg (for children 17–56 kg) to provide adequate sedation for up to 20 minutes [5]. The US Food and Drug Administration (FDA) prescribing information lists the anesthetic induction dose of ketamine as 1–4.5 mg/kg IV with an average dose of 2 mg/kg required for surgical anesthetic effect of 5 to 10 minutes, or 4–11 mg/kg IM with an anesthetic effect that lasts 12 to 25 minutes [18].

Subanesthetic doses of 0.15–1.0 mg/kg IV (bolus) or 0.1–2.0 mg/kg/hour IV (continuous infusion) have also been used in the pediatric population as an adjunct for postoperative pain or for sedation/analgesia in the PICU. Unfortunately, subanesthetic dosing of ketamine is not consistently defined in the literature, with one review setting the cutoff at <1.2 mg/kg/h [19]. Recent consensus guidelines on the use of IV ketamine for pain management have recommended (Grade C) that in general, ketamine boluses should not exceed 0.35 mg/kg/dose and infusions for acute pain should not exceed 1 mg/kg/h without intensive monitoring and that provider discretion and training in airway management is advisable [20].

Uses of Ketamine in the Pediatric Intensive Care Unit

Ketamine's primary benefits in PICU sedation lie in its ability to induce a dissociative state while sparing respiratory depression, its analgesic properties through its multiple actions outside of the opioid receptor, and its utility in reducing opioid

tolerance, central sensitization, and opioid hyperalgesia [21]. One of the driving forces behind the resurgence in ketamine use is the push to reduce chronic opioid exposure and risk of addiction, after acute exposure [22].

In the PICU setting, the IV route is most commonly employed, but the oral, transdermal, intranasal, subcutaneous, epidural, per rectal, and IM routes may still be considered [23]. For the purposes of this chapter, these will not be expounded upon, and the authors respectfully direct the reader to other articles [23, 24]. In the hospital, it is recognized that pain originates from several sources – medical pathology, procedural interventions, and surgery, particularly in the postoperative period. In the acute postoperative setting, the patients who benefit from ketamine infusions are those expected to have severe postoperative pain, those who are non-opioid naïve and thus possibly tolerant to opioid effects, and those at risk of opioid-induced ventilatory impairment (OIVI) [20].

Ketamine for Sedation

The safety profile of ketamine in hemodynamics and respiratory function has made it an attractive option for sedation in the critically ill patients. Ketamine has been used widely as a single or combination agent for procedural sedation in children in a variety of settings. This will be discussed in further detail in the chapter on Procedural Sedation: Ketamine.

Evidence with ketamine, as a continuous infusion in the PICU for sedation, has been limited to small series or case reports [25–27]. It is often used an adjunct to benzodiazepines and opioids or used to treat opioid withdrawal. Due to its bronchodilator effects, ketamine has been used at higher infusion rates for the treatment, or as a sedative agent, in children with bronchospasm and status asthmaticus in the PICU. Its use in brain injury has been debated due to its potential to cause cerebral vasodilatation and increase intracranial pressure [28, 29]. Subsequent studies in adults and children did not demonstrate ICP increase with ketamine in both traumatic and nontraumatic brain injuries and in some cases a reduction in ICP [30–32]. While the evidence is not strong for children given the small sample size of the pediatric population in these studies, its use for sedation and analgesia in children with traumatic brain injury is no longer an absolute contraindication.

Ketamine for Acute Pain

As an analgesic, ketamine is effective either as a stand-alone, particularly in procedural pain, or as an adjuvant. In the postoperative period, it is most commonly employed at subanesthetic dose as an adjunct to opioids in view of the expected acute nociceptive stimulus, for two important reasons – to reduce both postoperative

pain intensity and opioid requirements. Benefits of combination therapy of ketamine with postoperative opioids in reducing pain scores and the requirement of opioids are more established in adults [20]. In a meta-analysis of adult studies on ketamine use in spine surgeries, bolus doses ranging from 0.15 to 10 mg/kg and infusion rates ranging from 0.06 to 5.0 mg/kg/h resulted in reduced postoperative pain scores and less morphine consumption 24 h postoperatively [33]. A longitudinal cohort of children and young adults with heterogeneous medical conditions showed that ketamine doses ranging from 0.05 to 1 mg/kg/h could achieve a significant reduction in pain scores with minimal adverse effects. However, the effect was more prominent in the group with cancer-related pain and inflammatory conditions. The opioid-sparing effect in postoperative pain, however, was minimal. In a meta-analysis of 47 adult and pediatric randomized controlled trials, ketamine was shown to have an opioid-sparing effect, both in the reduction of opioid administered and prolongation of time to first analgesic [34]. The greatest benefit in opioid reduction was seen in upper abdominal and thoracic surgeries, and to lesser extent with intra- and lower abdominal and limb and spine surgeries, but not for tonsillectomies and dental and head and neck surgeries [12, 13]. However, the pediatric subgroup analysis which was highly represented by tonsillectomy studies revealed a lack of benefit in children. Similarly, a recent meta-analysis of 11 pediatric studies did not demonstrate global opioid-sparing effect at 48 hours, nor did it reduce postoperative pain intensity [35]. However, this meta-analysis was limited by the lack of power to be conclusive about the primary outcome. Thus, it seems that despite the robust data in the adult population, there remain questions about ketamine's utility in the pediatric population for postoperative analgesia.

Apart from its use as a postoperative analgesic, ketamine as an adjunct also improves analgesia in circumstances not ascribable to surgery, such as cancer and inflammatory pain associated with pancreatitis and Crohn's disease, whereas patients with functional gastrointestinal disorders had the lowest benefit [36]. Adults and children with acute on chronic exacerbations of pain such as sickle cell disease, renal colic, or central pain from Ehler-Danlos syndrome have also been reported to have improved analgesia, but there have been no randomized controlled trials thus far [37–39].

Opioid-induced ventilatory impairment (OIVI) risk is increased in patients with obstructive sleep apnea and can be exacerbated by exposure to general anesthetics for surgery [40]. While subanesthetic ketamine has been shown to reduce opioid consumption postoperatively, there have been few studies that specifically address its utility in reducing the risk of opioid-induced respiratory depression (OIRD) or OIVI [34]. Healthy volunteers subjected to remifentanil-induced respiratory depression, in a randomized double-blind placebo-controlled crossover trial of esketamine vs placebo, demonstrated that esketamine effectively countered the OIRD [41]. In their statement on the principles for identifying and preventing OIVI, the Faculty of Pain Medicine of Australia and New Zealand had endorsed low-dose ketamine as a helpful adjuvant for opioid-sparing measure in patients who are sedated but still in pain [42].

Ketamine for Chronic Pain

The nonopioid-naïve population includes the children with painful chronic medical conditions, oncological or palliative cases, or children who have been on prolonged opioid infusions for sedation and analgesia. Current data on the short-term infusions suggest that potent analgesia is produced only during administration of ketamine, while prolonged infusions of 4–14 days may result in long-term effects of up to 3 months in patients with chronic pain with neuropathic components [20, 41]. In adults with complex regional pain syndrome, there is moderate evidence to support the use of ketamine infusions [43]. The evidence for ketamine use in children with chronic pain is scant. The use of intraoperative ketamine on a group opioid-dependent children undergoing orthopedic surgeries demonstrated a reduction in 48-hour opioid usage and lower pain intensity scores, suggesting at least a mild benefit for this population [44].

Ketamine has also been touted as an opioid tolerance-protective drug [45]. In experimental models, co-administration of ketamine and opioid attenuated the development of opioid tolerance to varying degrees [46]. Neunhoeffer described a retrospective study wherein 32 mechanically ventilated children with tolerance from prolonged IV infusion of opioids received ketamine infusions as an opioid substitute on a drug rotation protocol (median ketamine dose of 4 mg/kg/h and median duration of 3 days) [47]. This resulted in a significant reduction in subsequent fentanyl requirement, suggesting that ketamine has a role in reversing or reducing tolerance development [47].

The intensive care physician should be also aware of two oft-forgotten mechanisms which may contribute to abnormal pain hypersensitivity in the critically ill pediatric patient – central sensitization and opioid-induced hyperalgesia (OIH). In poorly controlled pain states, a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in nociceptive pathways results in central sensitization through what is termed the "wind-up" phenomenon. In severe cases, chronification of the pain occurs with secondary changes in brain activity, and pain becomes pathologic, manifesting as pain hypersensitivity, either through allodynia or hyperalgesia [48]. This often results in pain which is refractory to the usual analgesia cocktails and thus rapid escalation of opioid use and, hence, tolerance. Prevention of central sensitization with low-dose ketamine infusions has been seen in basic science studies but has not always held true in clinical trials [48, 49]. In a systematic review of 17 studies, the overall risk of developing persistent postsurgical pain, a result of central sensitization, was not significantly reduced in the ketamine vs placebo group, but sensitivity analysis of exclusively IV ketamine studies did demonstrate statistically significant reductions in the risk of developing persistent postsurgical pain at 3 months and 6 months [50].

Contributing to the problem of pain hypersensitivity, a growing body of evidence suggests that opioids can elicit an exaggerated nociceptive response to noxious stimulation after continuous delivery, a common PICU postoperative sedation practice [51–53]. This is attributed to activation of μ opioid receptor resulting in a sustained increase in glutamate synaptic effectiveness at the level of the NMDAR with a resultant paradoxical hypersensitivity, OIH [54]. This translates to a need for an alternative or adjunctive analgesia since the use of opioids contributes to, rather than detracts, the

pain. The evidence suggests that development of OIH can be attenuated by ketamine in subanalgesic doses, thus potentially reducing opioid consumption [51, 55].

Ketamine Side Effects

Short-term ketamine use causes dose-dependent, transient, and self-resolving side effects including a decrease in mental sharpness, concentration, recall, and recognition, as well as explicit (episodic and semantic) and implicit (procedural) forms of memory [1]. Psycho-cognitive effects such as hallucinations, dreams/nightmares, and visual disturbances are dose-related and minimal at infusion rates of less than 2.5 mcg/kg/min [19]. It can lead to vestibular perturbations, including dizziness and nausea/vomiting. Sympathetic effects include tachycardia, hypertension, and palpitations. Respiratory depression is usually mild at clinically relevant doses. Other side effects include ocular effects (e.g., nystagmus, diplopia, dilation) and musculoskeletal effects (e.g., myoclonus, twitching, spasms, ataxia, fasciculation) [1]. Of note in PICU care, ketamine causes an increase in secretions which presents another problem for the caregivers to manage.

More crucial, however, is the neurodevelopmental effects of ketamine. Indeed, multiple other sedative drug options produce similar neurotoxic effects in the pediatric brain, and the pediatric intensivist needs to carefully weigh the risks and benefits of each sedative [56]. In animal and basic science studies, long-term ketamine use has been demonstrated to have potential neurotoxic effects including reversible neuronal vacuolation, necrosis, and loss of integrity within the posterior cingulate, retrosplenial, prefrontal, and frontal-thalamic-temporal cortices [57–60]. Even low doses of ketamine were shown to impair dendritic arborization [61].

It is, however, argued that unattenuated pain may also induce cell death in cortical, thalamic, hypothalamic, and hippocampal areas of the neonatal rat brain and the amygdala, and this may be followed by subsequent neurocognitive impairment, such as an impaired cognitive, emotional, and psychosocial functioning and impaired ability to form memories [62, 63]. Conversely, concurrent surgery and procedural pain has been shown to attenuate ketamine-induced neuroapoptosis, and ketamine has also been shown to inhibit pain-induced neurotoxicity in neonatal rat brains [64]. Thus, it seems that pain, in the absence of analgesia, is detrimental to neurodevelopment, while analgesia in the presence of pain may be protective.

Conclusion

Ketamine remains a useful drug in the anesthetic/sedative/analgesic armamentarium. Its ability to provide sedation and analgesia, while preserving hemodynamics and without blunting the respiratory reflexes and drive, makes it highly suitable for facilitating painful procedures in non-intubated patients or in postoperative patients. Its optimal dose, duration, and role in a multimodal regimen for acute pain will

require further elucidation. Given the neurotoxic concerns of repetitive ketamine exposure to the developing brain, it is not recommended for routine use in the absence of nociceptive stimulus which in itself is neurotoxic.

References

1. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70(3):621–60. PubMed PMID: 29945898. Pubmed Central PMCID: PMC6020109. Epub 2018/06/28. eng.
2. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci. 1982;71(5):539–42. PubMed PMID: 7097501. Epub 1982/05/01. eng.
3. Rolan P, Lim S, Sunderland V, Liu Y, Molnar V. The absolute bioavailability of racemic ketamine from a novel sublingual formulation. Br J Clin Pharmacol. 2014;77(6):1011–6. PubMed PMID: 24977293. Pubmed Central PMCID: PMC4093926. Epub 2014/07/01. eng.
4. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996;77(2):203–7. PubMed PMID: 8881626. Epub 1996/08/01. eng.
5. Hornik CP, Gonzalez D, van den Anker J, Atz AM, Yogev R, Poindexter BB, et al. Population pharmacokinetics of intramuscular and intravenous ketamine in children. J Clin Pharmacol. 2018. PubMed PMID: 29677389. Pubmed Central PMCID: PMC6195858. Epub 2018/04/21. eng.
6. Hijazi Y, Bodonian C, Bolon M, Salord F, Boulieu R. Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. Br J Anaesth. 2003;90(2):155–60.
7. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370–80.
8. Dayton PG, Stiller RL, Cook DR, Perel JM. The binding of ketamine to plasma proteins: emphasis on human plasma. Eur J Clin Pharmacol. 1983;24(6):825–31. PubMed PMID: 6884418. Epub 1983/01/01. eng.
9. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms toN-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002;30(7):853–8.
10. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology. 1997;86(4):903–17. PubMed PMID: 9105235. Epub 1997/04/01. eng.
11. Yamamura T, Harada K, Okamura A, Kemmotsu O. Is the site of action of ketamine anesthesia the N-methyl-D-aspartate receptor? Anesthesiology. 1990;72(4):704–10. PubMed PMID: 1969718. Epub 1990/04/01. eng.
12. Persson J. Ketamine in pain management. CNS Neurosci Ther. 2013;19(6):396–402. PubMed PMID: 23663314. Epub 2013/05/15. eng.
13. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. Anesthesiology. 1999;90(1):174–82. PubMed PMID: 9915326. Epub 1999/01/23. eng
14. Bowen WD, Hellewell SB, McGarry KA. Evidence for a multi-site model of the rat brain sigma receptor. Eur J Pharmacol. 1989;163(2–3):309–18. PubMed PMID: 2542066. Epub 1989/04/25. eng.

15. Robson MJ, Elliott M, Seminerio MJ, Matsumoto RR. Evaluation of sigma (sigma) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2012;22(4):308–17. PubMed PMID: 21911285. Epub 2011/09/14. eng.
16. Wang D-S, Penna A, Orser BA. Ketamine increases the function of γ-Aminobutyric acid type a receptors in hippocampal and cortical neurons. Anesthesiology J Am Soc Anesthesiol. 2017;126(4):666–77.
17. Herd DW, Anderson BJ, Keene NA, Holford NH. Investigating the pharmacodynamics of ketamine in children. Paediatr Anaesth. 2008;18(1):36–42. PubMed PMID: 18095964. Epub 2007/12/22. eng
18. Administration. UFaD. Ketalar (ketamine hydrochloride) injection. [updated October 3, 2017.]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf.
19. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82(2):111–25. PubMed PMID: 10467917. Epub 1999/09/01. eng.
20. 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(5):456–66. PubMed PMID: 29870457. Pubmed Central PMCID: PMC6023582. Epub 2018/06/06. eng.
21. Visser E, Schug SA. The role of ketamine in pain management. Biomed Pharmacother = Biomedicine & pharmacotherapy. 2006;60(7):341–8. PubMed PMID: 16854557. Epub 2006/07/21. eng.
22. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med. 2016;176(9):1286–93. PubMed PMID: 27400458. Epub 2016/07/12. eng.
23. Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD. Role of ketamine for analgesia in adults and children. J Anaesthesiol Clin Pharmacol. 2016;32(3):298–306. PubMed PMID: 27625475. Pubmed Central PMCID: PMC5009833. Epub 2016/09/15. eng
24. Kronenberg RH. Ketamine as an analgesic. J Pain Palliat Care Pharmacother. 2002;16(3):27–35.
25. Tobias JD, Martin LD, Wetzel RC. Ketamine by continuous infusion for sedation in the pediatric intensive care unit. Crit Care Med. 1990;18(8):819–21. PubMed PMID: 2379394. Epub 1990/08/01. eng.
26. Hartvig P, Larsson E, Joachimsson PO. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. J Cardiothorac Vasc Anesth. 1993;7(2):148–53. PubMed PMID: 8477017. Epub 1993/04/01. eng.
27. Barbi E, Rizzello E, Taddio A. Use of ketamine continuous infusion for pediatric sedation in septic shock. Pediatr Emerg Care. 2010;26(9):689–90. PubMed PMID: 20838196. Epub 2010/09/15. eng.
28. List WF, Crumrine RS, Cascorbi HF, Weiss MH. Increased cerebrospinal fluid pressure after ketamine. Anesthesiology. 1972;36(1):98–9. PubMed PMID: 5006995. Epub 1972/01/01. eng.
29. Wyte SR, Shapiro HM, Turner P, Harris AB. Ketamine-induced intracranial hypertension. Anesthesiology. 1972;36(2):174–6. PubMed PMID: 5059108. Epub 1972/02/01. eng.
30. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr. 2009;4(1):40–6. PubMed PMID: 19569909. Epub 2009/07/03. eng.
31. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care. 2014;21(1):163–73. PubMed PMID: 24515638. Epub 2014/02/12. eng
32. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on intracranial pressure in nontraumatic neurological illness. J Crit Care. 2014;29(6):1096–106. PubMed PMID: 24996763. Epub 2014/07/06. eng

33. 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. 2018;43(5):E299–307. PubMed PMID: 28700455. Pubmed Central PMCID: PMC5846492. Epub 2017/07/13. eng.
34. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth Journal canadien d'anesthesie. 2011;58(10):911–23. PubMed PMID: 21773855. Epub 2011/07/21. eng.
35. Michelet D, Hilly J, Skhiri A, Abdat R, Diallo T, Brasher C, et al. Opioid-sparing effect of ketamine in children: a meta-analysis and trial sequential analysis of published studies. Pediatr Drugs. 2016;18(6):421–33.
36. 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. PubMed PMID: 28435316. Pubmed Central PMCID: PMC5388303. Epub 2017/04/25. eng
37. Zempsky WT, Loiselle KA, Corsi JM, Hagstrom JN. Use of low-dose ketamine infusion for pediatric patients with sickle cell disease-related pain: a case series. Clin J Pain. 2010;26(2):163–7. PubMed PMID: 20090444. Epub 2010/01/22. eng.
38. Abbasi S, Bidi N, Mahshidfar B, Hafezimoghadam P, Rezai M, Mofidi M, et al. Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial. Am J Emerg Med. 2018;36(3):376–9.
39. 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. PubMed PMID: 27695362. Pubmed Central PMCID: PMC5029839. Epub 2016/10/04. eng
40. Mulier JP. Perioperative opioids aggravate obstructive breathing in sleep apnea syndrome: mechanisms and alternative anesthesia strategies. Curr Opin Anaesthesiol. 2016;29(1):129–33. PubMed PMID: 26595546. Epub 2015/11/26. eng.
41. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, et al. Esketamine counters opioid-induced respiratory depression. Br J Anaesth. 2018;120(5):1117–27. PubMed PMID: 29661389. Epub 2018/04/18. eng.
42. Anaesthetists AaNZCo. Statement on principles for identifying and preventing opioid-induced ventilatory impairment (OIVI). Available from: http://www.anzca.edu.au/resources/endorsed-guidelines/oivi-statement.
43. 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(5):521–46. PubMed PMID: 29870458. Pubmed Central PMCID: PMC6023575. Epub 2018/06/06. eng.
44. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113(3):639–46. PubMed PMID: 20693876. Epub 2010/08/10. eng
45. Raith K, Hochhaus G. Drugs used in the treatment of opioid tolerance and physical dependence: a review. Int J Clin Pharmacol Ther. 2004;42(4):191–203. PubMed PMID: 15124977. Epub 2004/05/06. eng
46. Lilius TO, Jokinen V, Neuvonen MS, Niemi M, Kalso EA, Rauhala PV. Ketamine coadministration attenuates morphine tolerance and leads to increased brain concentrations of both drugs in the rat. Br J Pharmacol. 2015;172(11):2799–813. PubMed PMID: 25297798. Pubmed Central PMCID: PMC4439876. Epub 2014/10/10. eng.
47. Neunhoeffer F, Hanser A, Esslinger M, Icheva V, Kumpf M, Gerbig I, et al. Ketamine infusion as a counter measure for opioid tolerance in mechanically ventilated children: a pilot study. Paediatr Drugs. 2017;19(3):259–65. PubMed PMID: 28299720. Epub 2017/03/17. eng.
48. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain. 1991;44(3):293–9. PubMed PMID: 1828878. Epub 1991/03/01. eng.

49. Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. Anaesth Intensive Care. 2004;32(3):330–8. PubMed PMID: 15264726. Epub 2004/07/22. eng.
50. 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(10):1199–213. PubMed PMID: 25060512. Epub 2014/07/26. eng.
51. Kissin I, Brown PT, Robinson CA, Bradley EL Jr. Acute tolerance in morphine analgesia: continuous infusion and single injection in rats. Anesthesiology. 1991;74(1):166–71. PubMed PMID: 1986642. Epub 1991/01/11. eng.
52. Martin WR, Eades CG. Demonstration of tolerance and physical dependence in the dog following a short-term infusion of morphine. J Pharmacol Exp Ther. 1961;133:262–70. PubMed PMID: 13767428. Epub 1961/08/01. eng.
53. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain. 2003;106(1–2):49–57. PubMed PMID: 14581110. Epub 2003/10/29. eng
54. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain. 1995;62(3):259–74. PubMed PMID: 8657426. Epub 1995/09/01. eng.
55. Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg. 2002;94(5):1263–9, table of contents. PubMed PMID: 11973202. Epub 2002/04/26. eng
56. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23(3):876–82. PubMed PMID: 12574416. Epub 2003/02/08. eng.
57. Sun L, Li Q, Li Q, Zhang Y, Liu D, Jiang H, et al. Chronic ketamine exposure induces permanent impairment of brain functions in adolescent cynomolgus monkeys. Addict Biol. 2014;19(2):185–94. PubMed PMID: 23145560. Epub 2012/11/14. eng.
58. Li Q, Shi L, Lu G, Yu H-L, Yeung F-K, Wong N-K, et al. Chronic ketamine exposure causes white matter microstructural abnormalities in adolescent cynomolgus monkeys. Front Neurosci. 2017;11:285. PubMed PMID: 28579941.
59. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science (New York, NY). 1989;244(4910):1360–2. PubMed PMID: 2660263. Epub 1989/06/16. eng.
60. Fryer HJL, Knox RJ, Strittmatter SM, Kalb R. Excitotoxic death of a subset of embryonic rat motor neurons in vitro. J Neurochem. 1999;72(2):500–13.
61. Vutskits L, Gascon E, Potter G, Tassonyi E, Kiss JZ. Low concentrations of ketamine initiate dendritic atrophy of differentiated GABAergic neurons in culture. Toxicology. 2007;234(3):216–26. PubMed PMID: 17418473. Epub 2007/04/10. eng.
62. Goulart BK, de Lima MN, de Farias CB, Reolon GK, Almeida VR, Quevedo J, et al. Ketamine impairs recognition memory consolidation and prevents learning-induced increase in hippocampal brain-derived neurotrophic factor levels. Neuroscience. 2010;167(4):969–73. PubMed PMID: 20338225. Epub 2010/03/27. eng.
63. Anand KJ, Garg S, Rovnaghi CR, Narsinghani U, Bhutta AT, Hall RW. Ketamine reduces the cell death following inflammatory pain in newborn rat brain. Pediatr Res. 2007;62(3):283–90. PubMed PMID: 17551412. Epub 2007/06/07. eng.
64. Liu JR, Liu Q, Li J, Baek C, Han XH, Athiraman U, et al. Noxious stimulation attenuates ketamine-induced neuroapoptosis in the developing rat brain. Anesthesiology. 2012;117(1):64–71. PubMed PMID: 22617253. Epub 2012/05/24. eng